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Cord Blood Transplantation and Treatment of Cancer

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Abstract

Cancer is one of the leading causes of mortality across the world. One relatively new form of treatment that has demonstrated remarkable promise in recent years is cord blood transplantation. The quick availability of cord blood and less stringent matching compared to hematopoietic stem cell transplantation gives it an edge over other techniques which helped it to emerge as a potential alternative source of hematopoietic stem cells in stem cell transplantation.

Keywords: HLA, HSC, UCBT, GVHD

Hematopoietic stem cell transplantation is one of the most effective therapy for cancers that originate in blood and bone marrow (1). It involves the intravenous infusion of autologous or allogeneic stem cells to reestablish hematopoietic function in patients whose bone marrow or immune system is damaged or defective. But both allogeneic and autologous transplantations have its own limitations such as Minimal immune response against the tumor, risk of developing relapse and graft versus host disease (2). Relative ease of procurement, the absence of risks for mothers and donors, the reduced likelihood of transmitting infections, has made cord blood transplantation as an established alternative source of hematopoietic stem cells transplantation in wide variety of malignant and nonmalignant diseases. Cord blood transplantation is therefore a promising alternative to bone marrow derived stem cells. Cord blood which is collected from the umbilical cord and placenta of healthy newborns can be used as an alternative source of hematopoietic stem cells (3). The cord blood cells can be collected without risk to the donor, cryopreserved, stored for long periods of time without damage and can be shipped easily to any transplant center (3). In the year 1988, umbilical cord blood has become the alternative use of hematopoietic stem cell (HSC) in transplantation, with the first successful donor and recipient related transplantation in treatment of Fanconi anaemia (3,4).

Metastatic tumours remain largely incurable, causing 90% of all cancer deaths (43). Years of research and clinical trials in metastatic breast cancer paved the way for researchers to test whether allogeneic stem cell transplantation could benefit metastatic tumours, including those found in the esophagus, stomach, colon/rectum, liver, pancreas, lung, breast, prostate, bone, and kidney (44). Today, clinical trials are underway to test this approach in patients who do not respond to standard therapy. These patients receive a 'mini-transplant' of peripheral blood stem cells from a brother or sister. They are also given intense immunosuppressive drugs in an attempt to reduce transplant-related side effects and to help the grafted stem cells and immune cells, called lymphocytes, thrive. The idea is to see if lymphocytes in the donor transplant can successfully attack the tumour to extend patients' lives or even cure them.

Cord blood contains many different types of stem cells, mainly the haematopoeitic stem cells, mesenchymal stem cells, endothelium stem cells, cord-blood derived stem cells and monocytes-derived stem cells (5). Transplanted stem cells from cord blood can restore the bone marrow's ability to make healthy cells. Hence, within years, umbilical cord blood transplantation (UCBT) has progressed dramatically in the treatment of cancer. In 1993, UCBT has proven that graft versus host disease (GVHD) as well as human leukocyte antigen (HLA) matching can be minimized, from the first successful unrelated donor and recipient related UCBT (6,7). This results in the development of the UCBT worldwide (4).

Sources of stem cell and treatment of cancer

Stem cell transplantation is usually used after a high dosage of chemotherapy, or sometimes, radiotherapy, to replace the stem cells in the bone marrow (8). The process known as stem cell engraftment a complex medical process in which during the first few days after transplantation, the reinfused stem cells migrate to the bone marrow and begin the process of producing replacement blood cells, by a process called engraftment. The stem cells start to produce new blood cells within 12 to 15 days following infusion. Colony-stimulating factors may be administered during this time to stimulate the process of blood cell production.

Until stem cell engraftment is complete, a transplant recipient is susceptible to infection, anemia, and bleeding caused by low blood cell counts. Therefore, special precautions are necessary during recovery. Patients may be given red blood cell and platelet transfusions during the recovery period to help prevent anemia and bleeding. For the first 2-4 weeks after the transplant, patients are very susceptible to developing infections. This is because the effects of the high-dose chemotherapy and the loss of blood cells weaken the body's immune system. Antibiotics are often prescribed to help prevent infection (45, 46).

Stem cell transplantation is categorized into 2 types, mainly autologous and allogeneic, where autologous stem cells are taken from patient's own blood or bone marrow (8). This ensure that there will be no GVHD or other infection as it is taken from one's own body (8).

Autologous transplantation is commonly used to treat leukemia, lymphoma, neuroblastoma, testicular cancer as well as multiple myeloma (8). However, there is a risk of collecting cancer cells together with healthy stem cells and then transplanting it back into the body. Cancer stem cells can originate from mutation in normal somatic stem cells that deregulate their physiological programs. Alternatively, mutations may target more committed progenitor cells or even mature cells, which become reprogrammed to acquire stem-like functions (47). Hence, even though autologous transplantation is done within the same body, the cancer cells can go overcome body's immune system before transplanting new stem cells, resulting in a failure in treatment (8).

