Bone Marrow Transplantation

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Abstract: Stem cells are the centre for regenerative medicine. Given a right signal these undifferentiated cells have a remarkable potential to develop into specialized cell types (blood cells, heart cells *etc.*) in the human body. Stem cells, therefore, can be used in cell-based therapies to replace/repair damaged tissues and/or organs. Ongoing research in the area of stem cells focuses on their potential application (both embryonic stem cells and adult stem cells) to create specialized cells and replace the damaged ones. Hence, this cutting-edge technology might lead to new ways of detecting and treating diseases. Stem cell transplantation can be considered as an option for the treatment of certain type of cancers. This medical procedure can also be used to treat neurological diseases, autoimmune diseases, heart diseases, liver diseases, metabolic disorders, spinal cord injury *etc*. The present review, therefore, focuses on the growing use of stem cell transplantation in regenerative medicine to treat a variety of diseases. This review also provides the current status of the field with a particular emphasis on bone marrow transplantation.

Key Words: Bone marrow, leukemia, multiple myeloma, Parkinson's disease, stem cell, transplantation.

1. INTRODUCTION

Two Canadian researchers from the Ontario Cancer Institute, Ernest A. McCulloch and James E. Till (early 1960s) were the first to show the existence of self-renewing stem cells in the mouse bone marrow [1-3]. Their landmark studies revealed the properties of stem cells: (i) self-renewal capacity and (ii) ability to undergo differentiation pathways [4]. They laid foundation for the stem cell research. Since then stem cell research has opened doors for a new therapeutic avenue to explore regenerative medicine and treat myriad diseases. In 1968 an American physician, Robert A. Good performed the first successful human bone marrow transplants (using human leukocyte antigen-identical siblings) by treating an 8-year-old boy with severe combined immunodeficiency syndrome [5]. Now-a-days, bone marrow transplant is the commonest and best-known type of transplant [6,7]. In bone marrow transplantation a patient receives healthy bone marrow that contains stem cells with the capacity to mature into specialized cells. A transplant procedure restores stem cells after the administration of high-dose chemotherapy and/or radiation therapy. In addition, peripheral blood stem cell transplants are more common [8,9]. This type of transplant is increasing and has nearly replaced bone marrow transplantation. For instance, a systematic review showed the use of peripheral blood stem cells to speed the engraftment of neutrophil and platelets compared to the standard bone marrow transplant [10]. Umbilical cord blood stem cell transplants, however, are considered an alternate option because they are less prone to rejection [11]. In a systematic review and meta-analysis, Hwang *et al.* [12] showed that despite greater donor–recipient human leukocyte antigen disparity with unrelated donor cord blood transplant, this type of transplant in children and adults had consistently equivalent survival outcomes compared to unrelated donor bone marrow transplant. In addition, studies have shown that the graft-*versus*-host disease after cord blood transplant is less compared to bone marrow transplant or peripheral blood transplant. However, long time for engraftment, higher risk of infection, and availability of backup cells are some of the major hurdles to overcome for a successful transplant. To make more cells available, cord blood is stored in a facility known as 'cord blood bank'. After the baby is born, the cord blood is collected from the umbilical cord and placenta by a process that poses minimal health risk. (For type of transplants based on stem cell source see Table **1**).

Thus, over time there is advancement in identifying various sources of stem cells for the purpose of transplant and evaluating the effectiveness of transplant. Researchers are currently working on stem cells (embryonic and adult stem cells) from both animals and human beings. They believe that stem cells are the best candidates for regenerative medicine. However, the questions regarding reasons for the stem cells to exist in undifferentiated state and signals required for demonstrating their plasticity need to be addressed.

