Review: Basics of Stem Cell Transplant
Basics of Stem Cell Transplant
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BACKGROUND

- First successful transplants—late 1960’s
- 30,000-40,000 transplants performed yearly worldwide
- >20,000 patients have survived > 5 years

Introduction:

What is Hematopoietic stem cell transplantation? It refers to the Intravenous infusion of autologous or allogeneic stem cells, from bone marrow, peripheral blood or umbilical cord blood.

What is its function:

Quite simply, it is to re-establish hematopoietic function in patients with damaged/defective bone marrows or immune systems. Due to this it is potentially curative for a wide variety of disorders.

Highlights in Stem Cell Transplant:

- Studies of atomic bomb victims showed that the bone marrow was most sensitive to radiation
- Bone marrow infusion rescued mice from radiation
- Murine and canine models were therefore developed for transplants
- This then led to the discovery that immune response is controlled by genetic factors, i.e. histocompatibility antigens or factors
- Thus, bone marrow from histocompatible animals could rescue those suffering from bone marrow failure due to exposure to lethal radiation.

What are Stem Cells?

The most important thing to remember is that they are:

1. Not characteristic of specific tissues
2. Divide for the lifetime of the organism
3. Can replenish themselves
4. Stem cells act as “seed cells” for the body
5. Stem cells may exist in all organs
6. Serve in injury as a source of repair
7. Serve as a “trust fund” to replace cells as they die off
8. Stem cells may circulate from one tissue reserve to another
**Figure 1: Hematopoietic Stem Cells and differentiation**

**Adult stem cells**
1. Replenish cells lost through age or injury
2. They are the Largest reservoir in the marrow
3. Stem cells circulate in blood
4. “Relocate” to fill empty stem cells lost in other tissues
5. Harvested from bonemarrow or peripheral blood
6. Stem cells can also be isolated from the Skin, brain, prostate and muscle

**Bone marrow transplant**

In a Bone marrow or a stem cell transplant, the graft sources are:
- Allogeneic: from another person
- Syngeneic: from an identical twin
- Autologous: from the patient
- Choice of graft is based on disease type, patient condition, donor compatibility and health of patient

**AUTOLOGOUS TRANSPLANT:**

Autologous transplant can only be performed when there is no evidence of disease in the blood or bone marrow.
- It has the lowest Transplant related mortality (TRM), of all graft sources at (<5%).
• The disadvantage is that relapse rates are higher depending on the disease.
• Also, there is an absence of graft versus tumor effects.

**ALLOGENIC TRANSPLANTS:**

Allogeneic transplants carry a much higher transplant related mortality of (30-50%). This is because patients always develop graft versus host disease –GVHD, due to the body reaction to the infusion of a foreign substance. However, they have lower relapse rates due to graft versus tumor effects.

**They are of three major types:**

1. They can be between **matched related donors** or siblings:
   - 25% chance a sibling will be a match- The more siblings a patient has the better chance for a match
2. If no siblings match or the patient has no siblings, then alternative donors are considered.

   These are known as **Matched unrelated donors (MUD).**

   These transplants can result in Severe GVHD (Graft Versus Host Disease,) which in turn causes higher transplant related mortality.

3. **Haplo identical donors:**

   This is another type of allogenic transplant where the stem cells are obtained from the parent, child or sibling.

   These require a large number of stem cells to overcome risk of graft rejection. Increased risk of GVHD is also present.

