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HAEMOPOIETIC STEM CELL TRASPLANTATION (HSCT)

Kamal Pandey[1], Sonu Thapa[2], Prem Bhusal[3] and Rabindra Chaudhary[4]

[1,4]Department of Clinical Pharmacy, Aditya Bangalore Institute of Pharmacy Education and Research, Bangalore.

[2]Dhanwantari Nursing College, Karnataka.

[3]Department of Pharmacy Practice, Bharathi College of Pharmacy, Karnataka-571422, India.

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***Corresponding Author**
Kamal Pandey
Doctor of Pharmacy, Aditya Bangalore Institute of Pharmacy Education and Research, Kogilu Road, Yelahanka, Bangalore -64, Bangalore, India.

ABSTRACT

Haematopoietic stem cells transplantation (HSCT) is an established therapy firstly developed by E. Donnall Thomas in 1956 AD has seen rapid expansion over the last decade in the treatment modality for haematological, oncological, hereditary and immunological diseases, which consists in the intravenous infusion of hematopoietic stem cells to re-establish the patients' medullary and immune function. Depending upon the donor, the transplantation is classified as autologous, allogeneic, or syngeneic. BMT has been performed for a large number of conditions. The five most frequent ones include CML, Thalassaemia Major, Aplastic Anemia, Multiple Myeloma and Acute Leukaemia. Development of infrastructure and human resource has lead to more and more patients being given the benefit of this potentially curative mode of therapy. The major sources for stem cell transplantations bone marrow, Peripheral blood stem cells and umbilical cord blood or hematopoietic stem cells. Selection of donor depend upon the types of malignancy, availability of suitable donor ,types of malignancy, status of disease, a tumour free autograft and malignancy susceptibility to GVM. Conditioning (preparative) regimens are given with main aim of preparing the space in bone marrow space for the incoming graft, suppressing immunity of to prevent GvHD, and eradicate tumor cells when patients are treated for malignant disease. The most common complications of the procedure may be due include mucosititis, Hepatic veno-occlusive disease, haemorrhagic cystitis, convulsions, infections, bleeding, viral, bacterial or fungal infections,Graft Versus Host Disease in allogeneic transplantations only.

KEY WORDS: Transplantation, Graft versus host Disease, Complication, Mobilization, Apheresi.

INTRODUCTION

Haematopoietic stem cells transplantation (HSCT) is an established therapy and has seen rapid expansion over the last decade in the treatment modality for haematological, oncological, hereditary and immunological diseases, which consists in the intravenous infusion of hematopoietic stem cells to re-establish the patients' medullary and immune function.[5, 6]

EBMT defined HSCT as the infusion of haematopoietic stem cells given with the intention to replace the pretransplant recipient haematopoietic system.[7]

Bone marrow (BM) is consists of two parts known as osteoblastic and vascular Microenvironments. The mobilization of hematopoietic stem and progenitor cells (HSPCs) from bone marrow into the blood circulation has been used as principle for bone marrow Transplantation.[8]

Mobilization can be defined as the forced migration of HSPC from BM into peripheral blood. Mobilization is considered as a basic procedure which allows for HSPC collection. Both autologous and heterologous bone marrow transplantation utilized HSPCs in peripheral blood. Traditionally, bone marrow stem cells have been collected and injected into patients for bone marrow transplantation, though this method is regarded painful. However, today in bone marrow transplantation, HSPCs entering into peripheral blood via mobilization process are the first choice, specifically in autologous transplantation. Use of HSPCs in peripheral blood has been shown to be even better than cord blood HSPCs in bone marrow transplantation. Several factors of HSPCs, including G-CSF, GM-CSF, SDF-1/CXCR4 axis, integrins and chemokines play a role in mobilization.[9]

Types of Bone Marrow Transplantation

Pluripotent stem cell is the main component of bone marrow which ensures hematopoetic regeneration which has been characterised by immunophenotyping (identification of the cell surface protein/ antigen CD34+ will demarcate cells represent a heterogeneous group including the most primitive blood forming stem cell). Depending upon the donor, the transplantation is classified as autologous, allogeneic, or syngeneic. In each case, bone

marrow, peripheral blood or umbilical cord blood stands the source of these hematopoietic stem cells as mentioned above.[10]

There are three general categories of BMT based on the type of marrow donor: syngeneic, allogeneic and autologous.

In syngeneic transplants, transplantation is done in between identical twin. Patients receive stem cells from their identical twin. Syngeneic transplantation is rare as identical twins represent a small number of births. There is less chance of the transplant being rejected because identical twins have the same genes; they also have the same set of human leukocyte associated antigens.[11]

In allogeneic HSCT, stem cells harvested from another person are infused into the patient following high dose chemotherapy, whereby donor and recipient are not immunogenically identical (Figure 1). The preferred donors are human leukocyte antigens (HLA)-matched sibling donors. In the pre-transplant work-up, class I and class II HLA antigen compatibility is tested via serological or molecular techniques and compared between the patient and siblings. Class I includes HLA-A, HLA-B and HLA-C while Class II includes HLA-DR, HLA-DP and HLA-DQ. Fully HLA-matched matched sibling has all HLA loci identical to the recipient and this will reduce the possibility of GVHD and graft failure. However, an HLA-matched sibling donor is only available in 30-40% of patients.