2. STEM CELL TRANSPLANT

Stem cell transplants are routinely used medical procedures to treat various diseases. These transplants are further categorized (based on the donor) into (i) autologous stem cell transplants (autografts) – patients receive their own stem cells, (ii) allogeneic stem cell transplants (allografts) – patients receive stem cells from their family member or a genetically similar individual, (iii) syngeneic stem cell transplants – patients receive stem cells from their identical twin, (iv) tandem autologous transplants (double autologous transplants) – a patient receives two planned transplants within a short period, and (v) mini allogeneic transplants (nonmyelo-

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Table 1. Types of Stem Cell Transplants Based on Source

Types	Bone Marrow Transplant	Peripheral Blood Stem Cell Transplant	Umbilical Cord Blood Stem Cell Transplants
Sources	• Stem cell-containing bone marrow • Stem-cell content is adequate	• Mobilized stem cell in peripheral blood • Stem-cell content is good	• Stem cell in umbilical cord blood and placenta • Stem-cell content is low
Procedures	• A medical procedure that restores stem cells after the administration of high-dose chemotherapy and/or radiation therapy • This is a commonest and best-known type of transplant • Close human leukocyte antigen-matching is required • Engraftment is moderate	• A medical procedure in which stem cells are mobilized and collected by apheresis, stored, and infused following high-dose chemotherapy and/or radiation therapy • This type of transplant is nearly replacing bone marrow transplant • Close human leukocyte antigen-matching is required • Engraftment is the fastest	• A medical procedure in which stem cells are obtained from the umbilical cord and placenta and frozen for future use • This is considered as an alternate option • Engraftment is the slowest
Risks associated and complications	• Donating bone marrow involves the use of anesthesia and may cause discomfort at the harvesting site • Risk of tumor cell contamination from autologous source is high and negligible with allogeneic source • T-cells are low • Graft-*versus*-host disease may develop due to allogeneic transplants. Infections, disease recurrence, and prolonged immunodeficiency may be associated with this type of transplant • Risk of acute and chronic graft-*versus*-host disease is similar to peripheral blood stem cell transplant	• Apheresis may cause minimal discomfort • Risk of tumor cell contamination from autologous source is high and negligible with allogeneic source • T-cells are more in number compared to bone marrow • Graft-*versus*-host disease may develop due to allogeneic transplants • Risk of acute and chronic graft-*versus*-host disease is similar to bone marrow transplant	• Higher risk of infection to recipient and a minimal health risk to both mother and child • Risk of tumor cell contamination is negligible • Contains functionally immature T-cells • Fewer issues with graft-*versus*-host disease. Risk of acute and chronic graft-*versus*-host disease is the lowest

ablative) – lower doses of chemotherapy/radiation are used, ensuring bone marrow is not completely destroy [13-17]. The process of stem cell transplantation is complex. Autologous and allograft procedures are almost similar, involving harvesting of bone marrow or peripheral blood, processing and cryopreservation (autologous transplants alone), transplantation of stem cells after conditioning (chemotherapy or chemoradiotherapy), engraftment and recovery [18].

Bone marrow aspiration (bone marrow tap; See Fig. (**1**)) involves the removal of a small amount of bone marrow fluid and cells through a needle. This process is similar in autologous, syngeneic, and allogeneic stem cell transplants. The donor receives anesthesia, and a needle is inserted into the skin over the pelvic bone or sternum until it reaches the bone to draw a small amount of bone marrow fluid. As the time progresses this fluid is replaced by the donor's body; however, the risk associated involves the use of anesthesia. The donor may recover within a few days or weeks. Later, the bone marrow is processed to remove blood and bone fragments. The harvested bone marrow is combined with a preservative and cryopreserved for further use. Two applications of the bone marrow transplant include diagnosing a disease and monitoring response to therapy. During bone marrow transplant stem cells are procured by direct puncture and aspiration of bone marrow, filtered, and reinfused intravenously [7]. However, stem cells derived from the bone marrow can be liberated into the peripheral blood and harvested with a cell separation machine. Similar to bone marrow transplant, peripheral blood stem cell transplant is an autologous transplant procedure in which the stem cells are collected from patient's blood. The blood passes through a machine that removes stem cells and the blood is returned – a procedure called apheresis. This procedure can be performed along with an autologous bone marrow transplant. Both procedures are used to restore stem cells that are destroyed during high-dose chemotherapy and/or radiation therapy. The advantages with autologous peripheral blood stem cell transplants over bone marrow autografts are faster recovery, lesser morbidity due to transplant, shorter hospital stay and reduced cost. In addition, the peripheral blood stem cell transplantation requires no general anesthesia and engraftment is rapid with earlier discharge from hospital [7].

