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THE USES OF HEMATOPOIETIC STEM CELL TRANSPLANTATION TO RESTORE THE PRODUCTION OF BLOOD CELLS IN CANCER TREATMENT

Nur Athirah Binti Abu Hashim, Wan Nursyahirah Binti Wan Zawawi, Siti Amira Othman, Elizah Mohammed

Faculty of Engineering Technology,
Universiti Tun Hussein Onn Malaysia,
Pagoh Higher Education Hub,
KM 1, Jalan Panchor,
84600 Muar, Johor, Malaysia

Abstract— Hematopoietic stem cells (HSCs) are a limited group of all blood cell types. A study was performed on the spleen of mice undergoing bone marrow transplantation to determine the potential colonization of red blood cells. This bone marrow transplant has been leading in treating malignant diseases. High-dose chemotherapy with hematopoietic stem cells has been commonly used in the diagnosis of haematologic allegiances. This is a clinical trial of autologous and allogeneic transplants which takes the latest developments in blood progenitor cells into consideration. Prior to transplantation, patients underwent intensive myeloablative chemotherapy with a "rescue" stem cell. Autologous HSCT was performed using hematopoietic stem cells of the patient's own, pre-transplantation removed and after myeloablation re-injected. This century has produced a range of approaches and innovations that have been used including modern mobilization approaches and the in-vivo production of blood progenitor cells, the use of core cord blood as alternative cell source, and molecular techniques that could include other forms of purifying tumor cells from potential autologous lists.

Keywords— Stem cell, hematopoietic stem cell, bone marrow, allogeneic transplant, autologous transplant

8.1 INTRODUCTION

The human body consists of several different cells devoted to performing certain functions but not divisible, such as the red blood

cells that bring oxygen across the body to the blood. Stem cells are cells which have the unique ability to develop into several kinds of cell inside the body. These unique cells will give the body new cells to grow and substitute existing cells that have been weakened or lost. They have unique features which allow them to perform repeated divisions to create new cells [1]. As they split, they can turn into other cell types capable of forming the body. This allows stem cells to develop into more specialized stem cells and also more stem cells. It is possible to classify the stem cell into 3 types which are embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs) and mesenchymal stem cells (MSCs). ESCs are present in the early stage of embryonic nucleus, usually in the first week after fertilization prior to embryo implantation. Next, iPSCs are cells that are derived from skin or blood cells that have been reprogrammed back into an embryonic-like pluripotent state. This state is enabling the production of an infinite supply of any form of human cell required for therapeutic purposes. The MSCs are the type of adult stem cell that remains in the body during adulthood, renewing and differentiating into specialized cells continuously.

8.1.1 The Possible Uses of Human Stem Cells

Stem cells have many applications in this creation including those used in fields of study where people try to understand the fundamental nature of how life functions and what is happening with different cell types during illness which is called medical biotechnology. Medical biotechnology includes the research and development of technology that is being applied in the uses of living cells and cell materials. In fact, the aim of medical technology is to research and produce pharmaceutical and diagnostic products that help treat and prevent human diseases. Hence, the use of stem cell transplant is a part of medical research studies. Additionally, it is often used in medicine (therapy) to replace damaged cells which the body cannot naturally replace. Stem cell biotechnology appears to be a scientific and technical field that emerges as a therapeutic source by altering stem cells that are useful in regenerative medicine. Stem cell work gives hope of a variety of malignant and non-malignant diseases being treated successfully. There are many possibilities for experimental and clinical application of human stem cells. Human embryonic stem cell studies may provide insight into the complex events occurring during human evolution.

The core impartial of this exertion is to determine how differentiated stem cells become differentiated tissue and organ-forming cells. Scientists recognize that this mechanism is important for turning on and off genes. Cell division and differentiation typically involve many of the worst medical conditions, including cancer and birth defects. A more thorough knowledge of this process's genetic and molecular causes will provide insight about how the disease occurs, and will propose new therapeutic strategies. More fundamental work is essential on molecular and genetic indicators controlling cell division and specialization. Although recent advances in iPSCs indicate several different factors that may be involved, it's important to establish techniques to safely integrate these influences into the cell and regulate the processes triggered by these factors.

The practice of human stem cells for the manufacture of cells and tissues that can be used to treat basic cells needs further research in the future. Contributed organs and tissues are mostly used for the forms of malignant tissues, and current stocks provide room for tissues and removable organs. Stem cells, which are built to divide into various cell forms, provide important sources of effective cell replacement and tissue for the treatment of diseases including macular degeneration, spinal cord injury, stroke, burns, cardiac disease, diabetes, osteoarthritis and rheumatoid arthritis. For example, in the laboratory, healthy cardiac muscle cells can develop and then pass them on to patients with chronic heart disease. Initial tests in mice and other animals have shown that cells transplanted into a damaged heart may have beneficial effects on the bone marrow's stromal cells. It is currently being actively investigated whether these cells can produce heart muscle cells or encourage the development of new blood vessels that replenish heart tissue, or help with many other mechanisms.

In this study case, the emphasis will be on the use of hematopoietic stem cell transplantation (HSCT) in cancer therapy. Many patients dealing with cancer must undergo surgery, chemotherapy and/or radiotherapy. Traditional methods of care still are not effective though. For certain cases of cancer, such as leukaemia, this stem cell transplant may be another alternative to cancer therapy. HSCT is one of the technology treatments that transfers blood directly into a vein, which is called intravenous therapy. It was designed to develop marrow and immune function through intravenous infusion of HSCs and progenitor cells in patients with a variety of acquired and inherited malignant and non-

malignant disorders. Patients undergoing these hair loss and constipation following chemotherapy experience the side effect. Many people would take supplements as a healthy way to boost health because they want to help the natural defenses of their body battle the cancer and accelerate their chemo recovery. But some vitamins might make chemo less effective. Hence, HSCT is the technology or gene therapy that can be used after chemotherapy to restore the production of blood cells. So that red blood cells that are restored can cure the effect of chemotherapy.