   **For successful transplants precise matching between the patient and the donor, or HLA typing is required.**

**HLA typing: (Histocompatibility Locus Antigens):**

• HLA typing became feasible in the 1960s
• They are Linked on chromosome 6
• Inherited as haplotypes
• 1 in 4 chance a sibling will be identical

**HLA matching refers to a match between Donor and Patient:**

• 6/6, 8/8, or 10/10 match.
  - HLA loci is on chromosome 6
- HLA-A, HLA-B, HLA-C, HLA-DR, HLA-DQ, HLA-DP are the various HLA TYPES
  
- ABO incompatibility is not an exclusion

**HLA and Marrow Transplantation:**

- Histocompatibility locus antigens (HLA) are determinants of immunologic “self”.
- They form the Immunologic “password”.
- They allow for an effective immune response against infections and cancer
- T cell reaction to foreign HLA molecules, that is, those from the donor is a major problem of transplantation, this is called alloreactivity. Therefore, good donor and recipient matching for HLA sites is needed. HLA incompatibility causes acute rejection in organ transplant, it is also responsible for GVHD in allogenic transplants.

**HLA typing in transplants:**

- Family members typed with patient for HLA A, B and DR
  - Likelihood of 6/6 or 5/6 match depends on frequency of recipient HLA haplo type
- Likelihood of unrelated donor match related to haplotype frequency in general population
- Some HLA combinations more frequently found among ethnic groups

**Eligibility For Transplants:**

- Age < 65 for Autologous transplants
- Age < 55 for Myeloablative allogeneic transplants
- Exclusions: Congestive Heart Failure, uncontrolled diabetes mellitus, active infections, renal insufficiency

**Indications For Autologous Transplant:**

- Multiple myeloma
- NHL - Non Hodgkins Lymphoma
- Hodgkin’s disease
- AML - Acute Myeloid Leukemia
- Neuroblastoma
- Germ-cell tumors
- Auto immune disorders
- Amyloidosis

**Non Hodgkins Lymphoma:**

- Presents with generalized lymphadenopathy, low grade fever, anorexia and
weight loss.
- Often misdiagnosed and treated as Koch’s when it presents with cervical lymphadenopathy.
- Following first line chemotherapy, in case of relapse, a transplant in second line setting can be curative.
- Lymphomas can be cured even in stages 3 and 4 if treated correctly.
- Current regiments allow for treatment of pts of any age.

**Hodgkin's Lymphoma:**
- Presentation similar to Non Hodgkin's Lymphoma
- Young pts often present with a mediastinal mass
- Germ cell tumor is closest differential in those with a mediastinal mass.
- Relapsed & refractory Hodgkin's can be cured with a transplant.

**Germ Cell Tumors:**
- Two types - Seminomas and Nonseminomas
- Relapsed Germ Cell Tumors can be salvaged with a transplant, such patients may become long term survivors
- Transplant can be offered to stage 4 disease pts as well
- However, mediastinal tumors carry a poor prognosis and fall in a high risk category.
- Relapsed and refractory mediastinal germ cell tumor patients have a less than 10% chance of long term survival post transplant.

**Multiple Myeloma:**
- Patient will present with fatigue, backache & anaemia, usually followed by sudden development of Acute Renal Failure
- Myeloma is not curable but with correct treatment can become a chronic illness which can be well controlled.
- Average life span is 10 yrs in those with reversible renal dysfunction.

**Fig. 2: Plasma Cells in Myeloma:**

![Image of Plasma Cells in Myeloma]
Figure 3: Serum Protein Electrophoresis:

- Transplant is an option for patients in remission as second line therapy
- More often used now a days in refractory cases
- Myeloma cannot be cured with current therapies including transplant, but it can be controlled.
- Investigations for myeloma must include a  Serum and Urine Electrophoresis and Immunofixation.
- Light chain disease can only be detected on urine immunofixation.
- Bone scans is not recommended in myeloma workup, as it can precipitate Acute Renal Failure.