An allogeneic transplant is one in which stem cells harvested from another person are infused into the patient which can be related or unrelated as the stem cell source. The most preferred allogeneic donor is a histocompatible related sibling. Short arm of chromosome 6 consists three major genetic loci which coded the human leukocyte or histocompatibility antigens (HLA). Only six or sometime ten HLA antigen are involved with host-donor interactions although hundred HLA antigen are present. Two A antigens, two B antigens and two D/Dr antigens are 6 antigens tested for HLA. Each set of three HLA antigens (A, B, D/Dr) are inherited from each parent and are called as haplotype. Every individual inherits one paternall and one maternall HLA haplotype. Thus, there will be chance of 25% that any sibling will have inherited the same two haplotypes, that is, being histocompatible or HLA matched with the patient. Several alternatives of allogeneic transplantation are nowadays available in the absence of matched sibling donors which include matched unrelated donors (MUD),

unrelated umbilical cord blood (UCB) or haploidentical donors (3 out of 6 HLA alleles mismatched).[12]

An autologous transplantation the patient's own BM or PB stem cells as a rescue from the high-dose therapy given to cure their underlying disease and use for the procedure. In this method patients own stem cells which were harvested earlier will be infused as a rescue therapy after high-dose myeloablative therapy. The aim of administration of high-dose chemotherapy is to eradicate the remaining tumor cells.[13]

INDICATION OF TRANSPLANTATION

European centres of bone marrow transplantation (EBMT), formulated recommendation and report procedure to be followed for rational indications for transplantation based on research results sup- ported by their high quality.[15]

At present, the recommended by EBMT- 4 categories of indications are the following.

1 "standard indication" category – S (standard of care) which means that for a specific clinical condition and certain disorder the treatment with transplant was identified as appropriately defined and found more favourable than other treatments. However, it is necessary to take medical assessment as it might not be the best choice for every patient. In such situations, the procedure can be performed in every accredited transplantation centre with appropriate equipment and experience.

2 "clinical option" categories – CO refers situation in which, current knowledge, HSCT constitutes a good solution, holding promise for the patient that the benefits will be more than risk. Specific protocol should be carried out to follow the procedures reported so that they could facilitate the preparation of verified indications. Patient should be given information about his/her condition, benefits and risks of transplantation to identify whether procedure is benefits to patients or not. Patients Compliance and consent should be takes before starting the procedure. The procedure should be performed in specialist centres with extensive experience.

3 "developmental" categories – D refers to applications in which the experience will not be sufficient to draw final conclusions about the effectiveness of therapy and it is necessary to collect and creatively analyze observations regarding the course of treatment. It is recommended such kind of treatment is carried out as part of clinical studies or in the centres which have JACIE accreditation and are reported to the EBMT Registry providing detailed clinical data (B form).

4 “generally not recommended” categories – NR means that there is no any reason for indications HSCT which is mainly for 2 reasons: when other treatment brings good results according to current data and another is when the disease is advanced and/or the patient’s condition is too risky to perform transplantation.

BMT has been performed for a large number of conditions. The five most frequent ones include CML, Thalassaemia Major, Aplastic Anaemia, Multiple Myeloma and Acute Leukaemia. Development of infrastructure and human resource has lead to more and more patients being given the benefit of this potentially curative mode of therapy.[17]

Common Indications for Hematopoietic Transplantation[18]

A) MALIGNANT

i] Haematological

AML (1st remission; except APML)

ALL (2nd remission)

ALL (1st remission for high risk cases)

CML

CLL (young)

MDS

Non Hodgkin's Lymphoma (relapsed / high risk)

Hodgkin's disease (multiple relapsed)

Multiple Myeloma

ii] Non haematological

Breast Cancer

Neuroblastoma

Testicular Cancer

Ovarian Cancer

Intracranial neoplasm

Lung Cancer

Malignant Melanoma

Renal Cell Carcinoma (metastatic)

B) NON-MALIGNANT GENETIC DISEASE

Thalassaemia major

Severe combined immunodeficiency (SCID)

Sickle cell disease

Kostmann's syndrome

Chronic granulomatous disease

Chediak-Higashi syndrome

Diamond-Blackfan syndrome

Congenital aplastic anemia

Fanconi's anemia

Osteopetrosis

Hurler's syndrome

Lysosomal storage disorders

Wiskott Aldrich Syndrome

C) NONMALIGNANT ACQUIRED DISEASE

Severe Aplastic Anemia

SOURCES OF BONE MARROW TRANSPLANTATION

The main source of HSC until the 1990s was bone marrow, and is still 30% transplantations is done by bone marrow. After 1990s, most of the transplantations are done by peripheral blood of healthy donors and since 2005 this type of donation has been authorised throughout world. At present, about most of transplants are performed using haematopoietic progenitors cells from the peripheral blood.[21]

The major sources for stem cell transpalnatation bone marrow, Peripheral blood stem cells and umbilical cord blood or hematopoietic stem cells.[14]

Bone marrow: Bone marrow is considered to be classical source for hematopoietic stem cell. Stem cell is collected from the posterior iliac crest by administering general anaesthesia. Two physicians and two technicians are required to operate this procedure. The adequacy of the collected bone marrow is determined by the number of nucleated cells. For the successful "engraftments" recommended number of nucleated is 2-4x108 per body weight of recipient. In order to increase increases the amount of stem cell granulocyte colony stimulating factor are administered to the patients. Common problem faced during this process is post-harvest hip pain in donor and sometimes transfusion of red blood cell transfusion is required, It will take approximately 17-20 days time for the proper functioning of marrow in the patient after HSCT of BM.[22,23,25]

Peripheral blood stem cells

Peripheral blood (PB) HSCT is one of the most selected choices as source of stem cell throughout the world. It was firstly introduced in 1992[24]. In this process stem cells are harvested from donated blood of donor which can be own body or any other related patients. At first, stem are collected from donor blood and remaining blood are returned back to the donor. Bloodstream act as main source for stem cell and to obtain PBSCT a process called apheresis or leukapheresis is used. The donor will be prescribed with medication to increase the number of stem cells for 4 or 5 days which will release stem cells into their bloodstream. In apheresis process blood is removed through large vein in the arm of donor or a central venous catheter of donor in which a flexible tube that is placed in a larger vein in neck ,chest or in groin area. The blood from donor will go through the machine which will collect stem cell and will return into donor leaving stem cell into machine which will be infused into patients for transplantation. This entire collection procedure takes about 4 to 6 hours. The collected stem cells are then frozen until they are infused to the patients.[22] For autologous HSCT, stem cells which are collected they will be preserved in cryoprotective agents, then they are thawed and re-infused once preparative regimen has completed by the patients where as in allogeneic HSCT, apheresis process is carried out on the day of transplantation so that the stem cells can be transplanted without the need for cryopreservation.[23]