The application of other transplant procedures is discussed in the latter sections.

Fig. (1). Picture of patient on examining table getting needle inserted for a bone marrow tap. Mother shown with patient [Source: National Cancer Institute. Author: Bill Branson (Photographer)].

Now-a-days, stem cell transplant is rapidly evolving, enabling the translation into clinical applications. In the future, advancement in transplant procedures may be more promising. Trials are on the way to treat various diseases. Stem cell transplant is considered as an option for the treatment of certain type of cancers [19]. This medical procedure can also be used to treat neurological diseases [20], autoimmune diseases [21], restoration of sight [22], wound healing [23], heart diseases [24], liver diseases [25], metabolic disorders [26], spinal cord injury [27] *etc*. The present review, therefore, focuses on the growing use of stem cell transplantation in regenerative medicine to treat a variety of diseases. This review also provides the current status of the field with a particular emphasis on bone marrow transplantation.

2.1. Stem Cell Transplant for the Treatment of Certain Type of Cancers

Stem cell transplant is used to treat various types of cancers. Initially, blood cancers like leukemia, lymphoma, and myeloma are treated with chemotherapy and/or radiation therapy. Prior to these therapies stem cells are collected from a donor and the cells are later infused/reinfused into a patient. These cells thereby replace the destroyed ones. Thus, stem cell transplant performed after chemotherapy and/or radiation therapy restores the damaged cells.

2.1.1. Leukemia: A Cancer of Bone Marrow and Lymphocytes

In the past decade there has been enormous development in the treatment of leukemia. Leukemia affects lymphoid cells (lymphocytic leukemia) or myeloid cells (myeloid or myelogenous leukemia). Acute lymphoblastic leukemia, acute myelogenous leukemia, chronic lymphocytic leukemia, and chronic myelogenous leukemia are the commonest type of leukaemias. In 2008 an estimated 44,270 men and women will be diagnosed with leukemia, and the mortality due to leukemia will be 21,710 in both men and women [28] (Surveillance, Epidemiology and End Results). In the US alone (2005) about 220,063 men and women alive had a history of leukemia. Various trials were conducted to cure patients with leukemia. A meta-analysis of seven studies (1274 patients) showed that allogeneic hematopoietic stem cell transplant improves the outcome of patients with high-risk adult acute lymphoblastic leukemia [29]. Results from two trials, ALL-Berlin-Frankfurt-Münster 90 and ALL-Berlin-Frankfurt-Münster 95 revealed that stem cell transplant in first complete remission is superior to the treatment with chemotherapy alone for childhood high-risk T-cell acute lymphoblastic leukemia [30]. Ciceri *et al*. [31] analyzed 173 adults with acute myeloid leukemia and 93 with acute lymphoblastic leukemia who received haploidentical hematopoietic stem cell transplantation (Europe). Their study results showed that this transplantation is an alternative for the treatment of high-risk acute leukemia patients in remission, lacking a human leukocyte antigen-matched donor. A retrospective analysis of data from 58 adult Japanese patients (51 with acute myeloid leukemia and 7 with acute lymphoblastic leukemia) suggested that treatment strategies including allogeneic hematopoietic stem cell transplantation may be considered in the first complete response in acute myeloid leukemia patients with 11q23 abnormalities [32]. Hah *et al.* [33] showed (in a 15-year-old girl) that chemotherapy and autologous peripheral blood stem cell transplant seems to be potentially effective for multiple recurrent anaplastic oligodendroglioma occurring after childhood acute lymphoblastic leukemia. In a retrospective study (97 adult), Mohty *et al*. [34] demonstrated that reduced-intensity conditioning allogeneic stem cell transplantation is feasible in patients with high-risk lymphoblastic leukemia in remission at transplantation. Hayani *et al.* [35] showed the first report of autologous umbilical cord blood transplantation in the treatment of a 3-year-old girl with acute lymphoblastic leukemia. Results of the prospective Cord Blood Transplantation showed that umbilical cord blood transplantation in adults should be performed in specialized centers [36]. Bradstock *et al.* [37] demonstrated that unrelated cord blood transplant is feasible in adults with high-risk malignancy, with infection relating to immunocompromise being the major limitation. A report from the International Bone Marrow Transplant Registry and the European Group for Blood and Marrow Transplantation showed that leukemia-free survival rates were higher after peripheral blood stem cell transplant (33%) compared to bone marrow transplant (25%) in advanced chronic myeloid leukemia patients, but were lower for those in first chronic phase (41% *vs*. 61%); however, these rates were similar for acute leukemia [38]. In a retrospective comparison, Lemoli *et al.* [39] showed that allogeneic peripheral blood stem cell transplant performed in the early stage of the

