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Treatment for Leukemia: An Increasing Cause of Death Through Stem Cells Collected from Umbilical Cord

Anjana Shankar[1, 2], Hasanka Madubashetha[2], Nimali De Silva[3]*

[1]*Department of Biotechnology, Faculty of Applied Sciences, UCSI University, Kuala Lumpur, Malaysia*

[2]*Section of Genetics, Institute for Research and Development in Health and Social Care, Battaramulla, Sri Lanka*

[3]*Department of Nanotechnology, Faculty of Technology, Wayamba University of Sri Lanka,Kuliyapitiya*

*Corresponding author: Nimali De Silva, Department of Nanotechnology, Faculty of Technology, Wayamba University of Sri Lanka, Kuliyapitiya.

Abstract

Cancer is a serious public health issue burden faced worldwide leading to millions of deaths yearly. This involves the abnormal growth of cells which proliferate uncontrollably and spreads to the other sites of the body by metastasis which is referred to as the Cancer stage IV. This can be formed in different parts of the body where the treatment is provided targeting the particular site by identifying the site of origin but still there is no effective treatment method to completely cure the disease while the available treatment methods possess serious side effects. Moreover, Leukemia is a blood cancer which is more difficult in target treatment hence Umbilical cord blood transplantation (UCBT) is expected to be a good treatment method. Since the first UCBT, their use has been increasing with the establishment of several cord blood banks worldwide with thousands of transplants yearly for adults as well as children. Hence, this review focus on providing with an insight on UCBT as an effective treatment method for Leukemia which is a more difficulty facing cancer in targeting site for treatment. Infusion of double-cord blood units, intrabone infusion and ex-vivo culture of cord blood is expected to increase the cell number which can overcome the problem of reduced cord blood cell count. Also, the different methods of conducting UCBT and the challenges along with its current status and future aspects are discussed.

Keywords: Leukemia, Umbilical cord blood transplantation (UCBT), double-cord blood unit, intrabone infusion, ex-vivo culture

Introduction

Leukemia, a type of cancer is an increasing threat to the world of medical science obtaining the second place to cause deaths worldwide and killing millions per year has unfortunately failed to still find a remedy for complete cure. Several different treatment methods such as chemotherapy, surgical resection and radiotherapy have been found but still the rate of success is low due to various factors like resistance towards drug, side effects from the undertaken therapeutic treatments or off-target effects. Moreover, metastatic cancer which is the most critical part said to be the Stage IV (four) cancer which is the spread of cancer cells to other parts of the body is the stage where most of the patients identify the presence of cancer and unfortunately the above-mentioned treatment methods find difficulty in providing an effective treatment. Hence, there is an utmost need in discovering an efficient treatment method for the complete cure of cancer as soon as possible. Several different researches are being undertaken to find an efficacious treatment method and from these stands out the treatment method using the stem cells.

Stem cells are the immature cells found in human body which are rapidly dividing cells having the ability to change itself into different types of cells from the embryo stage till death. It is unique from other cells by its characteristic of self-renewal which means undergoes rapid cell division forming its replicates and secondly its ability of differentiation meaning it can be changed into different types of cell such as Red Blood Cells and Muscle cells under certain experimental conditions and thirdly their ability to

renew their own populated cells. In the case of cancer, stem cells have the capability to move towards the target cancer cells, produce bioactive factors and maintain the level of immune cells.

Most importantly, the major drawback in the failure of treatment methods such as chemotherapy is due to its excess power leading to killing body's own immune cells and weakening the immune system. Hence, inoculation of stem cells can be a good treatment therapy here producing immune cells rapidly and prevent from weakening of the immune system. This can also help by increasing the dosage of chemotherapy in killing the cancer cells where injection of stem cells can take place after the chemotherapy treatment of patients.

Brief overview about stem cells

The stem cells can be categorized further based on their origin and potency as embryonic stem cells (ESC), which are pluripotent cells originated from the blastocytes of embryo deriving from the three germ-layers ectoderm, mesoderm and endoderm. These cells can be differentiated into any types of cells except the cells found in the placenta, but its usage is limited due to certain ethical restrictions as it is obtained from the destruction of embryo. And at situations which require in vitro growth of pluripotent cells, induced pluripotent stem cells (iPSCs) are used which is another type of stem cell differentiated from the mature somatic cells which lacks ethical consideration as it does not need to be obtained from the embryo.