8.1.2 Types of cell Transplantation

Since the advent of HCT in the 1960s, several different methods of transfer have evolved. Currently, hematopoietic progenitor cells used for HCT are derived from bone marrow or peripheral blood. Decisions to use certain types of HCT by age, disease and condition of the patient, and the availability of the donor. In some cases, there may be several approaches that can be used.

i. Autologous stem cell transplantation

Cells are produced from the patient's own bone marrow from autologous stem cells, which are substituted during cancer diagnosis. They are most commonly used to treat illnesses including lymphoma and myeloma. Graft versus host disease (GVHD) have little or no resistance and thus use allogeneic transplantation to be healthier.

ii. Syngeneic stem cell transplantation

The same twin contributes to the process in which the patient receives stem cells that form blood (the cells that all the blood cells originate from).

iii. Allogeneic stem cell transplantation.

Stem cells originate from donors whose tissues are ideally prepared for allogeneic stem cell transplantation with the receiver. These cells possibly will be extracted from the central cord blood collected from the placenta after they are born and deposited in the central blood bank for use. The Blood Bank of MD Anderson is aggressively finding a central rope to help. Allogenous transplants are also used for treating different bone marrow diseases, such as leukaemia. Unlike autologous transplants, they establish new cancer-fighting responses to the immune system. The drawback is an increased chance of rejection or GVHD.

8.1.3 Hematopoietic Stem Cells in Cancer Treatment

Hematopoietic stem cell transplantation (HSCT) has developed into one of the best frequently applied modern medical principles. Transplantation of stem cells cannot simply cure cancer on its own, but it means restoring vital blood stem cells that have been devastated by chemotherapy with large doses. But certain types of stem cell transplantation can also help directly fight cancer cells as the donor cell is active against some of the remaining cancer cells. Stem cell transplantation unlike organ transplantation in which no surgery is needed. As in blood circulation, droplets inject the fluid which comprises the stem cells through the body. Stem cell transplantation is very exhausting both physically and mentally, which can lead to severe life-threatening complications. It is primarily attributed to the shortage of vital blood cells and high dose chemotherapy.

In addition, HSCs are the stem cells that allow other blood cells to grow. This progression is called haematopoiesis, as shown in figure 1. This process takes place inside the red bone marrow, which is the nucleus of most bones. The red bone marrow comes from a layer of embryos, called mesoderm, during embryonic expansion. Haematopoiesis is a mechanism by which all the mature blood cells develop. In this observation, the enormous developmental need of any human being capable of generating more than 500 billion blood cells every day is about controlling the amount of circulating blood cells. In vertebrates, hematopoiesis majority occurs in the bone marrow (BM) and is derived from a small number of hematopoietic stem cell that are multipotent and also able to extensive self-renewal.

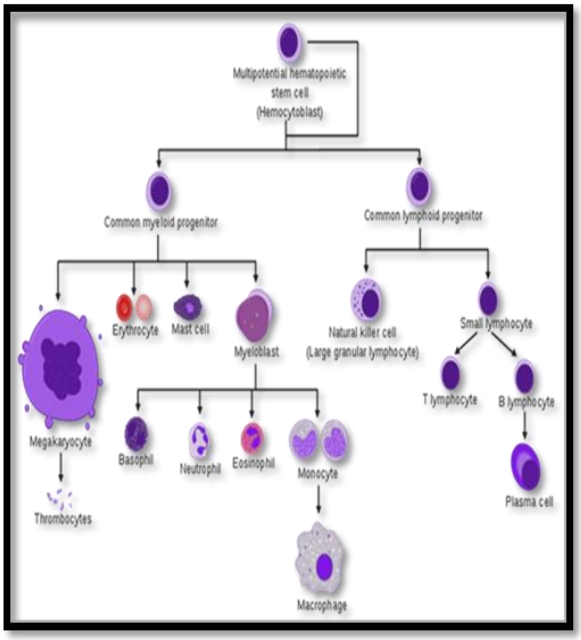

Figure 1: The overview of normal human haematopoiesis [2]

HSCT is a multipotent hematopoietic stem cell transplant, typically derived from the peripheral or core blood of the bone marrow (BM). They can be autological, allogeneic or syngeneic. It is commonly used in patients with diseases in the blood or BM, such as multiple myeloma or leukemia. Until transplantation, radiation or chemotherapy normally destroys the recipient's immune system. At the AGM (aorta-gonad-mesonephros), localized HSCs were initially identified in mammalian embryos, and then proliferated in the fetal liver before bone marrow was colonized before birth. Hematopoietic stem cell transplantation has several possible risks and is a dangerous procedure. Patients with life-threatening chronic illnesses are typically equipped with this. This is because the group's survival was improving after diagnosis.

8.2 BIOTECHNOLOGY ON HSCs

A. HSCs Purpose and Differentiation

Stem cells are a population distributed across the body that is distinct, yet capable of limitless regeneration and creates functional specimens of highly specialized nature. These stem cells also have a variety of proliferative properties and functions that are used in physical or tissue structures. HSCs have the special properties and ability to regenerate and discriminate between all blood vessels that exist. Hematopoiesis is an ongoing growth process in which HSCs make important decisions about cell fate when generating several types of blood. This process generates and preserves the appropriate number and type of cells from various structural networks of unknown cytokine-like receptors in which these cells serve as regulators for the differentiation and proliferation of hematopoietic cells. Among those that can be used for HSC ex vivo development are the most primitive HSCs with CD34 cell surface antigen and the kinase domain receptor (Fetal Liver Kinase [flk-1]), vascular endothelial growth factor, and positive hemopoietic growth regulators, c- kit and flt -3.