disease is safe and may be associated with a more rapid hematopoietic reconstitution compared to the bone marrow transplant. A report from the cooperative German Transplant Study Group revealed that allogeneic stem cell transplant in elderly (aged >50 years) with standard- or high-risk acute myeloid leukemia, donor type is not a major prognostic factor [40]. A retrospective, multicenter study of 63 children (aged 0.2–17 years) showed that allogeneic hematopoietic stem cell transplantation was able to rescue a significant proportion of children with acute myeloid leukemia in second complete remission – especially if a human leukocyte antigen-compatible relative is a donor [41]. In a case representing dispermic chimerism in a 32-year-old man diagnosed with acute myelomonocytic leukemia, Draper *et al*. [42] showed that molecular human leukocyte antigen typing is required to reduce transplant rejection in such patients. Majhail *et al*. [43] demonstrated that human leukocyte antigen mismatched umbilical cord blood is an alternative graft source for elderly who need a transplant but do not have a matched related donor. In a retrospective analyses, the results of 32 (11 autologous, 21 allogeneic) hematopoietic stem cell transplants showed that both type of transplants were effective in the treatment of children with relapsed or refractory acute promyelocytic leukemia [44]. In a retrospective multicenter study (73 patients; SFGM-TC) reduced-intensity conditioning allogeneic stem cell transplantation in advanced chemosensitive disease lead to a long-term survival despite associated with significant transplant-related mortality [45]. Results of the prospective multicenter LALA-94 study revealed that allogeneic stem cell transplant should be offered in first complete response to t(1;19)/E2A-PBX1 or t(4;11)/MLL-AF4 patients [46]. In a randomized prospective study of 30 patients with different hematological diseases (acute myeloid leukemia, acute lymphoblastic leukemia, chronic myeloid leukemia, myelodysplastic syndrome or severe aplastic anemia), Mahmoud *et al*. [47] showed that peripheral blood stem cell transplant is associated with faster hematopoietic recovery and the incidence of acute graft-*versus*-host disease does not exceed that observed with bone marrow transplantation. In a randomized trial of allogeneic related bone marrow transplant (40 patients) compared to peripheral blood stem cell transplant (32 patients) for chronic myeloid leukemia, a higher cumulative incidence of relapse (at 3 years) was observed in those who underwent bone marrow transplantation (7% *vs*. 0%) [48]. In the BGMT 87 study, Reiffers *et al*. [49] compared allogeneic bone marrow transplant, autologous stem cell transplant and chemotherapy in patients with acute myeloid leukemia in the first remission. There was no statistical difference between autologous stem cell transplant and chemotherapy for either disease-free survival, risk of relapse or survival, indicating that allogeneic bone marrow transplant may at least produce superior results. Furthermore, alternative source of stem cell for the purpose of transplant need to be explored, factor effecting transplant need to be identified, transplant techniques need to be further explored, transplant procedure must be performed in specialized centers, rejection due to transplant and incidence of acute graft-*versus*-host disease must be reduced.

