Review Article

Stem Cell Transplantation: Umbilical Cord

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ABSTRACT

Umbilical cord blood transplant is desirable and alternative therapeutic treatment with long term benefits. Umbilical cord blood transplantation has been increasingly used over the past years for both malignant and non-malignant hematologic and other diseases as an alternative to mismatched-related or matched-unrelated bone marrow or peripheral blood hematopoietic stem cell transplantation. It has unique advantages of easy procurement, absence of risk to donors, low risk of transmitting infections, immediate availability, greater tolerance of human leukocyte antigen (HLA) disparity, and lower incidence of inducing severe graft-versus-host disease (GVHD). The first transplantation was performed in 1988, it is estimated that approximately 4,000 patients, with malignant and non-malignant diseases, were transplanted withcord blood transplantation. Comparing to bone marrow transplants, cord blood's collection is easier and safer. Umbilical cord blood is an alternative hematopoietic stem cell source that can cause various diseases through transplantation. The expansion of umbilical cord blood has led to the establishment of UCB quality standard by professional groups such as AABB (American Academy Of Blood Bank) & the foundation for accreditation of cellular therapy. One of the disadvantage of cord blood is its low cell content which limits cord blood transplantation to generally low weight recipients, such as children. Various alternatives have been used to overcome this limitation, including co-infusion of two partially HLA-matched cord blood units.

Keywords: Accreditation, co-infusion, haematopoietic stem cell, low risk of transmitting infections, umbilical cord blood

Received 09 Jan 2015 Received in revised form 29 Jan 2015 Accepted 02 Feb 2015

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INTRODUCTION

Stem cell based transplantations are now being increasingly utilised with promising results in both malignant and non-malignant disorders [1]. Currently there are three sources of cells that have been used for hematopoietic reconstitution namely bone marrow (BM), peripheral blood (PB), and umbilical cord blood (UCB) [2]. UCB transplant, the most recently identified source of stem cells which appears to be effective as bone marrow performed when an HLA -matched donor is unavailable. The first successful cord blood stem cell transplant was performed in 1988 in Paris, France. The patient was a boy with Fanconi's Anaemia, a genetic and potentially life threatening type of anaemia [3]. Cord blood stem cell transplant was performed successfully for this patient. It was performed mostly in children with some 70 disease which include acute Lymphoblastic Leukaemia (ALL), Acute Myelogenous leukaemia (AML), Myelodysplastic syndromes (MDS), Thalassemia, Neuroblastoma and severe aplastic anaemia. More than 5,500 cord blood stem cell transplant was performed world-wide from unrelated donors and several hundred's from sibling donors. The stem cell transplant may be autologous transplant or allogeneic transplant. The patient may use own stem cells or donor stem cells (Autologous transplant) whereas donor cells may come from either a related or unrelated matched donor (Allogeneic transplant) [4]. The cord blood for stem cell

transplantation is collected from the umbilical cord and placenta after the baby is delivered out. The collected cord blood is frozen and stored at a cord blood bank for future use. The median age for patients who received umbilical cord blood transplant was slightly higher than for patients who received bone marrow transplant [5]. Before storing donated umbilical cord blood for patient use, processing, freezing and disease testing or otherwise called testing and validation are performed [6]. Umbilical cord blood stem cell transplant are less prone to rejection than either bone marrow or peripheral blood stem cells because the cells have not yet developed the features that can be recognised and attacked by the recipient immune system. Both the versatility and availability of cord blood stem cells makes them a potent resource for transplant therapies [7].

Current Cord Blood treatments:

Banking cord blood can change or even save a life. Today cord blood stem cells are used for the treatments of nearly 80 diseases including a wide variety of cancers, genetic disorders and blood disorders [8]. In a cord blood transplant stem cells are infused into a patient's blood stream where they go to work healing healthy new immune system has been created [9]. Today stem cell therapies continue to evolve, bringing new hope to patients and their families. Cord blood stem cells have certain advantages over bone marrow stem cells in transplant and have been used for 20 years to treat several life threatening diseases and disorders. Majority of cord blood transplant have been performed in patients younger than 18 years old [10]. However, with the advancement in regenerative medicine, it is forcible that individuals of all ages can benefit from stem cell therapies in the near future. Cord blood stem cell transplant have already changed and saved thousands of lives around the world. The first public banking on unrelated umbilical cord blood was started in New York in 1993 [11]. Today, there are about 225,000 cord blood units frozen in 38 public cord banks in 25 countries. There are few organizations like FDA(Food and Drug Administration) trying to ensure the quality of cord blood units registered for transplantation [12]. Based on last Eurocard Report of 3372 umbilical cord transplants in 1988-2007 done in 43 countries at 373 transplant centers, 2965 were unrelated donors, 359 were related donors but only 3 were autologous transplant [13].