HSCs for transplantation can be collected from bone marrow (BM) or peripheral blood. Hematopoietic remodeling after BM ablation is based on re-placement and "returning" to the hematopoietic microenvironment of the stem cells transplanted intravenously to BM recipients as shown in Figure 2. HSC ``Homing" is a stepwise mechanism that utilizes molecular activation for adhesion. The factor-1 chemokine receptor cell (SDF-1) is a substance that attracts specific types of motor cells, namely monocytes, lymphocytes, and CD34 + homing cells. The CD34 gene acts as a mediator of the extension of hematopoietic stem cells to the extracellular matrix of bone marrow or directly to stromal cells. The CXC chemokine receptor 4 (CXCR4 +) progenitor is activated by SDF-1 and vascular ligands, such as inter-1 adhesion molecules and vascular adhesion-1 adhesion molecules. It is a proginator that facilitates tight adhesion to endothelial cells. The transplanted cells will interact with BM cells rolling on endothelial and platelet selectivity. Cells expressing CXCR4 deficiency will be released and return to the bloodstream.

Next in the human body, SDF-1 will capture CXCR4+. It aims to facilitate extracellular transport through the extracellular BM matrix into the hematopoietic compartment. SDF-1 and macrophage-1 inflammatory protein are factors in the activation of CD34 + cells to extracellular fibronectin through antigen-5 (Very late antigen-5 [VLA-5]) and antigen- 4 (Very late antigen-4 [VLA-4]). The transplanted stem cells eventually reach a "stem cell niche" where they interact with supporting cells, adhesion molecules, SDF-1, and growth factors. The selected HSC progenitor is transiently depleted by the homing process and only a small number of recipient stem cell populations are formed. The right stem cell divides slowly. To avoid fatigue, it restricts

expansion and returns to inactivity when the compartment is fully reorganized. Despite adverse conditions in the host BM, the injected HSCs produce sufficient offspring to replenish the host hematopoietic system with mature cells. The granulocyte-macrophage colony forming unit returned to normal within 2 years of transplantation.

B. Transplantation Works for HSCs

HSCT depends on the type and source of stem cells for each patient and therapeutic purpose. These stem cells have been used in immune regeneration for several years after cancer growth or cancer treatment. The use of high dose HSCT chemotherapy is usually deadly in normal cases. Autologous or allogeneic HSCs used as "rescue" occur during life-threatening myelosuppression. Myelosuppression is a term used for a time when bone marrow activity is reduced, indicating a decrease in the production of red blood cells, white blood cells and platelets [1]. Myelosuppression is a medical side effect for other cancers. Autologous HSCT is an additional operation in the direct interaction between doses and chemotherapy reactions, and compilation of myelosuppression is a toxic dose limiting technique.

This is due to the regeneration of blood cells from different hematopoietic progenitor cells in the bone marrow. It is subject to a variety of stimulatory and inhibitory factors with a multi-faceted relationship between progenitor cells and the marrow microenvironment. Chemotherapy has been shown to activate inhibitory factors such as Tumor Growth Factor (TGF-β), Interleukin (IL-4), Interferon (IFN-π-IFN-α) and Tumor Necrosis Factor (TNF-α) with cytokines capable of myelosupression [3]. Training regimens in allogenic HSCT destroy malignant cells, malignant hematopoietic cells, and host immune cells. Donor cells can be selected by specific cells. HSCT was initially used to save patients from marrow aplasia.

HSCT is also a proven treatment for BM or congenital loss, immune deficiency and autoimmune conditions. The effects of GvT are not expected at such times and prevention of GvHD is a priority. HSCs can also be used as "therapeutic carriers" for different or missing enzymes, such as adenosine deaminases. Therefore, HSCs are also used to convert intermediate genes such as interleukin-2 to antitumor. Genetically modified HSCs maximize the effects of GvT and"suicide genes" to kill donor cells that occur during GvHD [4]. Lymphatic hematopoietic cells can be used in conjunction with solid organ transplantation. This is because microchemistry is beginning to require transplantation. Hematopoietic cells and progenitor cells were supplied intravenously from the donor marrow or other source of alogenic HSCT. The stem cells "enter" into the recipient's hematopoietic microenvironment, and hide in the BM niche. The donor's immune effector cells are in contact with the recipient's immune cells and continue to eat them without any cause for GvHD. Finally, there is chimerical stability, coupled with functional B-lymphocytes, T-lymphocytes, and natural killer cells, and GvT results continue.

C. Selection of Stem Cell

HSCT is composed of autologous, syngeneic, and allogeneic forms. Selecting the HSC source depends on the instructions and specifications of the donor transfer. Other barriers to the use of autologous HSCs are extensive cytotoxic treatment and strong involvement of malignant bone marrow or peripheral blood. The donor's requirement for adherence to the Human Leukocyte Antigen (HLA) is suitable for alogenic transplantation. However, relationships between 30% of patients are appropriate donors [5]. Non-donor patients have a 30% - 40% chance to use voluntary registrations to find donors not related to HLA [6]. The most well-known location for HSCs is bone marrow. Bone marrow transplantation has become synonymous with hematopoietic cell transplantation, and bone marrow itself is rarely used as a source due to invasive harvesting that requires general anesthesia. In adults, in stable condition, the majority of HSCs reside in the marrow.

