



ISSN: 0975-766X

CODEN: IJPTFI

Research Article

Available Online through

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BONE MARROW TRANSPLANTATION

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Received on 25-02-2015

Accepted on 30-03-2015

Abstract

Bone marrow is a specialized type of soft connective tissue called myeloid tissue. It serves as the site for production of blood cells and found in the medullary cavities of certain long bones and in the spaces of spongy bone in some areas. Bone marrow transplant is the intravenous transfer of red bone marrow from a healthy donor to a recipient, with the goal of establishing normal hemopoiesis and consequently normal blood cell counts in the recipient. Bone marrow transplant results in replacement of the host myeloid, erythroid megakaryocytic, lymphoid and macrophage-monocyte systems with those of donor origin. It is a therapeutic option for disease involving the haematopoietic system and many other diseases such as anemia, certain types of leukemia, thalassemia, sickle cell disease, multiple myeloma, severe combined immunodeficiency disease (SCID), breast cancer, ovarian cancer, testicular cancer and hemolytic anemia.

This article provides information about blood and marrow stem cell transplantation for the treatment of blood cancers. It cover some of the issues that come with transplants, transplant process (HLA matching, HLA-Typing test, Matching related to Donar, Conditioning treatment) and precaution after transplantaion.

Keyword: Blood, Stem Cell, Bone Marrow Transplant.

Introduction

Need Stem Cell Transplants:

In some diseases like leukemia, Lymphomas, Aplastic anemia, Sickel cell disease, Thalassemia, Blackfan- Diamond Anemia certain inherited blood diseases, and some diseases of the immune system, the stem cells in the bone marrow don't work the way they should, and they has been damage or destroyed due to intense treatment of radiation or chemotherapy. The donated cells can often find and destroy cancer cells better than the immune cells of the person who

had the cancer ever could. This is called the “graft-versus-cancer” or “graft-versus-leukemia” effect. It means that certain kinds of transplants actually facilitate fight the cancer cells, rather than simply replacing the blood cells.

The bone marrow transplant can be used:

1. Replace bone marrow that has been destroyed by disease, chemo, or radiation.
2. Replace bone marrow and restore its normal function (Rescue) for disease such as Brest cancer, Lymphoma, Neuroblastoma.
3. Replace bone marrow with genetically healthy functioning bone marrow to prevent further damage from genetic disease such as Hurler syndrome, Adrenoleukodystrophy.

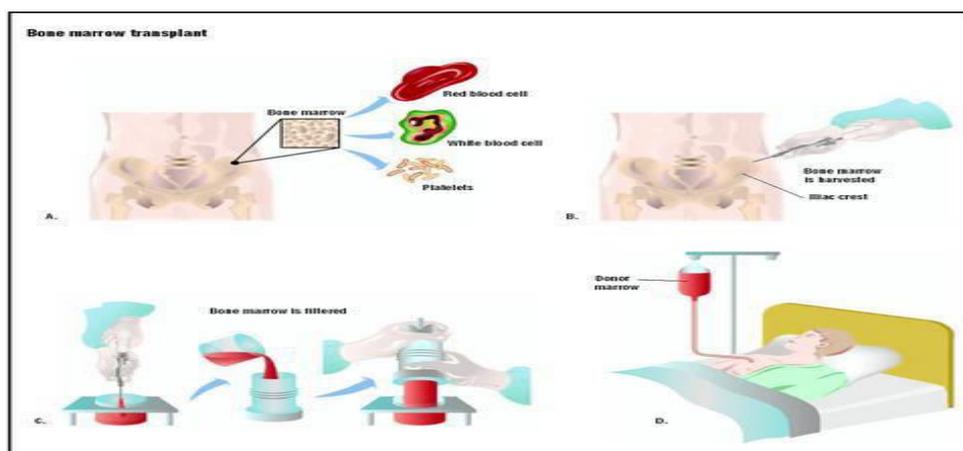


Fig No. 1: Bone marrow consists of red blood cells, white blood cells, and platelets (A). In a bone marrow transplant, bone marrow is harvested from the donor's pelvic bone at the iliac crest (B). The marrow is filtered (C) before being introduced into a large vein in the recipient's chest via a catheter (D).