Success of UCB transplantation:

Nowadays, Umbilical cord blood transplantation is increasingly considered as an alternative source to bone marrow for patients who find an unmatched donor [14]. There are many donors recently accessible worldwide but many do not get an HLA (Human Leucocyte Antigen) matched donor. By the introduction of UCB transplant, there is a marked expansion in the human stem cell transplantation [15]. According to the research conducted at Japan, they concluded that umbilical cord blood transplantation with a mismatched donor is an effective criterion if an unmatched donor is unavailable [16]. In a report of patients with Myelodysplastic syndrome, UCB transplantation was found to be the only potentially curative treatment. Several other studies also support UCB transplant as compared to other source of hematopoietic cells. In the current study Japanese researchers analysed a data that a three year survival for the patients who received a UCB transplant was found to be 47%.The survival rate for patients who received bone marrow transplant from donors with two HLA mismatches was 38%.Both related and unrelated cord blood transplants have been performed with high rates of success for haemolytic disorders and metabolic storage diseases in paediatrics [17]. The paediatric UCB transplant has opened the way to a new field in allogeneic human cord transplant as it showed that a single umbilical cord blood contain enough human stem cells which definitely reconstitute the host Lympho - haematopoietic compartment [18]. In a study published in January 17th edition of Nature Medicine, of stem cells from a unit of cord blood in the laboratory that were infused into the patients resulted in successful and rapid transplant. The longer the transplantation takes place, the chances for the patients to acquire life threatening infections are more because there are no essential WBC's

to fight with them [19]. The use of expanded cord blood stem cells would decrease the risk of early death. The stem cell expansion was also possible by activating the Notch signalling pathway in stem cells which was initially published in Nature Medicine in 2000 [20]. In the same year, in the Centre of international blood and marrow transplant, the researchers of Eurocord study compared the paediatric bone marrow transplant and umbilical cord blood transplant from HLA B identical siblings. This was the first analysis demonstrated that Graft Versus Host Diseases(GVHD) was reduced when umbilical cord blood cells were used instead of bone marrow. Therefore, Umbilical cord blood transplant has gained large popularity and acceptability as an alternative transplant source for patients lacking appropriate donor [21].

Collection & Storage:

The Umbilical cord is routinely discarded after the baby is delivered out. Certain parents may choose to preserve the blood remaining in the umbilical cord and placenta after delivery [22]. The parents with healthy children and no transplant is required can choose to donate their Newborn's cord blood to cord blood banks [23]. During delivery, the focus is on the mother and baby. After the baby is delivered out, the umbilical cord is clamped and the blood from the umbilical cord and placenta is collected either before or after the placenta is delivered which depend upon the procedure at the hospital [24]. The blood is collected into a sterile bag; this bag of cord blood is the cord blood unit. The collected blood has given an identification mark and stored temporarily. The cord blood unit is transported to a cord blood bank for testing, freezing and long- term storage. The testing of cord blood unit involves certain procedures which include HLA typing to determine the level of matching to potential recipients, cell count and testing for infectious agents such as AIDS virus, cytomegalovirus and hepatitis virus [25]. The cord blood unit is also checked to assure that it has enough blood-forming cells for a transplant. In the case of few cells, the cord blood unit may be used for research to improve the transplantation process for future patients. The blood is allowed to freeze and held at a very low temperature [26]. Usually liquid nitrogen is preferred when future use. It is not known how long cord blood can be frozen and stored before it loses its effectiveness. Cord blood samples have been preserved for as long 10 years and have still been successfully transplanted [27]. When the transplant is required, the cord blood unit is shipped within a few days to the transplant centre which is infused into patients. All hospitals do not collect cord blood for public banking. So parents need to find whether their hospital collect donations for public banking [28]. The Centre for Cord blood at the National Marrow Donor Program maintains a list of participating hospitals that collect cord blood units for their network of public cord blood banks [29]. A cord blood bank may be private (the blood is stored and cost is paid by donor families) or public (stored and made use by unrelated donors).While public cord blood bank is widely supported; private cord blood banking is applicable for both medical and parenting community. Public cord banks store cord blood for the benefit of general public while private cord blood bank usually store for profit organisations for the exclusive use of the donors or donors relative [30]. Public cord banking is supported by the medical community. However, private cord banking is generally not recommended unless there is family history of specific genetic diseases [31].

