Cord Blood Stem Cells: Revolutionary Impacts on Translational Medicine

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Introduction

Since the first report of successful pioneering umbilical cord blood transplant (UCBT) conducted in 1988 on a 5-year-old boy with Fanconi anaemia by Dr Eliane Gluckman and her colleagues in the Hospital Saint-Louis in France in collaboration with the team led by Dr Hal Broxmeyer of Indiana University in USA1, approximately 10,000 UCBTs have been performed worldwide so far, and umbilical cord blood (UCB) has been utilised as an alternative rich source of haematopoietic stem cells for transplant. Clinical experiences and scientific breakthroughs gained and achieved in the past two decades provided ample evidence and encouraging results proving that UCBT is a safe and effective treatment modality for a number of incurable diseases.

UCB is an invaluable source of stem cells for treatment of haematologic malignancies, immune deficiencies, and metabolic disorders2. Unlike the bone marrow donor registry, UCB collections with the typing of human leukocyte antigens (HLA) are physically stored and banked to allow a quick access compared to a relatively long period of three to four months for the search of HLA-matched unrelated bone marrow donors3,4 (National Marrow Donor Program, 2004). In fact, some patients can hardly wait for completion of the bone marrow donor search, as their diseases may progress to a clinical condition ineligible to transplant and die. Besides, episodes of loss and attrition of bone marrow donors are inevitable.

UCB offers the advantages of having a higher proportion of primitive haematopoietic stem cells and naive immune cells in UCB than adult bone marrow, rendering the long-term engraftment and lower risk of severe graft-versus-host disease (GVHD) post transplant, and a reduced risk of transmission of infectious diseases as compared to matched unrelated bone marrow transplant. However, the limited number of stem cells in an UCB confines the general use and restricts UCBT in patients of small body weight, unless double or multiple units are employed otherwise.

Recent advances in stem cell technology provide an exciting and potentially new approach to finding a cure for many other currently incurable disorders such as neurological disorders, coronary artery diseases and defected metabolism. Multiple stem cells with the ability to self-renew and differentiate into different types of cells have been found and isolated in UCB. They may be applied to cell therapy for diseases related to cell loss and degeneration. The promising readouts derived from pre-clinical stem cell studies prompt the exploration of translational medicine to currently incurable diseases. The current clinical practice, research progress and pre-clinical studies of UCB stem cells are discussed.

Current Clinical Application of UCB

The episodes of successful UCBT in children rose quickly since the first report of UCBT in 1989 in which the patient has been deemed disease-free1. Thereafter UCBT has been particularly successful in children, and was regarded as a curative treatment modality for many malignancies and hereditary diseases such as leukaemia and thalassaemia. The availability of HLA-identical graft is critical for successful transplant. However, successful engraftments of up to two-antigen mismatched UCB allografts were evident suggesting that transplant of HLA-disparate UCB could be tolerated without a significant increase of graft rejection and a greater extent of GVHD. A recent study reported that unrelated UCBT for acute leukaemia in children had clinical outcomes comparable to that encountered in unrelated bone marrow transplant. This may be attributed to the preponderance of immature immune cells present in UCB that are less likely to elicit GVHD.

Compared to bone marrow transplant, a longer time interval of neutrophil engraftment was noted in UCBT with a median number of 22 - 24 days. The total nucleated cell count is a critical determinant that correlates significantly with engraftment after UCBT. UCBT was thought to be effective for children rather than adults, pertaining to the limited volume of and number of nucleated cells in UCB being harvested in a single UCB collection which is usually good enough for transplant of a patient with small body weight. In 2004 onwards, a substantial number of reports describing double unit UCBT emerged. Transplantation of double unit of partially HLA-matched UCB was shown to be feasible and efficacious in more than 200 episodes suggesting that UCBT may be eligible to more than 90% of adults in need. To date, the employment of double unit of UCB becomes a standard procedure for transplant in adults if a single UCB with a predetermined cell number is not achieved.

Research Progress

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Other promising strategies have been undertaken to improve the outcome of UCBT in adults. UCB stem cells were ex vivo expanded in cultures supplemented with various growth factors to meet the requisite cell numbers for transplant. Ex vivo expansion resulted in tens to hundreds of folds of increase of CD34+ cells and total nucleated cells in UCB. However, clinical trials of ex vivo expanded UCB have not yet been reported.

Injection of haematopoietic stem cells into the bone marrow has been suggested to potentially facilitate homing and hasten engraftment after transplant. The limited number of cells in UCB makes the injection into the bone marrow attractive. A clinical trial has been conducted to compare the intra-bone marrow injection to intravenous infusion in adults in bone marrow transplant. There was no conclusive evidence to support a better clinical outcome for patients undergoing intra-bone marrow injection.

Stem cells in UCB which under appropriate micro-environmental cues are able to be reprogrammed and contribute to a much wider spectrum of differentiated progeny than previously thought. A plethora of reports demonstrated that UCB-derived haematopoietic stem cells are able to give rise to the cells of the other germ layers. The putative stem cell plasticity suggests the almost unlimited potential of transplanted haematopoietic stem cells to trans-differentiate into cell types that do not belong to the haematopoietic system. The potential ability of stem cells to cross beyond lineage barriers has drawn much attention. Studies have been conducted to investigate the application of UCB in regenerative medicine on other morbidities related to cell loss or degeneration.