Cord blood stem cells

Cord blood stem cell is used as the alternate stem cell source from 30 years ago for the first time. In this method stem cells are collected from a mother's placenta immediately after a child is born and also be collected from umbilical cord blood. Blood is retrieved from the umbilical cord and placenta after the baby is born and the umbilical cord has been cut. Various cord blood bank have been established so if the child mother agree then the stem cells are collected and are frozen in cords blood bank for the process for transplantation in other small children and small adult. This stems cell are allogeneic HSCT. About 900 cord blood transplants are performed annually in Europe. In comparison, cord blood units contain fewer hematopoietic stem cells than marrow or PBSC products. Its major advantage is there is low risk of viral contamination to patients and easy accessability.[22,23, 25]

Fugure: sources of stem cells.

SELECTION OF DONOR

Selection of donor depend upon the types of malignancy, availability of suitable donor ,types of malignancy, status of disease, a tumour free autograft and malignancy susceptibility to GVM.

Autologous transplantation

In autologous transplantation it is not necessary to identify an HLA-matched donor as stem cells are collected from patients body, harvested, frozen stored then it is given back into patients body after therapy. In these types of transplantation there is low risk of life threatening complication and GVHD. Patients are not prescribed with immunosuppressant drug for prevention of GVHD and graft rejection. In this there is low risk of opportunistic infection and Immune reconstitution is more rapid than after an allogeneic transplant. However, autologous transplants have several drawbacks. Like chance of relapse in higher and contaminated of autograft with clonogenic may occur.[26]

Allogenic donor selection

Hematopoietic stem cells can be obtained from a variety of sources. a) Monozygotic twins (syngeneic) b) Siblings or other relatives, c) Unrelated persons, and d) Cord blood.

a) Monozygotic twins (syngeneic): when the transplantation is done from monozygotic twins Graft Versus Host Disease (GVHD) does not develop in HSCT and it is not necessary to give any immunosuppressive therapy to the patients. When compared with HLA matched siblings there is high risk of relapse. A monozygotic twin in allogeneic HSCT is consider as the most appropriate donor if there is no any risk of relapse.

b) Siblings and other relatives: in allogenic stem cell transplantation a fully matched sibling is consider to be first choice donor. There is average of 25% of having chance of a person with

fully HLA-matched sibling. When the number of sibling is higher than only the chance of having a fully HLA-matched sibling. Patients can undergo HSCT when a sibling had 1 mismatch if a fully HLA-matched sibling is not observed. A haploidentical transplantation is indicated from a 1st degree relative if sibling have multiple mismatch (8/10, to 5/10).

c) Unrelated transplantation: Unrelated transplantation is carried out when syngenic or sibling transplantation fails but there is high complication risk when unrelated transplantation is done. This condition is usually due to serologically undetectable HLA mismatch. There is high chance of GVHD, recurrence rate and graft failure, increased compared to fully matched siblings.

d) The cord blood: The cord blood is used for hematopoietic precursor cells, although the cell count is less in adult but they have more immature cell where low cytokines are produced. Although engraftment is slower when compared with SCT but risk of the risk of GVHD and transplantation-related mortality are lower. Cord blood with SCT is consider as good alternative to unrelated SCT especially in paediatric age group but shouldn't be consider if there is more than 2 mismatch.[27]

PROCEDURE FOR TRANSPLANTATION

THE TRANSPLANT PROCESS[28,29, 30]

There is a common series of events that all patients undergoing a transplant will perform. These steps include.

- Initial Physician Visit
- Pre-transplant Testing
- Central Line Placement
- Stem Cell Mobilization
- Stem Cell Harvest
- Conditioning
- Stem Cell Reinfusion
- Follow-up Physician Visits

Once you are accepted into the transplant program, please do not take any new medicines, especially ones that affect bone marrow or platelet function (aspirin type drugs), unless you get permission from the transplant team.

Initial Physician Visit

An initial physician visit will determine whether transplantation can be done on candidate. During these visit candidates Candidate past medical records, including radiologic studies (MRI, CT scans, x-rays) are observed by physicians and will undergo detail about history and physical examination and the transplant process, along with potential complications that can occurred due to transplantation and explained to candidates .candidates can any question if he have regarding transplantation to team. In addition, if physicians felt that candidate is eligible for the transplant, candidates will be given the protocol consent form to take home and read.

Pre-Transplant Testing

Physicians will determine various tests that candidates need to undergo to assess the status of disease and to ensure whether candidates are eligible for a hematopoietic stem cell transplant. Protocol consent form need to sign by the candidates prior to start any test by physician or transplantation team.

Central Line Placement

Patients need to have a plastic tube placed into a large vein in upper arm or chest (a central line) during the course of transplantation. Central line is usually placed in the upper arm and has two “lumens” or entry points exiting out of your upper arm (this type of central line is commonly called a PICC line) during autologous or syngeneic hematopoietic stem cell transplants while, the central line is usually placed in your upper chest and has three lumens exiting out of your upper chest during allogenic stem cell transplantation.