In contrast, allogeneic stem cell transplantation is taken from a matching donor, for example close siblings. The latest source for allogeneic transplant is from the placenta and umbilical cord blood of newborn (8). Usually, there will be high number of stem cells multiplying fast in a small amount of blood, however, it is only enough for young children but not adult (8). It is also used in treating leukemia, lymphomas, myelodysplastic syndrome and aplastic anaemia (8). The advantage of allogeneic transplantation is that the donor stem cells may produce graft-versus-cancer effect, where it induces own immune cells to kill cancer cells that remain after high-dose treatment (8). Donor CD4+, CD8+ and natural killer (NK) cells have been reported to mediate graft-versus-cancer effect, using Fas-dependent killing and perforin degranulation to eradicate malignant cells. Cytokines, such as interleukin-2, interferon-gamma and tumour necrosis factor-alpha potentiate the graft-versus-cancer effect (48).Howbeit, it may induce GVHD as well as infections that reoccurs after usage of immunosuppressants drugs (8). This multiorgan disorder results from immune-mediated attack by donor leukocytes on recipient tissues, and most commonly involves the skin, oral mucosa, lungs, intestinal tract, and liver (elevated bilirubin).

Acute GVHD occurs in 20–40% of allogeneic HSCT, and forms the basis for prophylaxis with potent immunosuppression,

Process of cord blood banking

Cord blood banking refers to the collecting, processing, testing and storing of cord blood units (CBU) for the use of haematological and immunological reconstitution of unrelated recipients (9). There are three types of cord blood banking, mainly, public banks, private banks and directed donor (10). Public cord blood banks store cord blood for allogenic transplants. The stem cells in the donated cord blood can be used by anyone who matches. Some public banks will store cord blood for *directed donation***.** Private or family banks store cord blood for autologous use or directed donation for a family member. Directed donor refers to the usage of cord blood directly given to own family member with existing medical condition that could save the patient (12).

Umbilical cord blood is collected from the umbilical vein either before the placenta is delivered (in utero) or following placental delivery (ex utero) (11,13,14).

The standard in utero method for cord blood collection uses a closed collection system to reduce the risk of infection and maternal fetal fluid contamination. The umbilical cord is double-clamped approximately 3 to 5 cm from the umbilicus and transected between the clamps. After the infant has been removed from the field, the cord is prepared for venipuncture using a povidone iodine applicator. The needle of the cord collection kit is then inserted into the umbilical vein and the cord blood unit (CBU) is collected by gravity. The time required to perform the cord collection procedure is approximately 5 to 10 minutes and additional personnel are not required. Factors known to reduce cord blood volume include maternal hypertension, smoking, multiple gestation, preterm delivery, intrauterine growth restriction, abnormal placentation, emergency c Section (CS), precipitous delivery, and maternal transfer (49,50,51). Factors associated with higher cord blood volumes and greater yield of nucleated cells include birth weight, placental weight, gestational age, induction of labour, prolonged labour, CS, early cord clamping, first born infants, Caucasian ethnicity, and female infant gender. Umbilical cord blood obtained after CS for acute fetal distress also appears to significantly increase total nucleated cells, CD34+ cells, and white blood cells without compromising cord volumes and should not preclude cord blood collection unless maternal and newborn safety may be compromised.

Ex utero, also known as open collection system, is carried out by trained personnel in a closed room immediately after placenta is delivered (11). This method is not preferable as it has lower volume of cord blood and total nucleated cell (TNC) counts (11). It is a simple technique; however, it increases the chance of microbial and maternal contamination (15). According to NetCord-FACT Standards, processing cord blood should within 24 hours upon collection in a closed system or a sterile room (13). Processing CBU using cryopreservation and freezing method must not alter the biological characteristics of the cells (16). DMSO act as cryoprotective solution, is mixed with CBU using an orbital rotator (16). As cryopreserved CBU is in a large volume and it occupies most of the storage space of the collecting bag, volume of CBU is reduced by depleting red cells and plasma, while maintaining the quality and volume of buffy coat as well as the stem cells (13,16,17). It is important to preserve maximum amount of TNCs and $CD34^+$ cells in the buffy coat layer (13). Collected CBU will be frozen and stored in conventional liquid nitrogen freezers (16).