However, cytokine mobilization can utilize the release of large quantities of HSCs

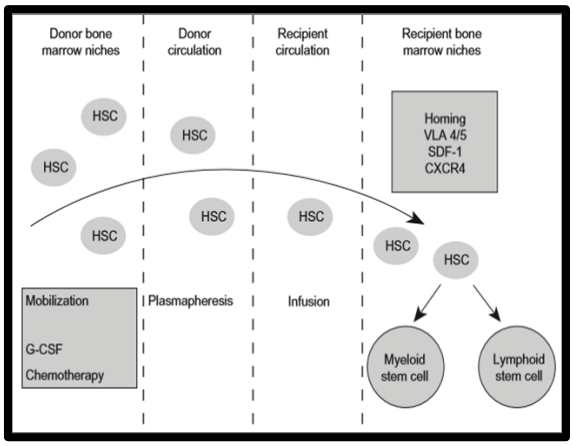

Figure 2: Distribution and homing of HSCs into transplant recipient bone marrow position [1]

into the blood (figure 2). As a clinical source of HSC, activated peripheral blood (PB) is now increasing bone marrow, as it is easier to take peripheral blood for donors to take up

bone marrow. Like bone marrow, peripheral blood is stimulated using a mixture of hematopoietic and ancestral cells. Common PBs pass through cells that enrich cells expressing CD34, markers on stem cells and heredity cells. As a result, cell preparations are made for users providing pure HSC preparations, using a mixture of HSCs, hematopoietic progenitors (key components), and a variety of contaminants, including T cells and, in the case of autologous grafts from patients with cancerous, large tumor cells. It is important to distinguish this type of listing, which is a regularly provided listing, from the highly purified HSCs, which are at a disadvantage to other types.

Table 1: Completed Clinical Trials use Different Strategies for Purging Stem Cells *in Vitro* and *In Vivo* [2]

Types of cancer (cells)	Purging technique	Conclusion
Myelomatosis	A two-step negative assortment technique with a mixture of monoclonal antibodies	Effective procedure to remove stem cells. Higher freestyle survival rate
Myelomatosis	CEPRATE SC method-continuous technique of immunoadsorption	No benefit of stem cell purge
Myelomatosis	CEPRATE SC method- continuous technique of immunoadsorption	Reduces dramatically the toxicity of tumour cells and guarantees healthy and rapid haematological recovery
Breast carcinoma	WR-2721 (amifostine) to 4-hydroperoxycyclophosphamide (4-HC)	Time reduced to engraftment
Breast carcinoma	Dielectrophoretic field-flow-fractionation (DEP-FFF)	Efficient separation with purity of > 99.2% was observed in 12 minutes
B-cell lymphoma	Rituximab	Rituximab can be used in stem cell purging
Myelomatosis	Pulsed electric fields	Auspicious technology for fast purging of stem cells

D. Ex vivo expansion of HSCs as a culture technology

The development of hematopoietic stem cells (HSCs) for therapeutic purposes has been a "Holy Grail" for many years. Various models have been tested in one model for breeding tumor cells. Commonly used in vitro methods include specially selected lines for growth in culture pumps in incubators. However, these limited guidelines are easily available, consistent and communicable. This is because it may not represent the disease or heterogeneity of the population in need. The in vivo model requires the whole living organism. This method has the advantage of compiling testing the overall

effect of the drug on the surviving subject. However, additional work and ethical approval are required.

Altès et. al (2002), study the clinical trials of different uses for purification of stem cells including the use of monoclonal antibodies, continuous absorption of immune flow, phase dielectric flow analysis, use of rituximab, pulsed electric fields, and hypertermia. Normal haematopoietic progenitor cells induced by alkylating agents used by stem cells have been shown to support amifostine. To optimize single treatment for low-grade proliferative prognosis problems, several methods use a combination of CD34 and CD19 negative selection [7].

In the case of this study, the culture-focused technique was more ex vivo with the aim of establishing a single central cord blood unit for adult transplantation, to achieve long-term multi-lineage reinforcement, neutrophil and platelet activation time, and use of immune regeneration [8]. Ex vivo is also aimed at improving the efficiency of the listing without the need for GVHD in addition to lower costs. With the development of HSCs ex vivo has become a new technique that can help reduce the shortage of materials. It is intended as a transfer and protocol for genetic modification. Parisa Tajer et al. have summarized the increase in blood development, the effects of specific and conservative pathways on HSCs in mice and humans, and have also evolved in ex vivo culture protocols of human HSCs with cytokines or small molecule compounds [9]. Different development protocols have been tested in clinical trials. However, the optimum conditions for ex vivo human HSC development have not yet been found. Translating and implementing new findings from basic research using genetic modification of human HSCs into clinical protocols is crucial to accelerate ex vivo development and ultimately improve cell gene therapy.

Ex vivo techniques of these cultures are carried out inside or on tissue in the natural environment outside the organism with minimal changes in the natural state [10]. Ex vivo experiments are more controlled than those in vivo. In cell biology, ex vivo procedures often use living cells or tissues extracted from organisms and cultured in laboratory equipment, usually in sterile conditions for up to 24 hours.