Types of Stem Cell Transplants ¹

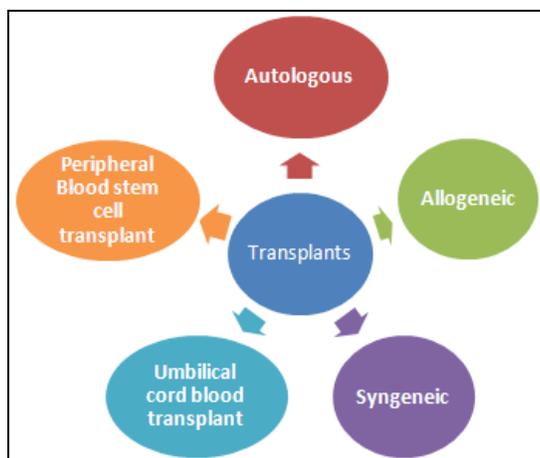


Fig No. 2: Types of Transplants

1. **Autologous** (Stem cells come from you)
2. **Allogeneic** (Stem cells come from a matched related or unrelated donor)
3. **Syngeneic** (Stem cells come from your identical twin or triplet)
4. **Umbilical cord blood transplant** (stem cells from saved cord blood, from self or donor)
5. **Peripheral Blood stem cell transplant** (Immature blood cells hematopoietic stem cells in the circulating blood)

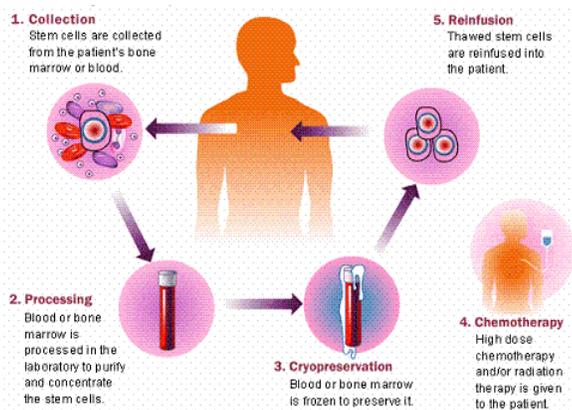


Fig No. 3: Autologous transplant process
repopulate recipient bone marrow

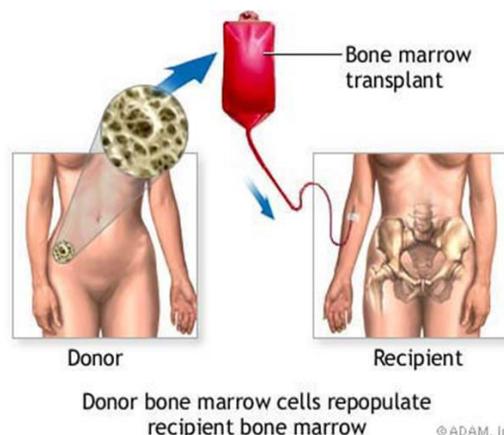


Fig No. 4: Donor bone marrow cells

Preparation of Recipient: A complete medical history and physical examination are performed including multiple tests to evaluate the child's blood and organ function.²

Condition regimen: This treatment to patient permits the engraftment of donor marrow. It ablates the haematopoietic system of recipient to create 'space' for the allogeneic bone marrow. It also destroys the immune system of recipient, thus cell capable of causing graft rejection. A standard regimen for malignant disease involves 120mg/kg cyclophosphamide followed by 1000-1375cGy total body irradiations in one or more fractions. The alkylating agent busulphan has been used in place of irradiation.²

GVHD prophylaxis: Usually cyclosporine and methotrexate with or without steroids are administered after allogeneic transplantation to prevent GVHD. Complete removal of T-lymphocytes from the graft may eliminate GVHD almost completely, but associated with an increased risk of graft rejection and relapse as a result of graft-versus-tumour effects. GVHD prophylaxis is not required for auto grafts and syngeneic transplant.²

Preparation of the Donor:

The ideal allogeneic donor is an HLA-A, B and DR- matched sibling. ABO blood group incompatibility is not a barrier. Donor sources usually available include: self sibling parent or relative, non related person or umbilical cord from a related or non related person. There are national and international registries for non-related person and cord blood. The recipient must be in good health and fit to undergo general anaesthesia for marrow harvest. Once a match for a bone marrow transplant is found then stem cells will be collected either by a bone marrow harvest or peripheral blood stem collection. Peripheral blood stem cell harvests do not require general anaesthesia.²

When a bone marrow is transplanted from a donor, the recipient's HLA type must closely match the donor's HLA type. Matching involves typing human leukocyte antigen (HLA) tissue. The antigen on the surface of these special white blood cells determine the genetic makeup of a person's immune system. There are at least 100 HLA antigens however, it is believed that there are a few major antigens that determine whether a donor and recipient match. The others are considered minor and little effect on a successful transplant is not as well defined.³

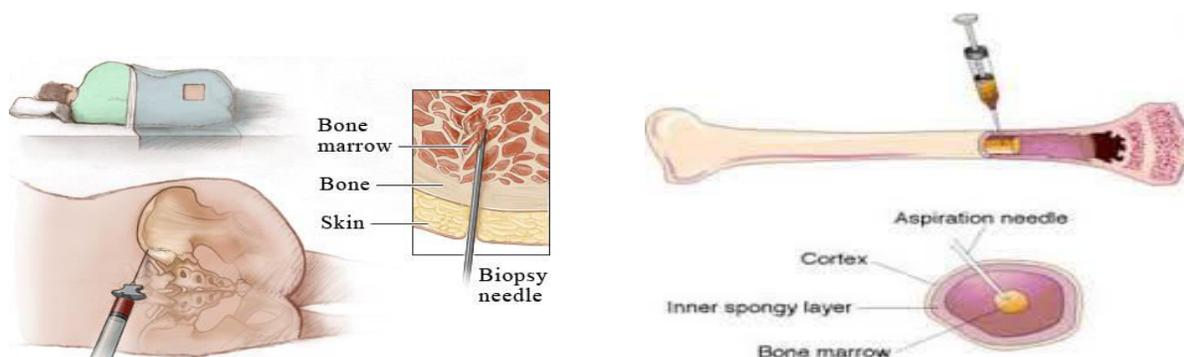


Fig No. 5: Bone marrow aspiration

The transplant procedure itself is simple usually while the donor is under general or spinal/ epidural anesthesia, marrow is aspirated from the posterior iliac crest through multiple punctures and collected in tissue culture medium with preservative-free heparin after filtration through a wire mesh or filter for removal of bony spicules. Adequate quantity of bone marrow must be harvested to provide adequate quantity of nucleated cell per kg recipient body weight for auto grafting and allografting. Depending upon donor recipient ABO compatibility, the marrow may have to be depleted of red cells and plasma. It may be depleted of lymphocytes in cases where the risk of graft-versus-host disease (GVHD) is very high. It may be purged of residual tumor cells in case of auto grafting.⁴

The number of haemopoietic progenitors circulating in the blood is greatly increased during recovery from chemotherapy or after the administration of growth factor such as granulocyte colony – stimulating factor (G-CSF) or granulocyte macrophage colony- stimulating factor (GM-CSF). Marrow with over metastatic disease is not considered suitable for transplantation due to the risk of contamination of the harvested marrow with malignant cells and reinfusion of diseases. Recovery of haematopoiesis is usually faster after infusion of blood cells than, after marrow with a shortened period of post – transplant pancytopenia. The faster haematologic recovery results in decreased incidence of infection, blood product requirements, duration of hospitalization and cost of procedure.