2.1.2. Multiple Myeloma: A Cancer of Plasma Cells

Multiple myeloma [50] accounts for 0.8% of all cancers worldwide with approximately 86,000 new cases per year [51]. This malignant disease is characterized by the accumulation of monoclonal plasma cells in the bone marrow and the secretion of paraprotein. Plasma cells are important components of immune system involved in the production of special chemicals called immunoglobulins (combat infectious agents). Conversely, malignant plasma cells produce abnormal immunoglobulins (monoclonal protein or paraproteins). Currently, various options for the treatment of multiple myeloma include radiation therapy, conventional and high-dose chemotherapy, autologous and allogeneic stem cell transplantation, and immunotherapy. Clinical trials, however, have shown that autologous stem cell transplantation is superior to conventional dose therapy in the treatment of multiple myeloma patients. Yet, no complete cure exists for this disease. Currently, the median overall survival of multiple myeloma patients after stem cell transplantation and targeted therapies is nearly 5 years, however those treated with conventional chemotherapy survived for more than 10 years. Therefore there is necessary to know the potentially favorable prognostic factors for the selection of targeted treatments [52]. Two meta-analyses on high-dose therapy and autologous stem cell transplantation in frontline multiple myeloma indicated highly significant associations between maximal response during or after high-dose therapy and autologous stem cell transplantation and long-term outcomes. Both meta-analyses provided evidence of highly significant associations between maximal response following induction therapy and long-term outcomes [53]. Allogeneic bone marrow transplantation using human leukocyte antigen-matched sibling donors appeared to be a promising method of treatment for some patients with multiple myeloma [54]. In a prospective, randomized trial, patients with multiple myeloma (under the age of 65 years) were randomly assigned to receive either conventional chemotherapy or high-dose therapy and autologous bone marrow transplantation. Intergroupe Francophone du Myélome 90 trial (200 patients) compared conventional-dose chemotherapy to autologous bone marrow transplant. The results showed that high-dose therapy combined with transplantation improved the response rate and progression-free and overall survival rates [55]. The 5-year rate of survival was 52% in the high-dose group and 12% in the conventional-dose group. In a Medical Research Council Myeloma VII trial (401 patients), patients with previously untreated multiple myeloma (aged <65 years) received either standard conventional-dose combination chemotherapy or high-dose therapy and an autologous stem cell transplant. The high-dose therapy with autologous stem cell rescue was an effective first-line treatment. The transplant provided superior progression-free survival and overall survival, and the median survival for transplant compared to chemotherapy was 54 months *vs.* 42 months, respectively [56]. In Intergroupe Francophone du Myélome 94 trial (399 patients), double autologous stem cell transplantation improved overall survival among patients with multiple myeloma compared to those who underwent a single autologous stem cell transplantation after a high-dose chemotherapy [57]. The double transplantation provided superior event-free survival and overall survival. The 7-year survival was with 42% and 21% with double transplant and single transplant, respectively. In a prospective, randomized study of comparing single *versus* double autologous stem cell transplant (Bologna 96 trial; 200 patients), Cavo *et al.* [58]

showed that double autologous stem cell transplant effects superior complete response or near complete response rate, relapse-free survival, and event-free survival, but failed to significantly prolong overall survival. The median survival was 60 and 50 months with the double transplant and single transplant, respectively. Altogether autologous stem cell transplant improves the median survival time and is considered as the standard of care for younger patients, however, questions regarding the management of myeloma need to be addressed. Studies have shown that peripheral blood stem cells can also be used as an alternate source of stem cell transplant because they are easily available and they reduce transplant-related toxicity [59]. The results of such studies are encouraging. Recently, an evidence-based practice guideline assessing the role of stem cell transplant in patients with multiple myeloma was developed. This guideline comprises six recommendations. This guideline recommends autologous transplant for patients with stage II or III myeloma and good performance status, whereas allogeneic transplantation is not recommended as a routine therapy [60]. In the future, stem cell transplantation in combination with novel drugs might provide cure for patients with multiple myeloma. In addition, achieving complete response will be the first step forward toward cure for those with multiple myeloma.