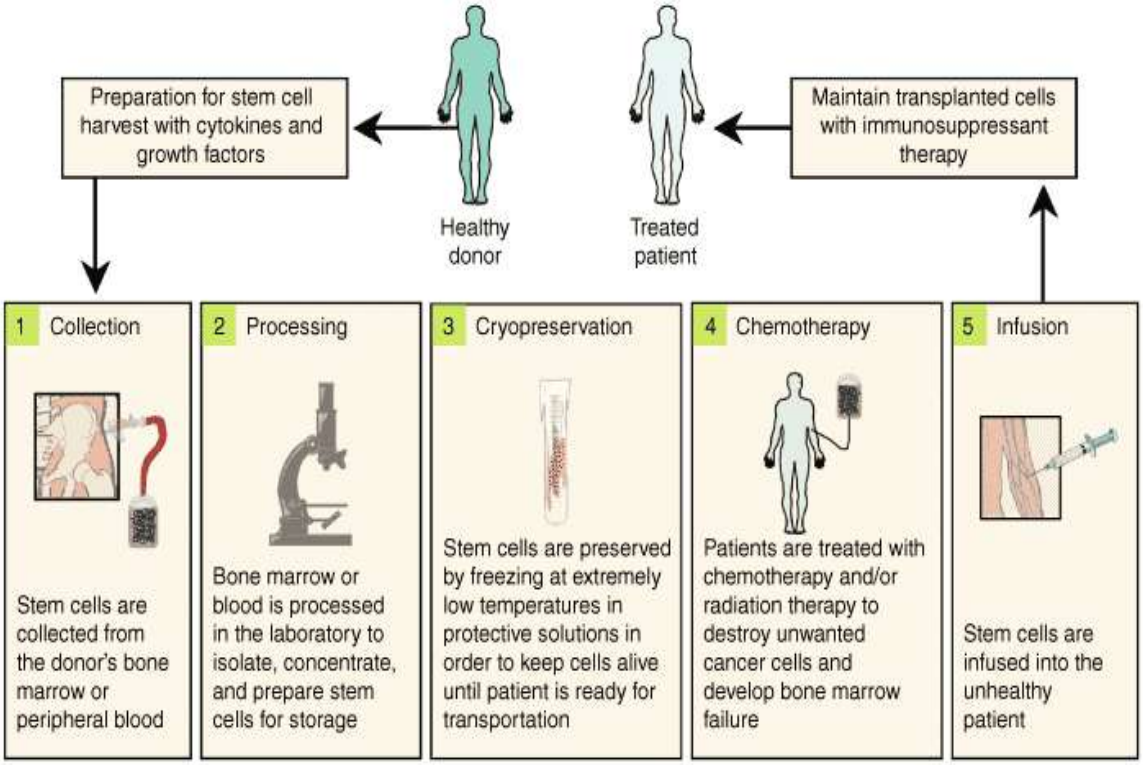
Central lines are placed with the main purpose of circumvent the pain and discomfort of multiple bloods draws that are done during the transplantation process. Along with this, chemotherapy, stems cells, medication, blood products can be regulate through the central lines.

Individuals who are undergoing autologous hematopoietic stem cell transplantation, the central line will generally be placed in the morning of that days when candidate will be admitted are scheduled to be admitted for mobilization chemotherapy. Whereas for syngeneic or allogeneic hematopoietic stem cell transplant, the central line will generally be placed in the morning after candidates are admitted for the transplant. Anyway in both instances, candidates will go home for a period of time with the central catheter, and will be clearly explained and taught how to care for the catheter.

Stem Cell Mobilization

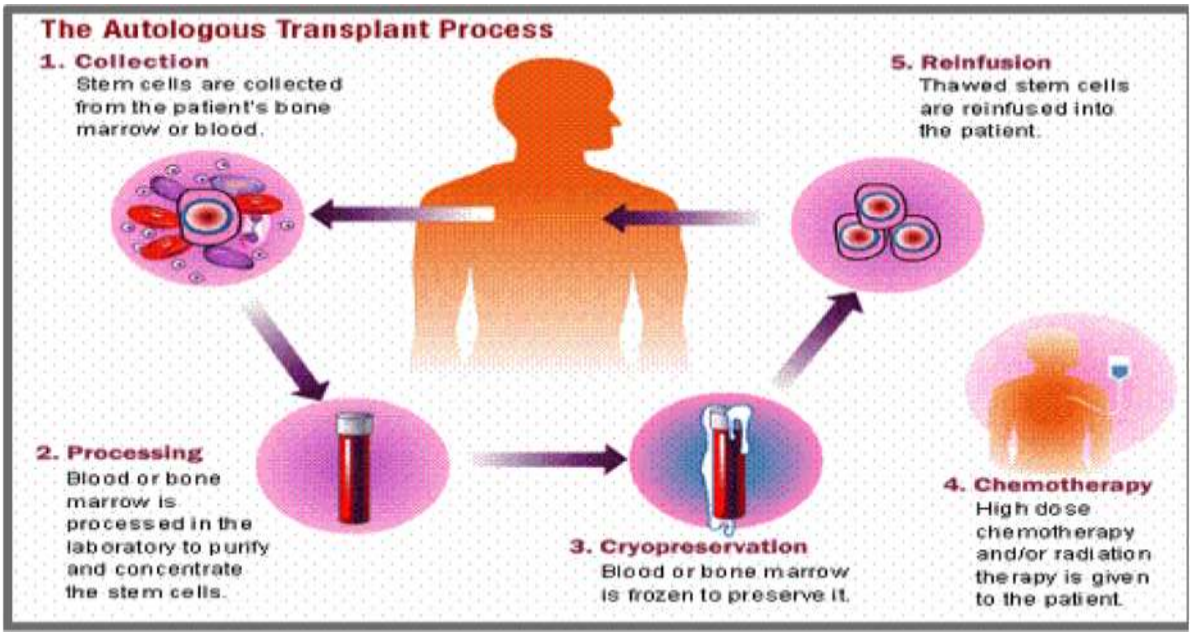
After pre-testing is completed and candidates are cleared for transplant, stem cells will need to be collected from own body (autologous transplant) or another donor (allogeneic or syngeneic transplant).

Allogeneic/Syngeneic Stem Cell Transplant. If patients is undergoing allogeneic or syngeneic hematopoietic stem cell transplant, stem cells will be "mobilized" from donor bone marrow to the peripheral blood and will be collected using growth factor called Neupogen® (GCSF) which is given daily by subcutaneous injection approximately for 3-4 days , then only donors stem cells will be collected (harvested). The stem cell harvest will take 1-5 days depending on how successful the harvest is each day in the donor.