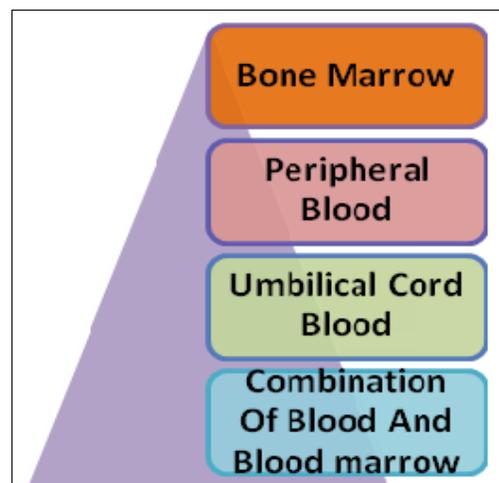
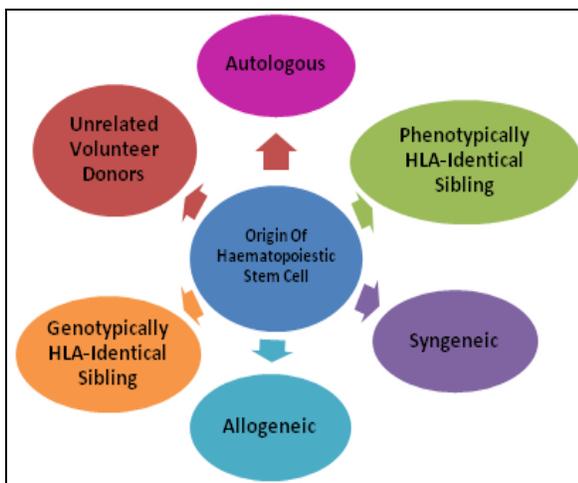


Fig No.6: Origin of Haematopoietic Stem cell

Fig No.7: Sources of Haematopoietic Stem cell

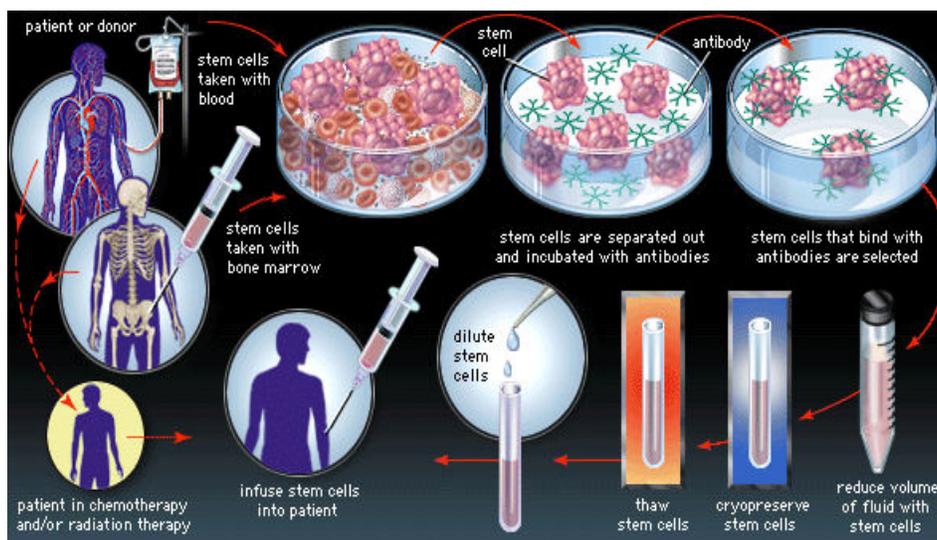


Fig No.8: Stem Cell Collection

The patient is prepared for transplant by administering high doses of chemotherapy or radiation. This serves two purposes Firstly; it destroys the patient's abnormal blood cells or cancerous cell. Secondly, it shows the patient's immune response against the donor marrow. The doctor then injects the marrow into the recipient's vein. The donor's bone marrow migrates to and takes root in the recipient bones and the cells begin to divide. Ultimately, if all goes well, the recipient's bone marrow is entirely replaced.⁵

Engraftment Process

Engraftment of the stem cells occurs when the donated cells make their way to the marrow and begin reproducing new blood cells. Depending on the type of transplant and the disease being treated, engraftment usually occurs around day +15 or +30. Engraftment can be delayed because of infection, medications, and low donated stem cells count or graft failure.⁴