3. DISCUSSION

Bone marrow transplant is a promising strategy for the treatment of various diseases. The key for a successful bone marrow transplant involves matching for the human leukocyte antigen system between donor and recipient and the migration of stem cells to find proper niche, expand and differentiate without depletion of the stem cell pool. Bone marrow (medulla ossea) [61] is a soft blood-forming tissue that contains hematopoietic, mesenchymal, and endothelial stem cells. Hematopoietic stem cells have the capability to differentiate into mature cell types of blood (give rise to leukocytes, erythrocytes, thrombocytes) and these cells can be used for successful transplant, whereas mesenchymal stem cells have the capability to differentiate into other cell types. Apart from the hematopoietic stem cells, umbilical cord blood stem cells can be used as an alternative source for transplant [62]. The advantage of using bone marrow for transplant is faster engraftment, whereas the disadvantages are lack of donor, longer search times, more graft-*versus*-host disease. Conversely, the use of umbilical cord blood has faster availability, rapid donor identification, decreased transmission of viral diseases, reduced graft-*versus*-host disease, and ease of scheduling transplant [63].

Bone marrow and peripheral blood stem cell transplants are used in the treatment of certain type of cancers, making it possible for patients to receive a high-dose chemotherapy and/or radiation therapy. Peripheral blood stem cell transplant, however, requires no general anesthesia and engraftment is rapid with earlier discharge from hospital [7]. Stem cell transplants, however, are associated with complications – as the allogeneic bone marrow and peripheral blood transplants are associated with graft-*versus*-host disease. While performing allogeneic stem cell transplant, the transplanted cells must closely match that of host, which is determined by the human leukocyte-associated antigens (surface proteins of cells). An individual has three pairs of major human leukocyte-associated antigens: human leukocyte antigen-A, human leukocyte antigen-B, and human leukocyte antigen-DR. The complication associated with post-allogeneic bone marrow transplant is graft-versus-host disease and autoimmune-like disorders. The successful transplant largely depends on the higher number of matches of human leukocyte-associated antigen tissue types between donor and recipient. And the patient is less likely to develop a common side effect known as graft-*versus*-host disease. Here, the immune cells of the host in the transplanted marrow recognize the patient as foreign and strikes an immunologic attack. This is prevented when the patient receives medications to suppress immune system. Human leukocyte-associated antigen matching is more likely in close relatives compared to unrelated donor; however, identical twins have same set of human leukocyte-associated antigens and syngeneic transplant is rare.

Research is more inclined toward decreasing graft-*versus*-host disease, overcoming the human leukocyte antigen histocompatability barriers. Efforts are to reduce transplant-related mortality. Conversely, umbilical cord blood (rich in hematopoietic stem cells) is successfully used as an alternative source of transplant. Currently, bone marrow transplant is used to treat acute myelogenous leukemia, acute lymphocytic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, myeloproliferative disorders, multiple myeloma, non-Hodgkin lymphoma, Hodgkin disease, breast cancer, testicular cancer, ovarian cancer, glioma, neuroblastoma, small-cell lung cancer, non-small-cell lung cancer, severe aplastic anemia, ß-Thalassemia, severe combined immunodeficiency, autoimmune disorders, amyloidosis, and hereditary metabolic disorders. In future, the advancement in these transplant procedures may hold potential to restore the function of damaged heart and regenerate damaged nervous tissue. These medical procedures may also be used to treat Alzheimer's disease, diabetes, liver disease, muscular dystrophy, Parkinson's disease, and spinal cord injury. For instance, Parkinson's and Huntington's [64] are the commonest neurodegenerative diseases that lead to the deterioration of neurons. These diseases are a major global health problem. Understanding the cause and identifying the novel pathways may help find interesting clues to unlock the mysteries. Although there is little possibility for brain cells to regenerate, preclinical studies using various stem cells have shown that they raise a new hope to repair and replace the destroyed brain tissue. Thus, seeking for therapeutic options like the application of stem cells for the treatment of human neurodegenerative disorders may sound very interesting; however, there are various hurdles to overcome. The human neural stem cells may be cultured, genetically modified, and transplanted to restore normal function of the brain. Currently, scientists are attempting to use stem cells to make dopamine producing neurons. Stem cells might one day be programmedable to replace the dead cells with healthy ones – providing a step forward in stem-cell based treatment for Parkinson's disease.

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