**Indications For Allogeneic Transplant:**

- AML- Acute Myeloid Leukemia
- ALL- Acute Lymphoblastic Leukemia
- CML- Chronic Myeloid Leukemia
- MDS- Myelodysplastic Syndrome
- MPD- Myeloproliferative Disorders
- NHL- Non Hodgkins Lymphoma
- Hodgkin’s Disease
- CLL- Chronic Lymphocytic Leukemia
- Multiple myeloma
- Juvenile Chronic Myeloid Leukemia
- Aplastic Anemia
- PNH-Paroxysmal Nocturnal Hemoglobinurea
- Fanconi’s Anemia
  - Blackfan-Diamond Syndrome
- Thalessemia Major
- Sickle Cell Anemia
  - SCID- Subacute Combined
- Immunodeficiency
- Wiskott-Aldrich Syndrome
- Inborn Errors of Metabolism

**Transplant is a curative and the only option in:**

- Aplastic Anemia
- Thalassemia Major
- Sickle cell anaemia
• All thalassemia and sickle cell patients must undergo curative Allogenic transplant by 2-3 years of age.
• Waiting till an older age predisposes to development of hepatic hemosiderosis.
• Such patients can lead a normal life post transplant.

In **AML And ALL:**
• Transplant is the only option available in those with complex chromosomal changes.
• Indicated in all relapsed patients.
• Can treat the leukemia and provide long term survival.
• Can prove life saving in refractory cases.

**Fig. 4:** *Acute Myeloid Leukemia: Bone marrow picture*

![image](image1.png)

**Fig. 5:** *Acute Lymphoid Leukemia: Proliferation seen in bone marrow*

![image](image2.png)
• Refractory backache may be an early sign of leukemia.
• CBC with peripheral smear examination should be done as a routine investigation in all pts.
• A large no of asymptomatic leukemias can be picked up in the initial stages.

**Interesting Case:**
• 40 year old lady, living in Chicago, no comorbidities.
• Presented with backache in July 2011
• Received symptomatic treatment with no relief.
• MRI spine done was normal.
• Received repeated pulses of steroids for the pain.
• Had short term relief each time.
• Given Methyl Prednisolone epidural injection for pain.
• Came to India for treatment
• On examination was pale, in severe pain and very weak.
• I asked for a CBC with a peripheral smear(PS) examination which showed:
  • HB-3GM%, TLC-60000, PLT-8000
  • Ps showed 80% blasts
• Diagnosis-Acute Lymphoblastic Leukemia
• Patient had not had a CBC done in 6 months of treatment.

**TAKE HOME MESSAGE:**
• Always ask for a CBC with peripheral smear examination.
• Leukemia scan present with low grade backache, gum pain, sore throat etc.
• Tingling pain in teeth and gums could mask an underlying leukemia.
• Look for hepatosplenomegaly and lymphadenopathy in such patients.

**Harvesting Stem Cells:**
• Adult stem cells are obtained by large volume marrow aspiration(1-2L).
• Cord blood stem cells are obtained at delivery by sterile emptying of umbilical cord and placenta into blood donation bag
• Stem cells are increasingly being obtained by processing of peripheral blood of patients and healthy donors. They are Isolated in “real time” from blood after
• Stimulation with white blood cell growth factors
• Stem cells can be frozen for up to 5-10 years

STEM CELL HARVESTING FROM PERIPHERAL BLOOD:

Fig. 6: Harvesting Stem Cells from Peripheral blood

Stem cells are increasingly being obtained by processing of peripheral blood of patients and healthy donors. They are isolated in “real time” from blood after stimulation with white blood cell growth factors.

Fig. 7: Stemcell collection bags

After Infusion:
• Stem cells are infused intravenously through a large bore, central venous catheter.
  – They “Home” to micro-environment niches in marrow and spleen
• This is by Recognition of arrays of adhesive and growth factors in the marrow stroma

Collection of Stem Cells: From Bone Marrow:

1) Bone marrow harvesting:
– Performed under General anesthesia. It is the equivalent of 50-100 bone marrow biopsies.
– It is a method used much less often nowadays.
– 2 deaths in 8000 collections, it is a safe procedure

Bone marrow harvesting: Performed under General anesthesia. It is the equivalent of 50-100 bone marrow biopsies.
The Posterior Iliac Crests are common sites for bone marrow aspiration and biopsy