Secondly, non-embryonic stem cells which are multipotent mature stem cells that can be found in various parts of body such as skin, bone marrow, umbilical cord blood along with placenta, ovary and sperm [1] that can be differentiated into various types of stem cells such as hematopoietic stem cell, neural stem cells, mesenchymal stem cells and endothelial progenitor cells [2]. Mostly, treatments were carried out from stem cells derived from the bone marrow but currently the interest is drawn towards the stem cells derived from the umbilical cord blood due to various advantages and effectiveness compared to the bone marrow derived stem cells.

Umbilical Cord Blood (UCB) as a source of stem cell

The umbilical cord is a cord-like structure which connects the fetus in the uterus with the placenta of mother which is approximately 50cm in length. The umbilical cord consists of the veins, carrying oxygenated blood and nutrients from mother to the fetus and the arteries, carrying deoxygenated blood and waste products from fetus to the mother. This important and nutritionally rich structure which has been detached after the birth of fetus and discarded in the biological waste is now found out to be a treatment for several incurable deadly diseases such as cancer. Recent research states that the umbilical cord blood is a rich source of hematopoietic and progenitor stem cells that can be obtained easily, risk-free and pain-free. This is done by extracting the blood from the detached umbilical cord which can be stored frozen for years and used to cure several life-threatening diseases in future. As it is stored, it makes them readily available for the treatment. The donor of UCB is also being tested and confirmed the absence of any hereditary or transmissible diseases which makes it safe for the recipient.

Also, it is found to be that the umbilical cord blood derived stem cells are much younger compared to the stem cells derived from bone marrow or peripheral blood which makes them more tolerant toward Human Leukocyte Antigen (HLA). Most importantly they minimize the rate of Graft Vs Host disease which is a major problem when it comes to stem cell transplant as it does not require a perfect matching of Human Leukocyte Antigen (HLA).

Evidence of Umbilical Cord Blood Derived Stem Cell Transplantation

The idea of using umbilical cord blood (UCB) as a source of stem cells dates back to 1980s, where three different groups were involved correspondingly, but the most significant work was carried out by H.E. Broxmeyer and his colleagues in 1989 who proposed the idea of human umbilical cord blood as a potential source of transplantable stem cell by conducting research collecting the UCB in humans and undergoing in vitro growth in laboratory for identifying the potential growth of hematopoietic stem cells and also provided effective methods for collecting and storing the umbilical cord blood for therapeutic use. This idea was influenced by the research conducted by E.A. Boyse on inbred mice injected with syngeneic neonatal blood which showed restoring of hematopoietic cells. Same time, A.D. Auerbach and colleagues involved in prenatal diagnosis of the potential donors for the umbilical cord blood stem cell transplantation of patients affected with Fanconi's anemia in 1989 [3].

The first successful umbilical cord blood transplantation was evidenced in 1988 for a patient affected by Fanconi's anemia by obtaining umbilical cord blood from his own HLA-identical sibling. The patient was a five-year old male diagnosed with pancytopenia at the age of two, a serious illness which cause deficiency of blood cells. The patient also lacked a left kidney, had an extra thumb in left hand, showed retarded growth and when the cells were examined with diepoxybutane he was diagnosed with Fanconi's

anemia which is the inability of bone marrow to produce the adequate blood cells. But, the test on parents confirmed they were healthy and showed no pass records on family history diagnosed with Falconi's anemia. When again mother was pregnant in 1988, studies were conducted culturing cells from amniotic fluid with diepoxybutane showed consistent range of chromosomal breakage confirming the newly born baby girl is not affected by Falconi's anemia and the HLA typing method confirmed its match with the donor.

Since the first successful transplant, increased number of transplants have been recorded and stored in cord blood banks (CBB) worldwide for future use. The first cord blood bank (CBB) was established by H.E. Broxmeyer at the laboratory of Indiana University of Medicine and its therapeutic effectiveness led to the establishment of CBB worldwide with units of HLA-typed which can be used for non-related patients [4]. With the initial transplantations carried out from related donors, later cord blood banks established an international standard in extracting, storing, cryopreserving and distributing of the UCB stem cells for unrelated donors with malignant and non-malignant diseases. Rubinstein et al was the first to carry out UCB transplantation from unrelated donors starting with two leukemia affected children and the positive results led to the initiation of increased number of unrelated donor transplantations since 1992. And within the next six years, 562 successful transplants were recorded concluding that the stored umbilical cord blood is a rich source of stem cells for patients with related donors [5].