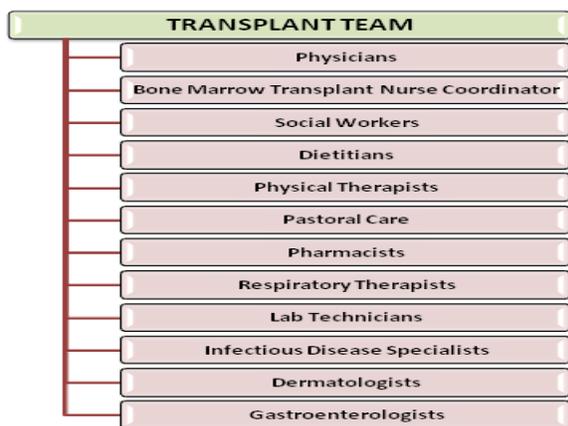


Fig No.9: team members for bone marrow transplant⁶

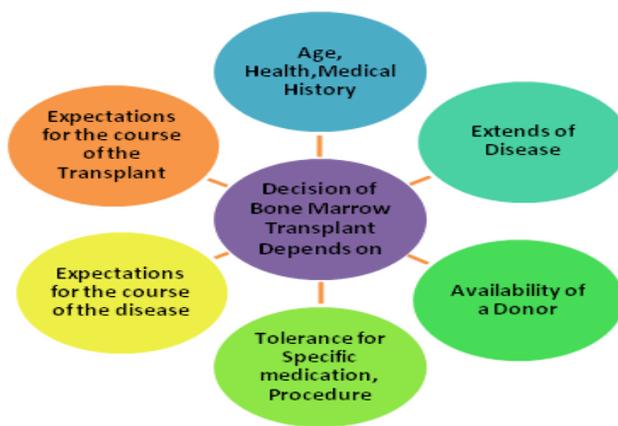


Fig No.10: The decision of bone marrow transplant based on many factors

Autologous Bone Marrow Transplantation

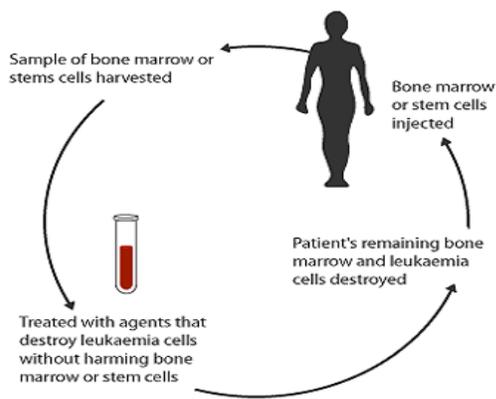
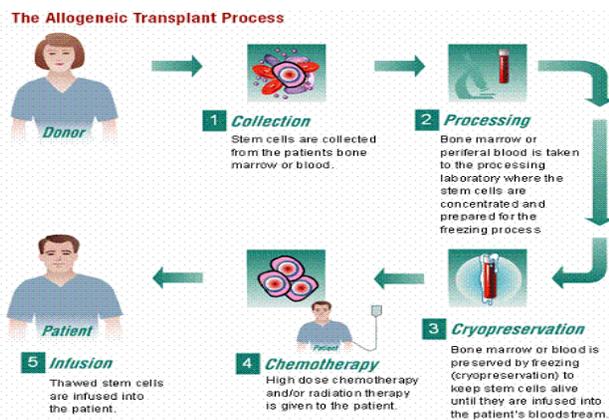


Fig no.11: Autologous bone marrow transplant⁷



An autologous bone marrow transplant involves harvesting your own bone marrow, preserving and storing it in frozen form and later after high dose chemotherapy and/or radiation therapy infusing it back into your body.

Some 5,000 autologous BMTs are performed each year, outpacing allogeneic and syngeneic BMTs two to one. Some complications associated with allogeneic BMTs such as graft-versus-host disease are avoided with autologous BMTs. Autologous BMTs (ABMTs) have expanded treatment options for thousands of patients diagnosed with life-threatening diseases such as Hodgkin's disease and non-Hodgkin's lymphoma, breast cancer, ovarian cancer, testicular cancer and pediatric solid tumors such as neuroblastoma.