Fig. 8: Sites of Stem cell collection
a) Bone marrow in Posteroid iliac crests  

b) Harvesting bone marrow site

Collection of Stem Cells from Peripheral Blood:

Stem cell collection(mobilization):

- Stem cells circulate in the blood. They are identified by CD34+ Cells, detected by flow cytometry
- Filgrastim and sargramostim growth factors are used to mobilize the stem cells from the marrow, into the peripheral blood in large numbers.
- Stem cells are collected through an apheresis catheter.
- More cells are collected than obtained in a bone marrow harvest.
- Therefore, there is a higher incidence of chronic GVHD
- More rapid marrow recovery than that seen in stem cells obtained from the bone marrow.

Fig. 9: Sterile technique and stem cell infusion

Stem Cell Cryopreservation:

Infusion Of Stem Cells:
• Stem cells may be infused fresh within a few hours of collection—this is usually done in Allogenic transplants

• May be frozen or cryopreserved, for future use, using DMSO (DIMETHYL SULFOXIDE), a cryopreservative. It has a creamed corn or garlic smell. This procedure is followed in Autologous and Cord blood transplants.

• Umbilical cord blood is obtained from the umbilical cord following delivery of the baby. It is collected and then frozen with an anticoagulant and Nutrient media.

### Stem Cell Infusion:

#### Stem Cell Manipulation:

**This is done in various ways depending on type of transplant.**

• If the patient and donor are ABO incompatible, then removal of isoagglutins from donors RBCs is carried out.

• T-cell depletion can be performed in allogenic transplants, of donor stem cells, to reduce incidence of GVHD, but this increases risk of graft failure and results in increased relapse rates.

• In vitro purging of patient’s stem cells can be done, for removal of tumor cells and for positive selection of CD34+ cells.

#### Preparation For BMT:

• Immunosuppression and myeloablation required in case of the patient, pre-transplant.
  
  – Bone marrow failure states require more immune suppression, eg. Aplastic Anaemia.

  – Immuno-deficiency without empty marrow leads to rejection.

• Chemotherapy induces aplasia to allow engraftment, always given to prepare patient for transplant.

• Additional merits of marrow ablation:
  
  – Provides marrow “space”
  
  – Eradicates malignant cells
  
  – Reset of the recipient immune system

Preparative or Chemotherapy regimens before transplant provide aplasia and immune suppression.
**Preparative Regimens: Are of various types:**

- **Myeloablative:**
  - High doses of chemotherapy or radiation are given to eradicate the marrow.
  - There are 3 goals:
    - Eliminate malignancy
    - Immuno suppression to allow engraftment
    - Decrease graft versus host effects

**Myeloablative Regimens:**

- Most common regimens:
  - Cyclophosphamide/TBI (Total Body Irradiation)
  - Busulfan/Cyclophosphamide
  - Stem cells are essential to restore marrow function, this is provided by the transplant.
  - Therapy is based on disease
  - Other drugs used are Etoposide, BCNU, Cytarabine, Melphalan
  - Graft versus leukemia effects in allogeneic donors are important to cure leukemia, when leukemic patients undergo transplants.

**Non Myeloablative:**

- Non myeloablative regimens are used in Mini-allogenic transplants.
  - They provide sufficient immune suppression to allow donor cell engraftment, while injury to organs is less, there are fewer infections and fewer transfusions are needed as marrow is not fully eradicated.
  - Disadvantage is that there are higher relapse rates.
  - Patients have mixed chimerism, ie. A mixture of donor and recipient cells for awhile, till donor cells can take over the recipient marrow completely.
  - Graft versus tumor effects occur, this is essential to eradicate the malignancy.

**Nonmyeloablative Stem Cell Transplants:**

- Here the host/donor marrow chimerism prominent. Early studies show efficacy in CML in patients upto 75yrs. A low level of GVHD is seen initially, until complete donor stem cells take over the recipient marrow. Following this, the GVHD increases.