E. *Stem Cells in Tissues Regeneration and Vehicle Delivery*

Furthermore to the long-term replication properties of stem cells, hematopoietic tissue stem cells require an 'extraordinary' capacity to produce or shift between hematopoietic and non-hematopoietic lineages, exhibiting exceptional growth or differentiation. This led to the use of HSC theory for the regeneration of some non-hematopoietic tissues [3]. Due to bone resorption after chemotherapy this procedure has special effects on the bone marrow, and is often a big issue. Bone marrow stromal stem cells are used after chemotherapy in osteosarcoma and Ewing sarcoma, and improvements in cell-based bone resorption. Jager et al demonstrated osteoblast regeneration from mesenchymal progenitor cells following COSS-96 polytherapy (cooperative osteosarcoma analysis) and their potential for in vivo use [11]. In general, clinical trials have shown cell death in the renewal of myocardial tissue following myocardial infarction. Many factors such as immune detection, the use of systemic drugs or gene therapy of non-specific groups of normal tissues and low permeability. Most anticancer agents have a limited effectiveness due to their toxicity or low life span. For instance, interferon β which exhibits in vitro anti-proliferative and pro-apoptotic activity with little direct in vivo effect on human invasion. [12].

The new theory of using stem cells as a distribution method stems from the fact that tumors, such as wounds, send chemotherapy agents such as vascular endothelial growth factor (VEGF) to recruit multi-potent stromal cells (MSCs) to form tumor supporting stromal, and angiogenesis of pericytes. MSCs transduced with an expression vector of an adenovirus resonant the interferon-β gene have been shown to raise a local development of interferon-β. However, the function of in vivo MSCs is partly dependent on signals from the target tissue microenvironment, such skin-like tissue may have high cell turnover where there will be more signals for MSCs than connective tissue where high cell turnover can only be seen during the healing process. Similarly, MSCs constructed to release interferon-β induce elevated local interferon-β levels in mouse gliomas [13]. The neural stem cells were known as a method for gene therapy for central nervous system (CNS) disorders. Correspondingly, interest is illustrated in the use of endogenous progenitor cells as a carrier for the

transmission of gene therapy due to their attraction to angiogenesis sites rather than to quiet blood vessels. Stem cells, immune cells, and other secreted proteins that spread brain and breast tumors.

8.3 ADVANTAGES OF HSCT TO THE CANCER PATIENTS

Cancer is an anomalous disorder in which a group of cells ignore the cell division's physiological rules and expand in an uncontrolled way. Cancer cells do not react to signals that trigger the normal cell cycle because they have a degree of self-sufficiency that results in uncontrolled growth and transformed cell proliferation [14]. Most cancer patients undergo surgery, chemotherapy and/or radiotherapy. These methods are some of the outdated and most widely used treatment methods. However, conventional forms of treatment sometimes do not work.

Stem cell transplantation may then be an option. Stem cell transplants have proven effective approaches for treating many cancers of the blood including acute myelogenous leukemia, acute lymphocytic leukemia, chronic myelocytic leukemia, Hodgkin lymphoma and myelomatosis. Having stem cells transplant can give a higher survival probability compared to the cancer patients who did not receive any treatment or received chemotherapy only. The study found that 5-year survival was 12% for patients without both chemotherapy and stem cell transplantation, 37.8% for the chemotherapy-treated community alone and 44.1% for those undergoing both chemotherapy and stem cell transplantation [15]. Figure below indicates the survival by treatment modality in acute myeloid leukemia:

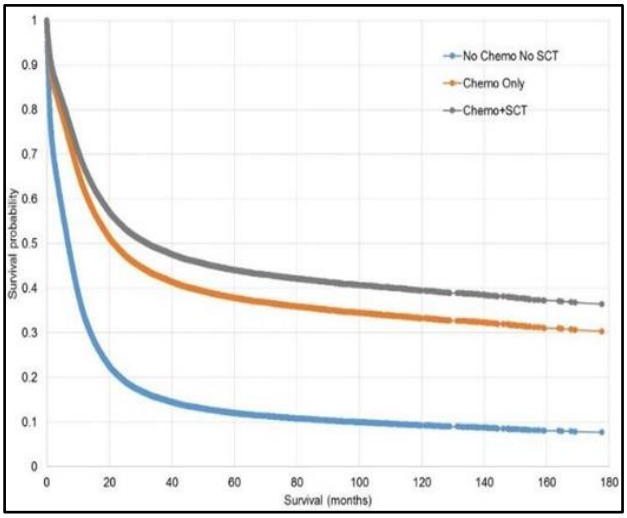

Figure 3: Entirely controlled survival rates of 2 years and 5 years for patients with both chemotherapy and SCT, chemotherapy only and neither chemotherapy nor SCT [15].

Stem cell transplantation has 2 types of differentiation which is allogeneic transplantation and autologous transplantation. Allogeneic grafting requires the nonappearance of malignant cells that contaminate the grafting process; the possibility for immunological anti-cancer grafting versus tumor effects and the possibility of treating malignant and non-malignant bone marrow disorders. These can include genetic and immunological disorders, as either the patient's own bone marrow or the peripheral blood are the reinfused stem cells. All these cells do not cause GVHD as either it come from that donated bone marrow or peripheral blood stem cells do not reflect the receiving body to be foreign, and donated cells or bone marrow do not attack the body and thus autologous transplantation is linked with less morbidity and mortality than allogeneic HSCT and reduces the number of patients seeking care at the upper age limit [16]. This chapter will emphasize the advantage of stem cell technology by using HSCs transplantation for the recovery of red blood cells that have been damaged by chemotherapy and will be compared with conventional way.

In the comparisons through a production between stem cell technology and conventional way, it can be discussed through the treatment period. For the autologous and allogeneic transplant, it has 4 steps that the patients must undergo when they get treatment. The first step that the autologous transplant's patients must undergo is collecting your stem cells. For this

part, the doctor will collect the patient's stem cells from the patient's large vein in the chest by using standard IVs or a catheter. It will take for several days for the patients to undergo this part only and after finishing this part, the patients are not required to stay in the hospitals and allowed to go home after that.