Autologous Stem Cell Transplant

If patients are undergoing autologous hematopoietic stem cell transplant, the patients will be admitted to the hospital to receive their own stem cell, will be mobilized using chemotherapy growth factor called Neupogen® (GCSF).



The main reason for mobilization chemotherapy is to start mobilizing patient's stem cells from the bone marrow to the peripheral blood, so that they can easily be collected from patients' peripheral blood. It may take approximately 10 for stem cell harvest after the administration of mobilization chemotherapy. The type of mobilization chemotherapy that the patients receive depends upon disease specific.

Patients may experience acute side effect of chemotherapy which mainly include nausea, vomiting, anorexia, diarrhoea so patients are prescribed with anti-nausea and anti-diarrheal medications during hospitalization, as well as when they will be discharged which can be long last up to several weeks following its administration. Along with this, patients may experience hair loose approximately 14 days after your mobilization chemotherapy which may take several months after the transplant to growing back.

It will take 24-48 hours for the admission of mobilization chemotherapy then patients will discharged from hospital on transplant centre. To prevent infection, patients will be prescribed oral antibiotics approximately 72 hours after receiving chemotherapy along with antibiotic patients need to take Neupogen® (G-CSF), which is an injection that needs to be taken every morning starting 72 hours after your chemotherapy. The injections will continue until stem cell harvest is completed. Neupogen® is mainly prescribed as they stimulate stem cells to grow and find their way from the bone marrow to your peripheral blood for a successful harvest.

Patients may experience some side effects of the Neupogen® may include

• Flu-like symptoms, including nausea, headache, fever, muscle pain/aches,

• Bone pain, which may be intermediate to severe.

• Generalized rash.

Patients blood count need to monitored several times during the following week which can be done in hospital or in home with eligible for home health care nursing blood counts need to be stable until approximately 7 days following mobilization chemotherapy. At that time, patients' white blood cells will decrease, and for 3 days patients will be neutropenic. It is during this time that patients will be susceptible to infections so it is advised that not come in contact with individuals who are sick. In addition, avoid large crowds.

Stem Cell Harvest

Allogeneic/Syngeneic Stem Cell Transplant.

The stem cells will be harvested from another donor for allogenic or syngeneic hamatopoietic transplantation. After the donor start taking Neupogen® shots stem cell harvest will begin approximately 3-4 days. It will take approximately 4-5 hours each day, for stem cell harvest which will continue on a daily basis until enough stem cells have been collected (approximately 1-5 days). In many instances, donors need to have a VASCATH placed on the morning of the first stem cell harvest. This catheter will be removed when enough Once the stem cells have been collected this catheter will be removed and donor need to take Neupogen® shots until the stem cell harvest is completed.

Autologous Stem Cell Transplant. If patients are undergoing an autologous hematopoietic stem cell transplant, patients will be consider as outpatients then stem cell will be harvest when patients white blood cell count and platelets have recovered or came into normal value, which is approximately takes about 10 days following administration of your mobilization chemotherapy. It is important to remember that Neupogen® should be given prior to coming to your harvest each day, ideally two hours prior to your scheduled visit. Patients will be advised where and what time they need to have blood drawn that morning and ready for the harvesting process.

Stem harvest will feel similar to a blood donation, only that collection time will take longer than blood donation. Each day patients will be hooked up to the machine for approximately 4-5 hours until needed stem cells are collected. Neupogen® shots needs to be continuing until

the stem cell harvest is completed. VASCATH will be removed once enough stem cells have been collected.

The Stem Cell Harvest Procedure

Both donor and receiver will sit in a recliner during the period of harvest. Patients are allowed with their friends or relatives and are allowed to eat and drink during the harvest .procedure that is followed during stem cell harvest is well tolerated. Sometimes patient's report of fatigue, discomfort at the catheter insertion site, and often experience tingling in their extremities and around the mouth due to a drop in their calcium from the harvest. For that patients receive calcium intravenously during the stem cell harvest. At the end of each harvest cells the types and numbers of different cells are calculated which will analysis and determine how many days the harvest will continue. Stem cell collection on each day will be updated to patients and to the donor.

Cryopreservation, a freezing storage technique will be used for the storage of collected stem cells, until the time of re-infusion (transplantation) into the patients.

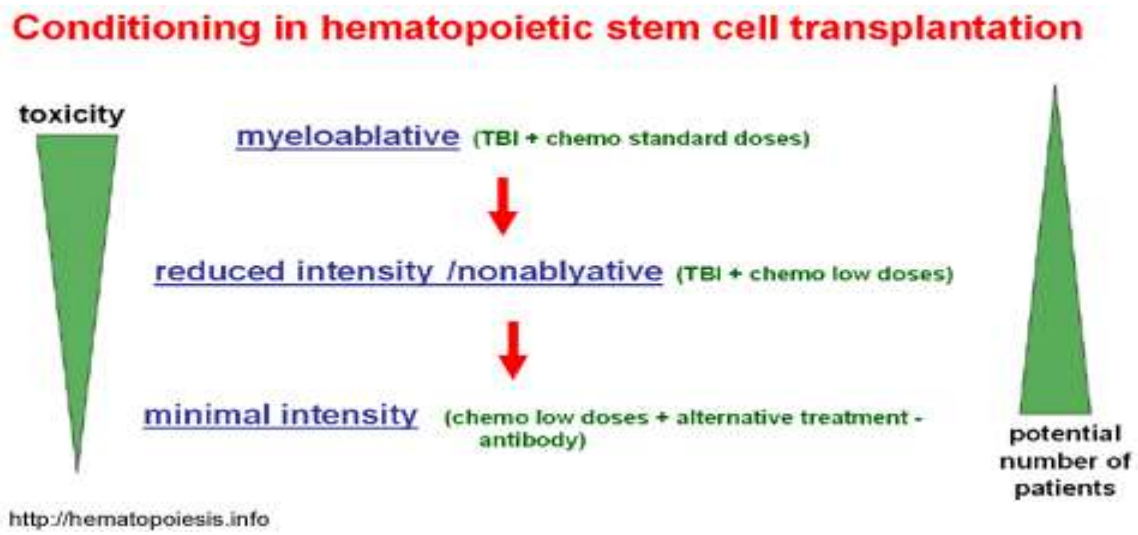
CONDITIONING REGIMEN[29, 31]

Conditioning is the phase during the hematopoietic stem cell transplant in which patients receive a treatment regimen which has been specifically designed to treat their disease. It consists of chemotherapy and, in some instances, medication to suppress your immune system.