**Donor T-cells eradicate the host’s malignant cells**
Non-myeloablative Regimens:

Non myeloablative Regimens are usually fludarabine based, they are combined with other drugs like Busulfan, Cyclophosphamide, Melphalan and Anti-Thymocyte Globulin.

- These regimens are better for slow growing cancers like CLL and NHL.
- The graft itself eradicates the cancer not the chemotherapy, which provides the immunosuppression.
- There are higher relapse rates associated with this type of transplant.

Non-Myeloablative Conditioning:

- Alternative to conventional myeloablative regimens.
- Used in older patients or patients with comorbid conditions.
- Therapeutic graft versus tumor effect is mediated by allogeneic T-cells from donor.
  - Donor T-cells eradicate the host’s malignant cells.

Reduced Intensity Conditioning Regimens:

Advantages:

- Reduction in mortality
- Reduction in non-relapse mortality
- Reduced Packed RBC and platelet transfusions
- Duration of neutropenia reduced
- Reduced incidence of infection
- Able to give to heavily pretreated patients, unfit for more aggressive transplants
In Case Of Rejection:

- Donor Lymphocyte Infusions (DLI) are used as treatment, to try and enable re-engraftment.
- T cells and NK cells from the donor lymphocyte infusion provide additional anticancer effects
- This also helps in preventing relapse or in eliminating active disease
- Used in relapsed or refractory CML and Multiple Myeloma

**Umbilical Cord Blood Transplants (UCB):**

- 1st UCB transplant was performed 16 years ago, in a child with Fanconi’s anemia.
- In these transplants, cell dose is given as per recipient weight, eg. 2x10^7 nucleated cells/kg,
  - 1.7x10^7 CD34+ cells/kg.
- 4/6 matched UCB with sufficient cells has a similar outcome to a matched or one Antigen mismatched Myeloablative Unrelated Donor Transplant.

**Umbilical Cord Blood Transplants:**

- Umbilical Cord Blood is cryopreserved at the time of delivery.
  - It contains a very small number of stem cells.
  - Higher incidence of engraftment failure is therefore common.
- Using more than one unit in adults reduces this risk of graft failure by providing more stem cells.
  - There is a lower risk of GVHD due to lack of T-cells in the umbilical cord blood.
  - Degree of matching does not have to be as stringent as a stem cell or bone marrow transplant.

**Pros of Placental and Cord blood transplants:**

- Lifesaver when there is no eligible donor
- Available quickly (about 2 weeks)
- Unlikely to harbor cytomegalovirus

**Cons of placental and cord blood transplants:**

- 1/10th the number of cells available compared to bone marrow transplant
- Longer time for the transplants to “take”
- Slight chance of maternal cell/ genetic disease contamination
- Adults need more than one cord blood donor

● Lower GVHD
● Transplant related mortality is similar to a Matched Unrelated Donor Transplant.
● Can be used with myeloablative or nonmyeloablative conditioning.

**Haploidentical Transplants:**

Parent, sibling or child can be the donor, donors are only 50% HLA Matched to the recipients.

High rate of engraftment failure is seen.

GVHD and high risk of infections make this a very high risk procedure.

**Hematopoietic Reconstitution Post Transplant:**

Bone marrow cellularity is decreased for months post transplant.

● Immunologic reconstruction usually occurs over 100 days post transplant
  – Graft-vs.-host disease (GVHD) delays immune reconstitution

● Immune deficits expected involve T cell and B cell dysfunction.
  – Low Ig (Immunoglobulin) levels for three months, normal IgG and Ig M by one year, IgA by two years.

● This predisposes to fungal, viral and bacterial infections.

**Transplantation Immunology:**

● In solid organ transplantation, the main relevant immunologic process is graft rejection.