The second step is the transplant treatment where the patients will receive a high dose chemotherapy with or without radiation therapy but giving radiation therapy is not very common. The patients need to undergo this treatment for up to 5 to 10 days and the patients need to stay in the hospital for around three weeks. After finishing these steps, the patients will receive their modified stem cells back which can take time for about 30 minutes or less than that for one infusion. However, the patients may get more than one infusion of their stem cells. Lastly, for the last steps, is a recovery step where it may end up taking 2 weeks and the patients need to stay in the hospital during this period for the doctor to monitor their health [17].

Next, for the allogeneic transplant, mostly the step is just the same as the autologous transplant but different with time and also the stem cells are taken from other donors, not the patient's stem cells. For the first step, the doctor will collect the stem cells from the donor. For this step, the patients for the allogeneic transplant are not participating. So, for these steps, the patients may save their energy compared to the patients who undergoes autologous transplant. For the next step, the patients need to get the transplant therapy where they need to undergo chemotherapy with or without radiation therapy. However, for this step, the patients only take 5 to 7 days which will take shorter time than autologous transplant. The third step is the patients will receive the donor stem cells that have been modified and usually its takes less than an hour and after that the patients need to rest in the hospital for 1 day. For this step, it's true that autologous transplant patients take shorter time to transfer the stem cells into their body, but they need to do it for more than one infusion which, when total up, takes more energy consumption for the autologous transplant patients than allogeneic transplant. Then the last step is the recovery steps which may take only a week for a reduced intensity transplant patient and around 4 weeks for the ablative transplant patients [17].

However, for the patients who do not undergo allogeneic or autologous transplant, they will receive chemotherapy treatment. For the patients who undergo conventional ways to treat cancer, the patients will undergo the treatment in cycles where it is the time between one round of treatment until the start of the next. After each round of treatment, the patients will give a break for their body to recover as at that time their immune system is very low, so they need to stop receiving chemotherapy for a while. For example, if the patients need to receive 4 weeks of the cycle, they will receive the treatment on the first, second and third days. Then they will get a break on the fourth until twenty- eighth days. Then the cycle of the treatment will start again. Usually chemotherapy will take around 3 to 6 months which takes longer time and energy of the chemotherapy patients than the patients who undergoes allogeneic and autologous treatment.

Then, after the chemotherapy, the patient needs to take a break and more time of the treatment, because the chemotherapy needs to destroy more cancer cells and the patients need to rest their body to recover from the side effects of the treatment. During this chemotherapy treatment, the doctor will prescribe drugs and vitamins for the patients to improve their immune system and reduce side effects and the doctor will advise the chemo patients to stay away from the people who had a sickness like cold as their immune system is very weak [18]. However, it is different to the allogeneic and autologous transplant where after they receive the chemotherapy treatment, they will receive either from their stem cells or from donor stems cells that been modified into their body to improve their immune body system where this stem cells will replace the cells that have been destroyed during the chemotherapy treatment.

Next, the use of energy can be contrasted between *in vivo* and *ex vivo* expression in terms of the cultured and isolation process of HSCs. Gene therapy is a promising technique to treat complex conditions even if the cost estimation can be over a million dollars, a person needs to value the technique as it may give the chances for a

cancer person to be better and prolong their lives. In gene therapy, a corrected version of a gene is introduced back into the patient's body by using their own cells, which eliminates any of the complications that occur with more standard therapies. For the gene therapy for in vivo technique, this method can only be applied in a specific, small area of the place that is a target. The *in vivo* technique is known for its simplicity and reduced material volume inserted into the body. In vivo gene transfer via a vector made from viruses, which the virus gene had been removed from, leaving only a tiny powerful vehicle that knows how exactly to enter the cell. However, there is a higher chance that the endogenous pathogenic viruses have been activated by the virus protein that has been expressed and introduced in the human body. It has also been suggested that recombinant viruses that are capable of replication may develop due to unexpected mutagenesis. There is the possibility that viruses, such as retroviruses, which integrate into the host genome, may cause accidental malignant transformation of the host genome. Also, of particular concern are inflammation and the immune response, even in an 'immune-privileged' organ.

For the ex vivo gene therapy, the advantages seem more real than in vivo gene therapy because the transfected cell that needs to insert into the patient can be verified first by looking at the expression of the gene and health of the transfected cells. This kind of method is very useful for the therapies as they can choose or select a specific cell type from the culture dish where the compound should be released or expressed before transplantation occurs. However, before the therapies insert new stem cells that have been modified into the patient's body, the patients must undergo chemotherapy to remove the old stem cells in the body which may lead the patients to feel weak and suffer from hair loss. Then, the new and improved stem cells with the new and improved genes will be introduced back into the patient's body and make copies, becoming all the cells that the patients need to feel better [19].

Furthermore, the benefit of this technology can be identified between the HSCT cost and conventional way cost. As new cancer treatments emerge and the U.S. population keeps growing, the cost of treating cancer is projected to hit $158 billion by 2020 [20]. Costs of cancer care differ greatly, depending on cancer type and treatment stage. For example, in the year after a cancer diagnosis, care costs for brain or pancreatic cancers may hit $110,000, while end-of-life costs for all cancers are much higher, hitting $200,000 in the last year of life for patients with leukemia or brain cancer [20]. Hospitals, hospital associations, third-party payers, physicians and patients all have an interest in hospital-related economic factors; however, not all new therapies or medications have been tested. Autologous bone marrow transplantation and allogeneic bone marrow transplantation are commonly used for a wider range of cancers, including breast cancer, and are also the primary therapies for leukemia, certain anemia and other immune disorders. With rising allogeneic transplantations of unknown donors, cord blood transplantation and autologous stem cell transplantation, it can be expected that the number of these procedures will continue to increase. Therefore the costs and cost-efficiency of these procedures are becoming increasingly important.