Human UCB were infused intravenously into Alzheimer’s disease mouse model. Amyloid plaques in the brains demonstrated a decrease suggesting the applicability of UCB to Alzheimer’s disease in humans. A clinical trial of UCB stem cells in a patient with spinal cord injury demonstrated an improved sensory perception and mobility.

**Future Promises for Incurable Diseases**

**Autologous UCB Transplant for Cerebral Palsy**

Cerebral Palsy is a non-progressive and non-contagious motor impairment disorder that causes a wide spectrum of life-long physical disability encompassing mental retardation, epilepsy, visual and hearing impairment, speech and language disorders, and oral-motor dysfunction. Its prevalence in Hong Kong is 1.3 per 1,000 children, which is significantly lower than 2 to 2.5 per 1,000 births in other countries. The current therapies are mainly palliative rather than restorative.

Intra-peritoneal administration of human UCB into a cerebral palsy rat model resulted in reduced spastic paresis with a significant improvement in walking. The therapeutic effects may be attributed to multiple stem cells in UCB including haematopoietic stem cells, embryonic-like stem cells, endothelial stem cells, epithelial stem cells and mesenchymal stem cells. Cell tracking demonstrated that UCB stem cells migrated to the injured areas of the traumatic rat brain. The homing of UCB stem cells into the brain lesion may be related to specific chemo-attractants being released and up-regulated on injury and the impaired blood-brain-barrier in the damaged brain allowing the penetration of donor cells to the central nervous system. The pre-clinical outcomes of UCB observed in the animal study of cerebral palsy are reproducible in a clinical trial.

A clinical trial of autologous UCB infusion was carried out in a cohort of cerebral palsy children. A cell dose of > 1 x 10⁷ UCB nucleated cells per kg body weight was injected intravenously. Post-infusion improvements in speech and motor function were evident in 60% of patients in the study cohort within 2 months or sooner. Among patients (n > 100) having undergone autologous UCB infusion, none experienced any adverse effect (personal communication with Tom Moore, CEO of Cord Blood Registry).

**The First Hong Kong Cerebral Palsy Patient Received Autologous UCB Transplant**

A 7-year-old girl with severe cerebral palsy has received autologous UCB transplant at Duke University Medical Center, USA. Her UCB was stored at our facility in 2002 and it was requested to be retrieved for cerebral palsy treatment. Confirmatory HLA-typing, colony-forming unit (CFU) assay, viability and cell count were performed before autologous infusion. The quality of her cord blood unit was reviewed and confirmed to be suitable for the treatment. Subsequently the UCB stem cells were infused through the vein on the foot over 2 minute followed by 2 hours saline infusion (Figure 1). The patient was discharged the same day and returned Hong Kong two days later without any adverse effect. The improvement will be thought to be seen after few months.

**Autologous UCB Transplant for Type 1 Diabetes**

Type 1 diabetes, which is an autoimmune disease that is characterised by T-cell-mediated destruction of insulin-producing pancreatic beta cells in all walks of life, is life-long and lethal unless properly treated with exogenous insulin administration. The prevalence in USA is 1 in 300 and continues to rise at approximately 3% per year. Allogeneic non-myeloablative haematopoietic stem cell transplantation (HSCT) has been proposed to reconstitute immune tolerance of diabetic patients. A pilot study using autologous UCB as a source of immunomodulatory cells to restore
proper immune regulation was initiated in a cohort of type 1 diabetes patients. Less than 100 mL of thawed UCB with cell viability more than 50% were infused intravenously and patients were allowed to return home after observation for at least six hours.

Preliminary data showed the administration of a less amount of exogenous insulin and a better maintenance of sugar levels in the test arm compared to the controlled arm (American Diabetes Association’s 67th Scientific Sessions in Chicago in mid-2007). Such significant benefits might be mediated by an increase of circulating regulatory T cells which were thought to reverse the autoimmune disease in general and help preserve insulin production. Perhaps the most intriguing finding is that no significant adverse reaction was encountered in the test cohort having the novel stem cell therapy.

Conclusion

In the past two decades stem cell technology and clinical experience of UCBT have pursued tremendous breakthroughs and the applications of UCB in the clinical arena are far more than thought of previously. According to recent data released by the National Marrow Donor Program, the episodes of paediatric UCBT in 2008 outnumbered bone marrow transplant in children, and the trend continues. It is apparent that UCBT is not merely confined to the availability of HLA-matched allografts. Patients, who were previously ineligible for HLA-matched unrelated bone marrow transplant, would be benefited with partially HLA-matched UCB transplants or double unit UCBT. The plasticity of UCB stem cells also allows the potential differentiation of UCB stem cells into cells of interest for treatment of morbidities related to cell loss and degeneration, such as neurologic disorders of cerebral palsy, stroke and spinal cord injury; metabolic disease of type 1 diabetes and functional defects related to myocardial infarct, coronary artery disease and etc., which were regarded as incurable at the moment. All of these have led to the increased awareness of the prerequisites in UCB collection and cryopreservation. In fact, the number of UCB collections stored in either public or private banks increase progressively implying that more patients will be benefited in the future.

References