Hodgkin's and Non-Hodgkin's Lymphoma's:

Autologous BMTs are most frequently used to treat patients diagnosed with Hodgkin's disease and non-Hodgkin's lymphoma. In Hodgkin's disease, an abnormal cell called the Reed-Sternberg cell may be present in one or more lymph nodes. In non-Hodgkin's lymphomas, defective lymphocytes (a type of white blood cell) are produced in the lymph nodes, bone marrow, spleen and/or gastrointestinal tract. Patients with advanced Hodgkin's or non-Hodgkin's lymphoma who undergo an autologous BMT have a 25 to 50 percent chance of long term survival. Without a BMT, their chances for long term survival are 5 to 10 percent.⁸

Leukemia:

Treatment of leukemia with an autologous BMT is becoming more common. Patients with acute lymphocytic leukemia (ALL) or acute myelogenous leukemia (AML) (also called acute non-lymphocytic leukemia or ANLL) may be candidates for an autologous BMT if their disease is in complete remission. Since a complete remission is rarely achieved in patients with chronic myelogenous leukemia (CML), an autologous BMT is usually not a treatment option for these patients

Leukemia is a disease of the bone marrow; a large number of abnormal white blood cells are produced in the bone marrow and interfere with the production of normal blood cells.

Without normal blood cells, the body's ability to fight infection, carry oxygen to tissues, and prevent bleeding is impaired. Patients with acute leukemia will die within a matter of weeks or months without treatment. Both autologous and allogeneic BMTs are an effective treatment option for ALL patients; some experts believe that too little data are currently available to reliably project long-term survival rates.⁸

Breast Cancer:

Breast cancer is the third most common cancer in women, in 1990, 150,000 new cases were diagnosed and 44,000 deaths from breast cancer were reported.

The results of early clinical studies in which high-dose chemotherapy and an autologous BMT were administered to Stage IV breast cancer patients who had previously undergone intensive chemotherapy treatment were encouraging. A remission was achieved in 27 percent of the patients.

Subsequent studies conducted with patients who had just become Stage IV, had not previously undergone intensive chemotherapy treatment or were in their first relapse after remission, found that administering a cycle of chemotherapy before the high-dose chemotherapy and an autologous BMT produced remissions in 50 percent or more of the cases, with some remissions lasting three years or more.

Studies are now underway to determine whether chemotherapy followed by high-dose chemotherapy and an autologous BMT will improve the survival rates of some Stage II breast cancer patients (in whom the disease has spread to lymph nodes under the arm) and some Stage III patients who are in a first remission and have not yet relapsed, but are in a high risk category for relapse (the disease has spread to 10 or more lymph nodes). Early results from the studies are encouraging.⁸

Childhood Neuroblastoma:

Childhood neuroblastoma is a cancer affecting the nerves that run from the neck down the inside of the back to the pelvis. Researchers have attempted to increase the cure rate with high-dose chemotherapy and an autologous BMT.

Other Diseases

Ovarian cancer, brain tumors, Ewing's Sarcoma, testicular cancer, and other solid tumor cancers may also be treated with autologous BMTs.

Purging bone marrow:

Purging is a technique used at some transplant centers to reduce the number of cancerous cells that may be in bone marrow harvested from certain patients undergoing an autologous BMT. By reducing the number of cancerous cells in the harvested bone marrow, the likelihood of relapse after an autologous BMT will be reduced.

Two different purging techniques are used. The first involves "monoclonal antibodies"-special proteins that distinguish malignant cells from normal cells and attach to the surface of the malignant cell. These "marked" malignant cells are then broken apart with additional proteins called "complement" or "immunotoxins". Alternatively, small magnetic beads or "microspheres" are coated with the monoclonal antibodies and mixed with the bone marrow. The marrow is then passed over electromagnets which remove the microspheres and malignant cells to which they've become attached.

A second technique is chemical or pharmacological purging. The bone marrow is incubated with chemicals more toxic to cancerous cells than normal cells. The marrow is then transplanted into the patient.

Purging has its drawbacks. Pharmacological purging can damage normal as well as malignant cells, causing delayed engraftment of platelets and granulocytes and extending the period in the hospital during which patients are susceptible to infection and bleeding. The prognosis for long-term survival varies according to the disease being treated, the stage of the disease at which an autologous BMT was performed, the patient's age, prior treatment history, and any complications that may have developed during transplant. An allogeneic bone marrow transplant involves harvesting bone marrow, from a family member or an unrelated donor.