Many people usually think about the cost of care, whether they can afford the transplant. In 1982, Welch et al. indicated that the cost for allogeneic bone marrow transplantation (alloBMT) and traditional chemotherapy was approximately $193,000 and $136,000, respectively, where the cost of treating patients with acute non-lymphocytic leukemia (ANLL) was estimated over a five year period [21]. Nonetheless, when the cost-per-life value was measured, it was estimated that allogeneic bone marrow transplantation (alloBMT) scored more than $62,000 per life-year gained in traditional chemotherapy compared with $64,000 per life-year gained [21].

The study was carried out at Washington University where there are 41 patients involved, consisting of 17 patients with match donor and bone marrow transplant, and 19 out of 41 patients received two combined chemotherapy courses. All patients had induction chemotherapy but later some of the patients received allogeneic bone marrow transplantation or chemotherapy from another hospital. The cost for both services was estimated for the number of procedures such as the number of patients remaining in

the hospital for a non- intensive care unit (non-ICU), the number of patients remaining in the intensive unit care hospital (ICU), the number of clinical tests conducted, the number of x-rays and the number of operating room procedures. The expense does not include the hospitals bill; thus, even between separate hospitals, the uniform data collection is appropriate.

In five years, 59% survival rate and 26% survival rate of the patients who undergo bone marrow transplant and chemotherapy respectively has been recorded. From the study, the average of the patients that were hospitalized was around 7 for the chemotherapy patients while 4.6 for the allogeneic bone marrow patients. This shows that patients who undergo allogeneic bone marrow transplant has lower rate of being hospitalized than patients who undergo chemotherapy even though allogeneic bone marrow transplant patients have high probability to get admitted in intensive ICU as they are more tend to have complications such as GVHD or cytomegalovirus (CMV) infections.

Time spent at ICU was the biggest difference in cost drivers. Just 5 percent of hospital-patient chemotherapy days were spent at the ICU, compared to 57% for patients with bone marrow transplant. Patients who survived five years were also estimated to have lower health expenses than patients who die. The average cost to an allogeneic bone marrow transplant survivor at five years was $166,000 compared to $232,000 for a non-survivor, while the average cost to a chemotherapy patient at five years was $79,000 compared to $157,000 for a non-survivor.

It shows the problems inherent in major costs. But allogeneic bone marrow transplant has been estimated to be profitable as the likelihood of full remission was much greater than in patients with chemotherapy as most of the BMT patients are from the young generations as at the young age they got no chronic illness yet and the survival rate was even higher. Therefore, the procedure cost just $10,000 per acquired life- year, which taken from the initial procedure cost around $193,000 over the duration of a patient's life by assuming the age of the transplantation is around 30 years. The research was completed in its review of allogeneic bone marrow transplant costs versus ANLL chemotherapy; but, need to remember that such results do not generally extend to another type of diseases and are only acceptable in the disease of the case study only.

However, a larger study may provide further insight into the cost drivers even though the study is only limited to 41 patients as their sample size and the findings are statistically significant. Lastly, the increase of the advancements in alloBMT procedures have been made decreasing the incidence of CMV and GVHD, which has enabled as many as BMT patients to stay longer at the ICU. This could be modified by the emergence of autologous peripheral stem cell transplantation services, changes in ambulatory support treatment systems and the development of innovative stem cell expansion techniques. Further developments which would reduce infections with GVHD and CMV would improve alloBMT's cost-effectiveness. Advances made by transplant teams would also reduce the logistical costs of streamlining procedures and staffing. The amount of time spent at the ICU in the United States has a huge effect on the total costs. So, to reduce the cost, the step-down units and outpatient transplant centers are now on the list to do research for the hospitals and doctors.

In Malaysia, the estimated costs of treating cancer consist of chemotherapy, radiotherapy and, in some cases, immunotherapy for each type of cancer as shown in table 2. While for HSCT costs usually differ among centres, ranging from RM 500 to RM 10000. It depends on the allogeneic transplant centres. Autologous SCT costs less, and ranges from RM500 RM to RM50000. The problem for the patient is mostly financial, as only two government hospitals have provided transplant services [23]. Conclusively it is better for the patient to use this gene treatment instead of the conventional or traditional way like taking vitamins that may interfere with the function of chemotherapy.

Table 2: Cost of cancer treatment in Malaysia [22]

Types of cancer	Cost
Breast cancer	> RM395,000
Colorectal cancer	> RM85,000
lung cancer	> RM56,000
Lymphoma cancer	> RM95,000

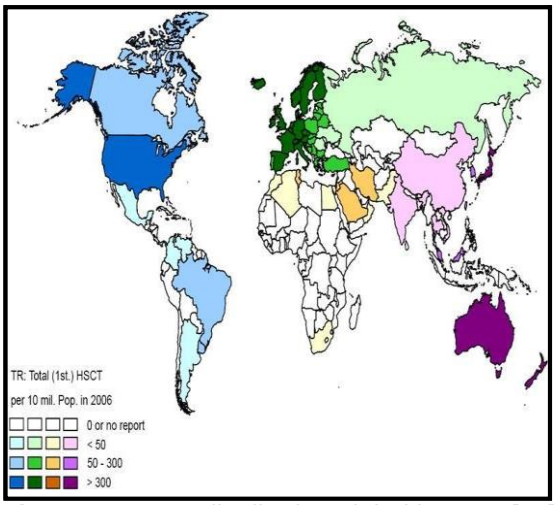

Figure 4: HSCT distribution global in 2006 [24]