Umbilical Cord Blood Transplantation in Adults with Unrelated Donors

A critical factor that must be considered during transplantation is the cell dose which highly affects the rate and time of cell reconstitution, rate of survival and success of the treatment. The required cell doses for a patient depends on the body weight of the patient where an adult weigh approximately 70-90 kg will need a higher amount of dose compared to children as they weigh only around 20-40 kg. Unfortunately, while a higher number of stem cells can be extracted from bone marrow of a single donor, amount of cord blood cells that can be yield is limited and hence using the limited amount of cord blood cells is a challenge when it comes to umbilical cord blood transplantation in adults.

Later, research was conducted by Laughlin and colleagues on UCBT in adults selecting 68 patients out of which 90% of patients results showed reconstitution of myeloid at a short period regardless of the HLA-mismatched transplant and only a probability of 20% for GVHD. Out of 68 patients 17 deaths took place due to other factors such as infections and preparative regimen which means the intake of high-dose chemotherapy and radiation resulting in destroy of our own immune cells.

Overall, UCBT in adults showed positive results regardless of the HLA-mismatch, limited amount of cord blood infused as well as low percentage of GVHD and the same findings that were conducted in different places [6,7] confirms that cord blood transplantation can be carried out in adults with unmatched donors as well. Hence, as cell dose being a crucial point along with the past studies it is required to find more efficient methods to increase the number of cord blood cells for transplant in order to improve the transplantation method for adults.

Methods and Challenges in Increasing the Number of Cord Blood Cells for UCBT

Infusion of double units of cord blood instead of the standard single unit transfusion method

Several researches have been undertaken in order to increase the effectiveness of UCBT in the means of engraftment. One of the main drawbacks of UCBT is the reduced number of cells per unit and delay in the recovery time of blood cells hence, to overcome this, two units of cord blood with partially matched HLA-markers was used instead of one unit [8]. This increased the number of transplants taking place and also showed lower relapse in patients [8]. But the result did not show a significant difference between the results of patients used single and double units. The reconstitution rate of hematopoietic cells is relatively low in two units of cord blood compared to one unit and only one unit has sustained a after month and the other unit has been removed or present in non-detectable amount. At the same time, unfortunately the succeeded unit out of two cannot be still found and predicted that it is been selected by an immune-mediated process. Moreover, usage of two units has led to higher rate of graft versus host disease (GVHD) compared to single unit of cord blood [9] and moreover, cost will also be higher when using two-units [10].

Perfusion of Cord Blood from Placental Vessels

Another method is the two-step collection method of cord blood which initially collects the blood from cord as the normal procedure then secondly perfusion of placenta to overall extract a higher amount of umbilical cord blood (UCB) which will increase its effectiveness by collecting a higher number of nucleated cells. Because the speed and success of graft depends on the amount of nucleated cell doses infused. Perfusion of placenta defines the extraction of cord blood from placental vessels as well [11].

As stated in the study by Bornstein and his colleagues, the standard technique of cord blood extraction collected around 10x108 units in which only around 25% reach the target cells which is approximately 2x107/kg that can be infused to patients weighing 50-70 kg undergoing UCBT. But the two-step cord blood collection method showed 20% higher collection rate of UCB units compared to the standard method and with a minimal rate of bacterial contamination which is highly advantageous. But this method has an issue in its feasibility due to difficulty in extraction of cord blood in each and every placenta in a hospital as it requires a more sterilized method where it was collected by selecting and distinguishing the artery and veins of the placenta and the perfusion of 50ml 0.9% saline along with heparin and collection of cord blood [11,12].

Intrabone Infusion of Cord Blood

This is another effective method that can be used in cord blood transplantation where the cord blood is directly infused into the bone marrow. This research was initially conducted in mice and confirmed that Intrabone infusion is 15 times higher than intravenous injection of cord blood in reconstitution of cells and increasing homing efficiency [13]. And another research conducted in patients with acute leukemia of different stages also showed good results in reconstitution of neutrophils and platelets, reduced rate of acute-GVHD and showing lesser chances of graft failure even when transplant done from unmatched HLA-typed donor while few death took place due to problem in transplant, relapse and other infections. Also, during intravenous infusion studies show that the cells are trapped in the peripheral organs and tissues whereas only less than 10% of cells reach the target bone marrow niche but during Intrabone infusion, more than 90% of cells release from marrow to bloodstream within 15 seconds and the direct contact between marrow niche and HSCs increase the homing efficiency as well [14,15]. According to the studies conducted, intrabone infusion of cord blood can be used in a high number of adult patients in future but due to its invasiveness and lack of confirmed results still this process is under further study.