Advantages of cord blood banking

Cord blood banking benefits everyone as it is rich in HSC, (10,18) as it multiplies quickly (23), and collecting it does not impose risk to mother or newborn (11,21). Cord blood is useful in repairing tissues, organs and blood vessels, and it has the ability to treat diseases, such as leukemia, lymphoma, aplastic anaemia and Hurler syndrome (18,19,20,23). Besides, cord blood contains immature stem cells and naïve T cells, thus, it does not require hundred-percent HLA matching and has a lower risk of having

GVHD (10,21,22,25). Unrelated cord blood banking expanded the diversity among the donor population, making it easier to provide suitable cord blood to any patients who needed cord blood for treatment (21, 22.26). Unrelated cord blood transplantation data suggested that engraftment could occur even with cord blood units that were mismatched at 2 HLA loci, that the risk of severe graft-versus host-disease was low, and a higher cell dose may be an important prognostic feature. Moreover, it has minimal risk of infections to newborn babies, especially transplant recipients, compared to adult stem cells donors (27). After processing and testing, the cryopreserved CBU can be used immediately upon demand, without any delay (15).

Cord blood therapy in treatment of leukemia and other blood related disorders

Blood disorders like leukemia requires chemotherapy as one of the treatment (18,22,29). Generally, anticancer drugs affect dividing cells. Cancer cells divide more often than healthy cells and are more likely to be affected by chemotherapy. Still, some healthy cells also may be damaged. The amount of dosage should be proportional to the effectiveness of the treatment. In order to minimize the toxicity the therapeutic dose is compromised, so the dosage finally given is therapeutically insufficient leading to tumor recurrence and chemo resistance. In chemo resistance the drugs may not significantly reduce tumor size, or the tumor may continue to grow despite treatment. Furthermore, the initial use of a drug may lead to higher toxicity when chemotherapy is given later in the course of treatment. Toxicity must also be studied to be sure that each different drug used in a combination is not toxic for the same organ (52).

Therefore, stem cells therapy is highly recommended. The main challenges faced by leukemia patients who requires HSC transplantation is the availability of ideal bone marrow donor with the matching human leukocyte antigens (HLA) (30). According to The New England Journal of Medicine, it was found that only 30 percent of leukemia patients are able to gain benefit from the donated stem cells due to the matching of the six important HLA (3, 30, 31, 32). Hence cord blood transplantation is becoming an acceptable alternative source of hematopoietic stem cells for patients with malignant diseases (30). In addition, patients are more likely to receive cord blood transplantation since it does not require HLAs matching unlike bone marrow transplantation (30). This is because stem cells from the umbilical cord are mostly immature, therefore, it does not need exact matching to patient's own HLAs (33).

Future directions

As cord blood therapy continues to progress, researchers hope that in the future, cord blood cells can be harvested from multiple donors to a single patient, increasing the speed of the blood cell replacement as well as combining both related and unrelated cord blood for future treatment (22). Currently, they are still investigating the possible ways in improving immune reconstitution (36) to minimize the rate of infections or viral reactivation, and engraftment by transplanting ex vivo expanded cord blood cells (13,15,25). It includes the expansion of mesenchymal progenitor cells, in which shown that neutrophil engraftment improved from 24 days to 15 days, (34,35) as well as increasing total nucleated cells (TNC) in the CBU (34,35). Another challenge to be explored is the immunotherapy protocols, (37) for example expansion of viral specific T cells and natural killer cells (NKC) that are currently used in bone marrow transplantation, also be applied to cord blood transplantation as an anti-tumour cellular therapy (13,25,37,38).. In addition, scientists are emerging into the field where cord blood can be used to repair neurological conditions, such as cerebral palsy, and other diseases like type 1 diabetes and liver disease (11,39).

CONCLUSION

The development of cord blood transplantation in the field of medicine has overcome the limitations of bone marrow transplantation, allowing patients to have alternative promising route of treatment (40,41).

Cord blood transplantation has lower risk of GVHD and viral infections due to well adaptation of the stem cells (21). Moreover, HLA matching is not required as stem cells collected from umbilical cord as not fully developed, thus, patient has the opportunity to receive stem cells transplantation from unrelated donor (21). The process of cord blood banking is easy and safe, and the cryopreserved cord blood can be stored for a long period of time (23). Furthermore, umbilical cord blood HSC has the ability to multiple quickly and generate new cells (23). As cord blood stem cells is naturally lesser than bone marrow stem cells, (42) researchers are now searching for better therapies that can increase the amount of stem cells in the cord blood artificially before transplanting (22). Although cord blood transplantation can treat many kinds of disorders categorized from cancers, blood disorders, metabolic disorders and immune disorders, (19) scientists are currently researching on the possibilities to treat more diseases, especially in the sense of neurological disorders (39,42).

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