The matching process is called human leukocyte antigen testing (HCA testing). Diseases frequently treated with

Allogeneic BMTS:-

- Aplastic Anemia
- Hodgkin's Disease
- Leukemia
- Non-Hodgkin's Lymphoma
- Multiple Myeloma
- Osteoporosis
- Severe Combined Immune Deficiency Syndrome (SCIDS)
- Thalassemia
- Wiskott-Aldrich Syndrome

HLA System

White blood cells carry a distinguishing "fingerprint" on their surface called the HLA system-the human leukocyte antigen system. (Leukocyte means white blood cell). These antigens are proteins that play a critical role in protecting the

body against invading organisms such as bacteria, viruses and other foreign matter. At birth, certain white blood cells called T-cells are programmed by the thymus gland to identify all the antigens that belong in that person's body. When a foreign antigen is encountered, e.g. antigens on the cell surface of invading bacteria or viruses, the T-cells summon the various components of the immune system to attack and destroy the invading organism. Similarly, when bone marrow is transplanted from a donor into a BMT patient, the patient's T-cells will examine the antigens on cells in the donated marrow, and will launch an immune system attack if they perceive the antigens to be "non-self". If the patient's immune system destroys the donated bone marrow, graft-rejection results and the BMT fails.⁹

HLA typing test

The first is a blood test that can detect antigen at HLA-A, -B and -DR loci. Secondary tests, such as the mixed lymphocyte culture (MLC) test, are used to assess whether or not the patients and donor bone marrow interact adversely. Newer tests such as typing will make HLA-typing more precise in future.^{10,11}

Umbilical Cord Blood Transplant:

Stem cells are taken from an Umbilical cord immediately after delivery of infant. These stem cells reproduce into mature, functioning blood cells quicker and more effectively than do stem cells taken from bone marrow of another child or adult. The stem cells are tested, typed, counted and frozen until they are ready to be transplanted. Because the stem cells are new they are able to produce more blood cells from each stem cell.⁹

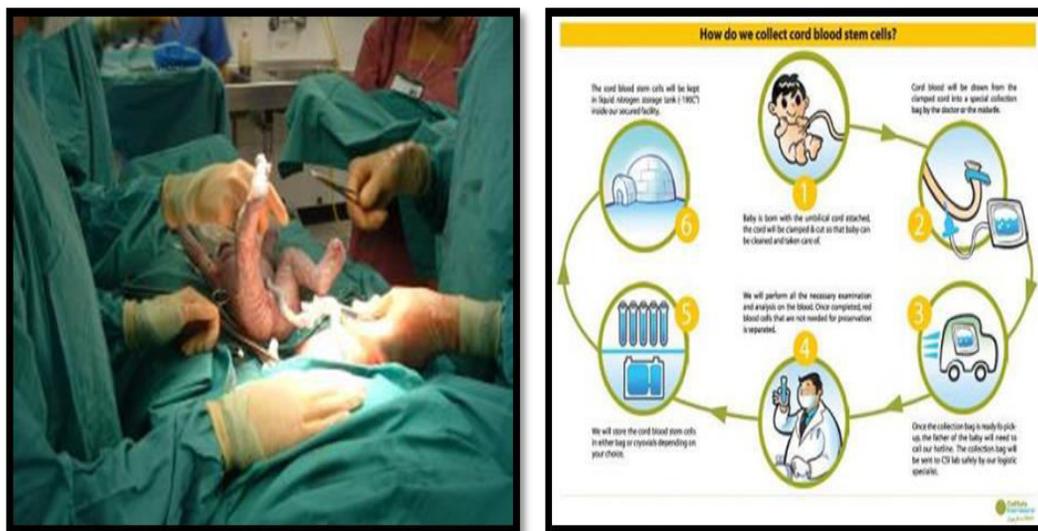


Fig No.12: A newborn baby boy having his umbilical cord cut after a cesarean section operation. Children with heart defects may someday receive perfectly-matched new heart valves built using stem cells from their umbilical cord blood.