Ex vivo expansion of hematopoietic stem cells (HSC) for cord blood transplantation

Along with the findings of different methods to increase the cell dose for cord blood transplantation, the knowledge about cytokines, microenvironment and growth factors that contribute to the function of human HSC led to using of this information to construct the idea of ex vivo expansion of hematopoietic stem cells. This was expected to increase cell number in transplantation. One of the methods carried out was the Notch cell-surface receptor and delta interaction in the cord blood culture medium along with chosen cytokines. This resulted in repopulation of HSC in a short-time period and have shorten the recovery of neutrophils engraftment than the normal unmanipulated HSC. This was used as one of the double-unit cord blood while other unit would be the non-manipulated cells [16].

Another process carried out was the culturing of mesenchymal cells along with the cord blood culture which also showed rapid recovery in neutrophil engraftment [17]. This was also used in double-cord blood like the previous mentioned method where one unit was from the unmanipulated CB and the other was ex- vivo cultured mesenchymal cells with selected cytokines. But still these methods are under research to confirm the efficacy and potency of cells cultured in ex-vivo in producing repopulating cells that could save the transplanted patient. The fast-growing advancement in technology will identify a solution for this method soon as possible and with both long-term and short-term hematopoietic cells with faster engraftment. The drawback in this process will be the high expense and the need for a cell processing unit to carry out the ex-vivo culture which is also a time-consuming process.

Current status and Future perspectives

A major limitation of cord blood transplantation is that the blood obtained from a single umbilical cord does not contain as many hematopoietic stem cells as a bone marrow donation. Scientists believe this is the main reason that treating adult patients with cord blood is so difficult because adults are larger and need more HSCs than children. A transplant containing too few HSCs may fail or could lead to slow formation of new blood in the body in the early days after transplantation. This serious complication has been partially overcome by transplanting blood from two umbilical cords into larger children and adults.

Results of clinical trials into double cord blood transplants (in place of bone marrow transplants) have shown the technique to be very successful. Some researchers have also tried to increase the total number of HSCs obtained from each umbilical cord by collecting additional blood from the placenta. Much research is focused on trying to increase the number of HSCs that can be obtained from one cord blood sample by growing and multiplying the cells in the laboratory. This is known as “ex vivo expansion”. Several preliminary clinical trials using this technique are underway. Current research aims to establish whether safe and effective treatments for non-blood diseases could be developed in the future using cord blood. Other very early-stage clinical trials are now exploring the use of cord blood

transplants to treat children with leukemia. However, such trials have not yet shown any positive effects and most scientists believe much more laboratory research is needed to understand how cord blood cells behave and whether they may be useful in these kinds of treatments. Experts believe that umbilical cord blood is an important source of blood stem cells and expect that its full potential for treatment of blood disorders is yet to be revealed. Other types of stem cell such as induced pluripotent stem cells may prove to be better suited to treating non-blood-related diseases, but this question can only be answered by further research. Beyond hematopoietic transplantation, additional potential applications of Umbilical Cord Blood include immunotherapy, tissue engineering and regenerative medicine [18-24].

Conclusion

The treatment of adult leukemia patients with unrelated donor hematopoietic stem cells is more complex. Patients with cancers other than chronic myelogenous leukemia in the chronic phase have high rates of transplant-related mortality after receiving bone-marrow transplants from unrelated donors. The use of cord blood in these patients could have a significant advantage over bone marrow in that it is less likely to induce severe GVHD - although this advantage could be offset by the limited number of cells available. The ultimate choice of stem-cell source ultimately depends on the availability of a suitable bone-marrow donor versus cord blood donor. Research and development of all aspects of cord blood transplantation from cord blood biology, to the clinical practice of cord blood transplantation, to banking procedures is proceeding rapidly. Although more prospective studies are needed in this field, this novel stem-cell source shows great promise in improving therapy for patients with hematological cancers.

Conflicts of interest

The authors have no conflicts of interest to declare on this work presented.

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Ethical Considerations

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*Corresponding author: Nimali De Silva Email- nimalides@hotmail.com