Conditioning (preparative) regimens are given with main aim of preparing the space in bone marrow space for the incoming graft, suppressing immunity of to prevent GVHD, and eradicate tumour cells when patients are treated for malignant disease. Normally, the conditioning regimen is given prior to the stem cell infusion for 4-10 days although its selection depends on the disease being treated and the type of HSCT. Conditioning regimens mainly include chemotherapy, radiation therapy, and immunotherapy. Chemotherapy act as backbone of the conditioning regimen and is used for most HSCT. Commonly used agents include busulfan, thiotepa, carboplatin cyclophosphamide, ,cytarabine, melphalan, , cisplatin, and etoposide. Radiation therapy in the form of Total Body Irradiation (TBI) provides immune suppression as well as treatment for sanctuary sites (central nervous system and testes). TBI is usually delivered in fractionated doses twice a day for 4–5 days. If patients

have a history of central nervous system disease than local control radiation therapy may be given before or after transplant.

Immunotherapy agents are used to bind with and destroy recipient circulating T-lymphocytes in an attempt to decrease the risk of non engraftment and GvHD and includes agents such as antithymocyte globulin (ATG) and monoclonal antibodies, such as Campath and CD45 antibody. These agents are usually given once a day for 3–4 days.



STEM CELL REINFUSION[29, 32]

The stem cells and/or bone marrow which were previously collected from patients or patient's donor have been frozen in special blood bags since the collection. Intravenous fluids may or may not be started prior to the procedure as it depends on the number of bags to be infused. Doctor will determine the appropriate amount of cells to be reinfused in the patients. Pre-medication are given to the patients thirty minutes prior to the actual reinfusion by the trained staff nurses in order to prevent complications during the reinfusion, such as an allergic reaction.

During the time of the reinfusion of stem cell, practice nurse (or a specially trained staff nurse) will monitor blood pressure, heart rate, and oxygen level every 15 minutes of the patients by connecting to machine. In addition, temperature and respirations of the patients will be checked every 15 minutes. Once the normal value is determined in patients technologist will bring the collected stem cells and/or bone marrow to room where they will be thawed. Once thawed, the stem cells and/or bone marrow will be infused through your intravenous catheter into the patient's body. This is a painless procedure where the entire

procedure generally lasts 15-30 minutes, which may long last up to 3 hours depending on the number of bags that need to be reinfusion. Patients' vital signs (temperature, respirations, pulse, and blood pressure) will be monitored every 15 minutes during the procedure and for one hour after the completion of the reinfusion.

During the reinfusion process patients may experience side effects which include.

1. Pink- to red-tinged urine for up to 24 hours (this is unlikely if the stem cells and/or bone marrow have gone through a special selection process).
2. Fever
3. Chills
4. Allergic reactions (due to the DMSO used to preserve the stem cells and/or bone marrow after collection). Allergic reactions may include itching, hives, swelling, facial flushing, and shortness of breath
5. Nausea, vomiting, diarrhoea
6. Slow or rapid heart rate
7. Low or high blood pressure
8. Smell of creamed corn or garlic for 1 to 2 days
9. Bitter taste
10. Tickling sensation in your throat during reinfusion

Most patients tolerate the reinfusion process without side effects or problems.

ENGRAFTMENTS AND COMPLICATION

Engraftment distinguish stable growth and circulation of hematopoietic stem cells, once the transplantation is over, this process require adequate immunosuppression of the host, CD34 cells and also donor T cells to prevent graft rejection.[35]

Engraftment can be defined as the process where new marrow on patient's body starts to produce red blood cells, white blood cells and platelets after the reinfusion of stem cells. Rising white blood cell count is the initial sigh of engraftments. Engraftment of the red blood cells and platelets takes longer than the white blood cells. After the stem cell is reinfused, it is important to administration of growth factor (G-CSF) which will helps the bone marrow engraft the new stem cells and start producing blood cells and platelets. Until white cell count is normal growth factor is generally given to the patients.

Approximately after 1 to 3 weeks of the stem cell reinfusion the new stem cell are expected to be engrafting. First sign that determine the engraftment is increasing in white blood cell count whereas it may take 10 days to 4 week for engraftment of red blood cells and platelets. In some patients it may take longer time period for engraftment depending on their disease condition.[33, 34]

As body takes times for body to engraft the new marrow, so in lack of blood cells patients experiences several complications which can be temporary and relatively minor, or they can be life-threatening resulting long-term side effects after HSCT, including non-malignant organ or tissue dysfunction, changes in quality of life, infections and secondary malignancy.[33.34,29]

COMPLICATION

The risk and the type of complications mainly depend on the preparative regimen that is received by the patients prior to HSCT, and also depends upon the age of the patient at time of HSCT, the presence of co-morbid conditions, and the time between the treatment and follow-up.[36]

Various complications include

- Rejection of marrow graft
- Relapse of malignancy
- Conditioning-related toxicity
  - Sinusoidal obstruction syndrome
  - Mucositis
  - Idiopathic pneumonia syndrome
  - Leucoencephalopathy
  - Neuropathy
  - Myopericarditis
  - Hepatitis
- Infection
  - Venous access line infection
  - Bacteremia,
  - Fungemia
  - Pneumonia
    - Viral

- Fungal
- Bacterial
- Pneumocystis jirovecii

➢ GVHD

- Acute
- Chronic

- Idiopathic pneumonia
- Bronchiolitis obliterans

Relapse and rejection

Rejection of donor marrow and relapse of malignancy are the uncommon complication. In the patients with recipients of HLA-identical marrow prepared with total body irradiation (TBI) immune-mediated graft rejection is distinctly uncommon. If HLA disparity or the patients with aplastic anaemia who were not prepared with TBI there is chance or incidence of rises of rejection. Recurrence of malignancy after transplantation is seen in approximately in 20% of patients who undergo transplantation while in early-stage leukaemia (i.e., in a first remission or a chronic phase) and in 50–70% of patients who undergo transplantation while in advanced leukaemia (a relapse or blast crisis) recurrence of malignancy was observed after transplantation.