8.4 EFFECT OF HSCT ON TODAY SOCIETY

Previously cancer patients, especially blood cancers are often related to no chance of recovery, but recent medical treatments have allowed some cancer patients to recover through somatic cell transplantation treatments. The use of stem cells offers people the hopes, and even the patients with cancer who were not receiving chemotherapy. The worldwide performed bone marrow transplant procedures were estimated in the range of 45,000-50,000 that proved the number of patients treated with hematopoietic stem cell transplant has dramatically increased over the last 20 years. Over 14 million registries from various worldwide have been registered as volunteers to donate their stem cells or organs for the patients who got no family donors from a worldwide perspective.

About 953,651 hematopoietic stem cell transplants are registered in 75 countries from 1516 transplant centers where a recent retrospective analysis on behalf of the Worldwide Blood and Marrow Transplantation Network (WBMT) has received this data. No transplants have been allocated in countries with a population of but 300,000 or a gross value of US$ 1260 or less per person. For countries with more money, more transplant teams and unrelated donor infrastructure, donation rates are even higher [24]. Countries with major socio economic problems have rock bottom success in transplanting hematopoietic stem cells. Transplantation rates for 2006 indicate major variations between the four continental regions:

- America: Means 48.5 with the range between 2.5 to 505.4
- Asia: Means 184 with the range between range 0.6 to 488.5
- Europe: Median 268.9 with the range between 5.7 to 792.1

EMRO / Africa: range between 2.8 to 95.3

Gratwohl et al. (2010) study the transplant rates (number of hematopoietic stem cell transplants per 10 million inhabitants) for all hematopoietic stem cell transplants, allogeneic and autologous by continental area, suggesting that hematopoietic somatic cell transplants are approved by society. The regions are well-defined by WHO state offices code. Blue: Americas; green: Europe; Asia magenta; EMRO / Africa yellow: [25].

An increase in somatic cell transplantation in some countries, however, may result in an increase in organ donation needs, and so it is of considerable importance to society and law. Donor and recipient interests in organ donation and transplantation will clash with each other and cause ethical problems. Therefore, the first priority must be on managing the possible risks and benefits for both donor and recipient, and preserving the therapeutic aspect of the whole donation or transplant process. When we move to a broader view, which also invests the social dimension of the phenomenon, the disparity between availability and desire becomes a central knot. Like organs, the demand for a few transplantation tissues and cells far exceeds the available supply. Terms of organ donation issues may usually include lack of information and confusion about organ donation, difficulties in obtaining family consent from the deceased in organ donation, and insufficient facilities. The ethical standards, belief, and religiosity of potential donors in society which overlap with institutional and organizational barriers to explain the shortage of organs available.

In this case, hematopoietic stem cell donation raises problems such as certain donations of organs and tissues, which are cultural and private values that potentially affect

the option to become a donor to hematopoietic stem cells, and scepticism about either the medical system as a complete or fair distribution of donations of hematopoietic stem cells. Satisfaction with the choice to donate or, on the opposite hand, fear to make donation and the consequences of their health could also be other factors that affect the organ and the stem cells donations. Hematopoietic stem cell donation poses particularities as opposition to other sorts of donation of tissues or organs which will influence the speed of donation. Hematopoietic stem cell transplantation may be said to be situated on the centre ground between blood donation and live organ donation. Hematopoietic stem cell donation, however, brings rather more risks and inconveniences than donating blood. It could include the use of medicinal products such as the colony-stimulating granulocyte factor (GCCSF) to remove enough stem cells from peripheral blood or mild surgery and anaesthesia inside the bone marrow donation. On the contrary, donation of hematopoietic stem cells is definitely less physically and psychologically burdensome than donation of organs as an example of the kidney and liver amongst living persons.

The oddity of transplanting hematopoietic stem cells, or even that with other transplant types, is that matching human leukocyte antigen (HLA) is of vital importance and may be a significant donor-related given the success of transplanting hematopoietic stem cells. Consequently, repeated donations may also be needed in transplantation of HSCs. As a result, there may also be an extended period of time from the time the prospective donor wants to donate and register for the registry or centres and the actual donation decreases as well. The time between enrolment and actual donation has been recorded to be eight years on the average. Thus, a dispute that will emerge with the unrelated donation of hematopoietic stem cells is that donors who wished to donate hematopoietic stem cells may change their minds because of the long delay between the primary incentive to reach the donor list and also the final donation act because it normally takes several years later [24].

8.5 CONCLUSION

Significant progress has been made for patients undergoing hematopoietic transplantation in order to achieve a greater understanding of hematopoietic stem cell biology and medical management. Hematopoietic transplant also gives a second chance to people with cancer in their lives, no matter how old you are, even though the transplant process is much more complex than chemotherapy.

Though hematopoietic stem cell transplantation activities are growing, the challenges are high. Some of the ethical problems must be dealt with in the safety of the Doctor-Patient relationship. Medical reasons for the transplantation of HSCs is because the potential effectiveness of HSCT, the patient's needs and expectations, his or her quality of life and the patient's subjective characteristics play the most important role in the decision-making process, representing the actual relevant facts relating to the event. However, when it comes to a patient who is a minor, all of these things can certainly become troublesome. Around the same time, however, physicians must be responsible for the wellbeing of mankind and the financial stability of the healthcare system, thus extending the benefits as equally as possible.

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