Transplant procedure:

Most cord blood transplants in US are performed on children because the amount of cord blood may not contain enough cells to treat adults. Cord blood transplants are often serious and often fatal disease such as leukaemia, sickle cell anaemia, lymphoma, immune system disorders and neuroblastoma [32]. The patients prior to cord blood transplant must undergo certain pre-transplant activity. The patients may have surgery to remove tumours and undergo several rounds of chemotherapy or radiation. The chemotherapy and radiation will remove the patient's body with disease and allow the healthy transplanted cord blood cells to grow [33]. Cord blood is collected from a cord blood bank derived

originally from umbilical cord at birth, approximately three or four ounces of blood. The transplant process begins with the patient receiving a high dose of chemotherapy or radiation to eradicate any cancer that is left in the patient's body and to ablate the patient's immune system as well. Then, the patients receive the transplanted cells intravenously similar to a blood transfusion which will take approximately 15 minutes. The post-transplant activity involves once the stem cells have transplanted into the patient, they enter the bloodstream travelling through the patient's bone marrow. The process is called "engraftment", the stem cells start to produce new white blood cells, red blood cells and platelets. The patient is kept in isolation for at least two to three weeks for the engraftment process to complete, though it can take months and years for the patients to restore their immune system [34]. Only through blood test, doctors are able to evaluate and confirm whether the cancer has returned back or not and new blood cells are forming. All cord blood transplant patients has lowered immune systems after the procedure. Some patients may stay in specially designed hospitals to keep out of infections [35]. Unfortunately, there are many side effects that would occur during the cord blood transplant process. One of the side effects is an increased probability of infection and bleeding from the high dose of chemotherapy and radiation given prior to the transplant. Doctors give them antibiotics to prevent or prevent this possibility [36]. Patients may also receive transfusion of platelets to prevent bleeding and red blood cells to treat anaemia. Other short- term side effect include nausea, vomiting, fatigue, loss of appetite, mouth sores, hair loss and skin reactions. Long term side effects may include infertility, cataracts, new cancers and damage to the liver, kidney, lungs and heart [37-41].

Dual umbilical cord transplantation:

The first dual umbilical cord blood transplantation was performed in Europe in 1999 on two adults with acute lymphoid and chronic myelogenous leukaemia. Both the patients have signs of donor engraftment but died three months after transplant; one from relapse and other from haemorrhage. Since 2005, the number of adult patients receiving double umbilical cord transplantation has surpassed the number of adults transplanted with single cord blood units [38,42]. To overcome the low cell content of single umbilical cord blood units, various alternatives like dual cord transplantation, ex vivo expansion etc. is used. It is more ideal for younger patients with lower weight. In dual umbilical cord blood transplant, two cord blood units each of which has low resolution typing of HLA-A and HLA-B or high resolution of HLA-A are infused together to transplant into adults or children. The two cord blood units chosen for transplantation must have at least 4\6 HLA match between themselves and with the patient [43]. When a cord blood unit is selected for transplantation, the TNC (Total nucleated cell) dose is used to determine if a single unit is sufficient for treatment [40], [44]. A greater mismatch between the two umbilical cord blood units requires a higher TNC count. Simultaneously transfusion of two umbilical cord blood units obtained from different donors of HLA mismatched UCB units showed lower time of engraftment than the median duration using single umbilical cord blood unit without influencing GVHD [45].

CONCLUSION

India has a greater potential for umbilical cord blood banking due to a birth rate and genetic diversity.. About 70% of patients of Indian origin whom in requirement of bone marrow transplantation do not find a matched donor, within their own family, UCB transplant were widely accepted source of hematopoietic stem cell transplantation. Umbilical cord blood was once thought as a waste product after birth, but now it is being valued for its content of stem cells. Today more than 20 years after the successful transplantation, many families are seeking information about whether to invest cord blood or not. However, to date the total number of UCB transplants performed in India has been very low mainly due to high cost and limited number of UCB units available. Private Banks are continuing to grow in India as many families opt to store umbilical cord blood in private banks with possible

advantages. To meet the future transplantation needs of the country, full participation and substantial investment of government is necessary.

SUMMARY

Umbilical cord blood (UCB), the blood remaining in the umbilical cord and placenta following the birth of an infant has emerged as an established alternative source of haematopoietic stem cells in allogeneic haematopoietic cell transplantation. The limitations of Umbilical cord transplantation include an increased risk of graft failure, delayed immune reconstitution and unavailability of donor for additional donations. The main criteria for selecting UCB units for transplantation are the human leucocyte antigen (HLA) haplotype and the cryopreserved total nucleated cell dose per kilogram recipient body weight. Other factors that influence UCB unit selection include the bank of origin, the red blood cell content and age of the stored unit, and screening for infectious hematologic disease. Large body of clinical and scientific data has been generated since the first cord blood transplantation was performed in 1989. Limited cell dose remains the setback of cord blood transplant particularly in adult population. New strategies such as dual cord transplantation or non - myeloablative conditioning have expanded the availability of cord blood transplant in adults with hematologic malignancies. Currently cord blood is considered as second best choice after bone marrow transplant.

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