- **Sinusoidal obstruction syndrome**

Sinusoidal obstruction syndrome (SOS) is a potentially fatal complication of HSCT formerly it was named as venoocclusive disease. Several chemotherapeutic agents, immunosuppressors and many drugs toxin have been associated with as main reason of SOS. SOS result to significant morbidity and mortality. For those patients who undergo transplantation for non malignant conditions without TBI, the incidence of SOS is less 2% whereas non malignant patients with chemotherapy with TBI have incidence of SOS 20-60%. For prophylaxis of and defibrotide as therapy for mild to moderate SOS heparin is used during the transplantation. SOS has mortality rate of 30%.

SOS is clinically characterizes based on patients condition which include weight gain, fluid retention with ascites, tender hepatomegaly and jaundice which can develops by 30 days after HSCT, although it can occur later. SOS mainly occurred due to damage of sinusoidal

endothelial cells and hepatocytes in the zone of the hepatic acinus by toxic metabolites generated during the conditioning regimen.[37]

- **Mucositis**

Incidence of OM lies in between 75% to 100% following myeloablative conditioning regimens and expected as the most painful and debilitating oral complication, affecting of the patients after HSCT. There is high prevalence of oral complication in both autologous and allogeneic HSCT recipients. Mucositis, infections, oral dryness, taste changes, and GVHD in allogeneic HSCT are mostly encountered oral complications after transplantation.

Oral mucositis (OM) can be defined as an inflammation of the oral mucosa and is one of the mostly reported side effects after HSCT. It is clinically characterized by mucosal damage ranging from mild inflammation presenting as erythematous atrophic lesions to extensive ulcerations penetrating the submucosa which is induced by radiation therapy or chemotherapy. In HSCT recipients, mucositis doesn't limit only on oral cavity but may also affect entire orodigestive tract. The mechanisms underpinning the pathobiology of mucositis are thought to be largely the same regardless of the location along this tract.[38]

Idiopathic pneumonia syndrome

Acute pulmonary dysfunction is a frequently fatal complication following hematopoietic stem cell transplantation (HSCT). Previously, idiopathic pneumonia syndrome (IPS) was defined to describe a subset of these patients who have signs and symptoms of pneumonia, and evidence for widespread alveolar injury in the absence of lower respiratory tract infection[39].

Idiopathic pneumonia syndrome (IPS) is termed after the development of pulmonary inflammation and fibrosis after bone marrow transplantation without any known identifiable infectious agents'. IPS is characterized pathologically by the presence of interstitial and alveolar pneumonitis, and interstitial fibrosis, in the absence of an identifiable infectious agent. Interstitial pneumonitis and fibrosis lead to alveolar congestion and decreased lung compliance, which is clinically manifested as hypoxemia, dyspnoea, tachyponea. The exact cellular and molecular mechanisms that give rise to IPS remain an enigma.[40]

Leucoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is caused by the reactivation of the unique JC virus. It is a rare demyelinating disorder of the central nervous system which usually occurs during severe immunosuppression, and the most common causes are

represented by human immunodeficiency virus infection, lymphoproliferative disorders and other forms of cancer. Clinically diagnosis as cerebellar syndrome, reflecting a productive infection of granule cell neurons, meningitis, meningoencephaliti, progressive myoclonic ataxia and muscle wasting associated with extrapyramidal signs.[41]

NEUROPATHY

Neuromuscular diseases such as polymyositis, dermatomyositis, peripheral neuropathy, and disorders of neuromuscular transmission are reported to be complications of hematopoietic stem cell transplantation (HSCT).[42]

Neurological manifestations of HSCT have a major impact on the disease course and the quality of life. The peripheral nervous system is more affected than the central nervous system after HSCT, starting usually several months to years which mainly involve nerve roots, peripheral nerves, neuromuscular junction, or muscles.[43]

HEPATITIS

Liver disease is common after hematopoietic stem cell transplantation leads to various liver complications. Complications mainly include viral hepatitis, fungal liver disease, cholestasis of sepsis, and liver injury.[44]

There is high evidence of occurrence of Hepatitis B (HBV) or Hepatitis C virus (HCV) in patients undergoing allogeneic or autologous stem cell transplantation (HSCT) poses several clinical problems, as these infectious complications can progression hepatic failure and also to possible evolution to chronic active hepatitis and cirrhosis. As patients are prone to becoming infected due to the lack of immune competence given both the haematological disease and the conditioning regimen they receive before HSC.[45]

INFECTION

The major complication that patients developed after HSCT is Bacterial infections. They mainly include bloodstream infections (BSI), which is followed by pneumonia and gastrointestinal infections, including typhlitis and Clostridium difficile infection. 25% of blood stream infection includes Enterobacteriaceae and coagulase negative staphylococci pathogens followed by enterococci, P. aeruginosa and viridans streptococci. After HSCT Bacterial pneumonia is frequent, and Gram-negatives are predominant. 15% of HSCT

recipients will be affected by Clostridium difficile infection, which is mostly observed in case of allogeneic than autologous HSCT.[46]