Syngeneic Transplant:

Peripheral stem cell transplant: The patient or donor donates stem cells collected from the circulating blood system instead of from bone marrow. PSCHs have been used instead of or in addition to autologous bone marrow harvest when transplanting patients with acute myelogenous leukemia, Acute lymphocytic leukemia, Hodgkin’s Disease, Non-Hodking’s Lymphoma, Brain Tumors, Breast cancer, Ovarian Cancer, Multiple Myeloma, Small Cell Lung Cancer, Testicular Cancer and Neuroblastoma.

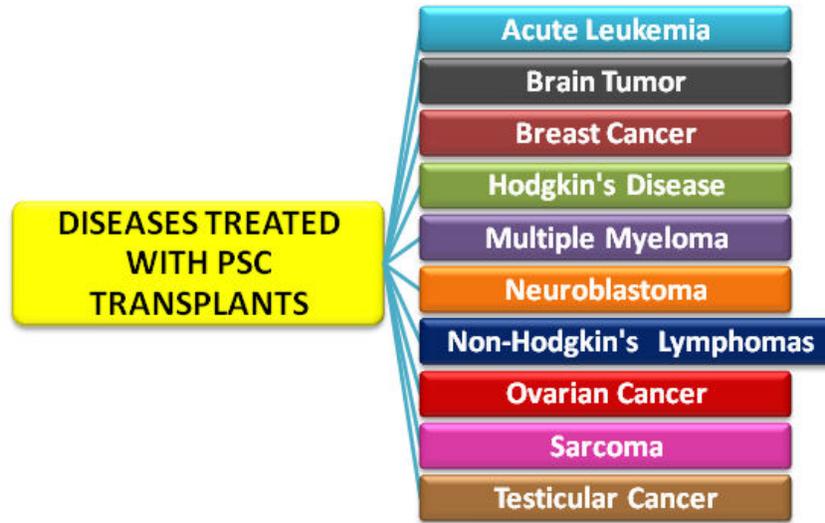


Fig No.13: Disease treated with PSC Transplants

Complications and side effects following bone marrow transplant 17: Complications may vary depending on the following conditions:

- Type of marrow transplant
- Type of disease requiring transplant
- Preparative regimens
- Age and overall health of the recipient
- Variance of tissue matching between donor and recipient
- Presence of severe complications

Other complications may also occur such as Graft-versus-host disease (GVHD), infections, interstitial pneumonitis, veno-occlusive disease (VOD), graft failure, low platelets and low red blood cells, pain, fluid overload, respiratory distress, and organ damage.

Nutrition after Bone Marrow Transplant ¹²

Good nutrition is a very important part of patient recovery. It helps patient's body resist infection and repair tissue damage caused by chemotherapy and/or radiation therapy. There is need to adjust diet to stay healthy and to prevent excessive weight gain. Maintaining a healthy weight can help prevent high blood pressure, high cholesterol and other negative health effects.

Nutrition supplements: When you are unable to eat a well-balanced diet, we recommend you try over-the-counter nutrition supplements to meet your nutritional needs, unless otherwise instructed. However, it is important to check the labels for the specific vitamin, mineral or nutrient levels.

Multivitamins: Daily intake of multivitamin, like chewable multivitamins twice a day if better tolerated. Excess doses of some vitamins and minerals might be unsafe . For instance, it is important to choose vitamins that do not contain iron or herbs. Also, due to your numerous red blood cell transfusions, additional iron supplementation is unnecessary.

Calcium and Phosphorus: Some medicines might deplete calcium, which is important for maintaining bone strength. Phosphorus is a mineral that helps to strengthen bones. Some transplant patients often need additional phosphorus.



Fig No.14: Diet high in calcium and phosphorus

Conclusion:

From the present it is concluded that the bone marrow transplant is a very important process. The bone marrow is responsible for the development and storage of about 95% of the body's blood cells. By the bone marrow transplant it is easy to maintain the healthy condition of our bone marrow which is very much important for production of normal blood

cells. Further, we can maintain the normal hemopoiesis process in our body and consequently normal blood cell counts in the recipient. Bone marrow transplants have been used to save life of many generation including young ones. Like bone marrow transplantation, several other organs have been transplanted such as kidney transplantation, liver transplantation, heart transplantation, lung transplantation and pancreatic transplantation. Thus, as a whole concluded that bone marrow transplantation is one of the important achievements in the field of medical science and research.

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