During HSCT, for the administration of chemotherapy, stem cell infusion, intravenous medication, electrolyte supplements, and nutritional support and blood products a tunnelled Central Venous Catheter (CVC) is usually placed. Once the catheter is placed there shouldn't be loss of permeability of pathways, if there will be loss than it should be treated quickly as it may result to permanent loss of access. Along with this there is high chance of risk of infection due to fibrin formation and adherence of bacteria and fungi worsened by the large number of catheter manipulations, amount of lumens, type of clothing and age of the patient.[47]

Fungal

Fungal infections are major complications after Hematopoietic Stem Cell Transplant (HSCT).Invasive fungal infections (IFIs) in oncology and transplant populations have been associated with significant morbidity and mortality. In addition, invasive aspergillosis (IA) surpassed invasive candidiasis (IC) as the most common IFI encountered in the HSCT population: Aspergillus accounted for 43% of infections and Candida accounted for 28%, followed by other or unspecified moulds including Fusarium and Scedosporium (16%), and finally, Zygomycetes (8%). Pneumocystosis, endemic fungal infections, and cryptococcosis were rarely encountered in the HSCT population.[48]

Viral complication

Viral complications can occur in both allogeneic and autologous recipients. Viral complication can occur but mostly it occurs in allogeneic transplants, although patients are advised with antiviral immunosuppressive drug therapy. Infections exist in the lung, skin, and genitourinary tract and are associated with the presence of indwelling catheters. Historically, viral complication of HSCT was observed by cytomegalovirus (CMV); Mortality rates of CMV pneumonia in HSCT recipients were near 85% before development of anti-viral drug therapy. Although prophylaxis and antiviral therapy was used in patients, CMV disease remains a significant complication of HSCT. HSCT recipients are additionally at risk for infections by other herpesviruses, varicella zoster and herpes simplex virus, as well as community-acquired respiratory viruses, such as influenza. Pseuodomonas aeruginosa and Klebsiella pneumonia represent important gram-negative bacterial infections in HSCT

recipients, and common gram-positive bacterial infections in HSCT populations are Staphylococcus epidermidis, Staphylococcus aureus, and viridians streptococci.[49]

Risks to donors

There are reports of severe even life-threatening adverse events for the donor during HSCT, such as death, vascular events, bleeding due to low blood counts, sore mouth, spleenic rupture, triggering of inflammatory disease, transient respiratory disturbances, acute lung injury or sickle cell crises as well as hematologic malignancies.[50]

Hematopoietic stem cell transplantation (HSCT) leads to developments of long-term complications, such as musculoskeletal disorders, endocrinopathies, cardiopulmonary compromise and subsequent malignancies.[51]

GRAFT VERSUS HOST DISEASE (GVHD)

The common complication that exists during allogenic complication is Graft versus host disease (GVHD) .In autologous hematopoietic stem cell transplant GVHD is not observed.

T-lymphocytes play important role in GVHD which is commonly called as T-cells t-cell comes under white blood cell that helps body in recognizing foreign matter in body mainly from bacteria, viruses, and other unrelated matter in body.

Human leukocyte antigen (HLA) is inherited set of genetic materials which are located on surface of human cells including T-cells .two person will not ha same HLA and protein marker unless they are twins. The t-cell play major role to distinguish foreign particle in our body by using this HLA marker and quickly activate the immune system to destroy it.

A test is done in between patients and donor before patients undergo allogeneic hematopoietic stem cell transplantation, to ensure that they are immunologically (same HLA type) matched. If patients T-cell identify that donor stems cell as foreign substance they will attack the stem cell and destroy stem cell which is called as graft rejection. In order to disrupt the ability of T-cell conditioning regimen is prescribed before transplantation is processed thus preventing graft rejection. Along with this while collecting stem cell from donor T-cells are also collected and infused in patients' body from donor in order to prevent rejection.

If your T-cells identify your donor's stem cells as foreign, or "non-self", they may attack the donated stem cells. This is called graft rejection. Your treatment (conditioning) regimen has

been designed to disrupt the ability of your T-cells to recognize your donor's stem cells as "non-self" thereby preventing graft rejection.[29, 52]

GVHD can be classified into two broad categories as acute GVHD and chronic GVHD. Acute and chronic GVHD differ in their symptoms, clinical signs, and time of onset. You may develop one, both, or neither.

Acute GVHD

Generally after the stem cell reinfusion in patients' body from donor acute GVHD occurs within first 30 to 40 days but sometimes it may occur within a week. Skin, liver, and the gut are mostly affected area by acute GVHD. The earliest clinical presentation of acute GVHD is a skin rash on patients face, hands, and feet that may spread to other parts of the body. Other early symptoms of acute GVHD are nasal stuffiness, congestion, and conjunctivitis (redness of the eyes). Other clinical presentation include abnormalities in liver function blood tests, jaundice (yellowing of the skin and eyes) along with gastrointestinal disorder like nausea , vomiting, heart burn, Watery and bloody diarrhoea, abdominal cramping, lack of appetite, and an inability to eat leading to life- threatening.[29]

Chronic GVHD

Once allogeneic hematopoietic stem cell transplant is processed, it will take around 100 days to develop Chronic GVHD generally although it can occur as early as 50 days. 50-60% of individuals will develop chronic GVHD after allogeneic hematopoietic stem cell transplant acute GVHD leads to development of chronic GVHD have had acute GVHD. If the donor is unrelated or if the stem cells are not perfectly matched or if the donor is unrelated there is more chance of developing chronic GVHD. Patients with chronic GVHD experiences skin problems that include a dry, changing in skin colour itchy rash, and tautness or tightening of the skin. Hair loss may occur. If chronic GVHD of the skin continues to progress, it leads to difficult in moving arms and legs of patients.

Chronic GVHD also can attack glands in the body that secrete mucous, saliva, or other lubricants. Individuals with chronic GVHD usually experience dryness or stinging in their eyes because the glands that secrete tears are impaired. Dryness of mouth, difficult in swallowing, abnormal liver function blood test, diarrhoea, nausea, weight loss, and person will be unable to perform normal daily activities once he is affected by chronic GVHD.[29, 53]