● In marrow transplantation, a novel immunologic condition arises due to the immunologic competence of the graft itself.

**Complications Of Transplants:**

**Early:**

1) Mucositis
2) Sinusoidal obstructive syndrome (VOD)
3) Fluidretention, jaundice, hepatomegaly
4) Transplant related infections
5) Damagetmouth, gut and skin
6) Prolonged neutropenia and pancytopenia

**Graft-Versus Malignancy Effect:**

This results in a lower incidence of leukemic relapse in patients who get acute or chronic GVHD
7) Acute and Chronic Graft Versus Host Disease

**Supportive care is needed with:**
- Packed RBC and platelet transfusions till marrow recovery
- Broad spectrum antimicrobials in case of fever and infection, till neutropenia resolves
- Antifungals if prolonged fevers lasting over 3-5 days

**Pathophysiology Of GVHD**
- Essential factors necessary for GVHD to occur:
  - Immunologically competent donor graft
  - Histoincompatibility between donor and host
  - Immunologically incompetent host

**Graft-Versus Malignancy Effect:**
- This results in a lower incidence of leu-kemic relapse in patients who get acute or chronic GVHD.
  Higher relapse rates are seen in syngeneic (transplant between identical twins) vs. allogeneic BMT, due to absence of this effect.
- Absence of this effect also causes higher relapse rates in T cell depleted transplants.

**Other Complications:**
- Early Graft Rejection can occur
- Drug injury to marrow can result from the conditioning regimens
- Viral infections can occur like CMV (Cytomegalovirus), HHV-6 & 8 (Herpes Virus)
  - Interstitial Pneumonitis
- Diffuse alveolar hemorrhage
- ARDS (Acute Respiratory Distress Syndrome) is often caused by CMV

**Delayed Complications:**
- Chronic GVHD
- Scleroderma, Sjogrens Syndrome
- Bronchiolitis
- Keratoconjunctivitis
- Malabsorption
- Cholestasis
Esophageal stricture

**LongTerm Complications:**

- Infection risk prolonged with persistent acute or chronic GVHD
- Infertility (Women >> men)
- Hypothyroidism 15-25%; seen more often when Total Body Irradiation is used for conditioning (TBI)
- Cataracts, seen with use of TBI and steroids
- Avascular necrosis of bone when high dose steroids are used
- Autoimmune dysfunction can occur due to chronic GVHD
- Dental complications like dry mouth, caries occur due to GVHD and use of TBI
- Malignancy risk is increased, like Post Transplant Lymphoproliferative Disorder, Non hematologic cancer risks from use of conditioning regimens using TBI and High Dose Cyclophosphamide
- Secondary Tumors like Acute Leukemias, Solid Tumors, Myelodysplastic Syndromes can occur months to years after transplant
- Late Infections - Bacterial, viral, fungal can be seen months after transplant, these are commonly associated with active GVHD

  - Transplant patients need repeat vaccinations post marrow recovery, with Hepatitis B, Hemophilus Influenza, Polio virus, Diphtheria/Tetanus.

**Take Home Message:**

- Chemo therapy today is safe, painless and effective if correctly given.
- Transplants are life saving in a number of cancers if pts are provided with this option at an appropriate time.
- Facilities in India are as effective as those abroad.
- A number of malignancies can be detected early with good clinical examination.
- Many can now be treated with oral therapy.
- Stage 4 cancer patients can expect 4-5 yrs of good quality life with correct treatment. Eg. Breast, Lung and Ovarian cancer patients.
- Main intervention is immune suppression
  Safety and side effect profile is improving for stem cell transplants
- Transplants can be considered in patients with severe Autoimmune Disease when it is:
- A Life-threatening disease
  Disease of major morbidity like diffuse Scleroderma
- When disease is unresponsive to standard therapy like Systemic Lupus Erythematosus
- In progressive or relapsed Multiple Sclerosis

**New Directions:**

Stem cell transplantation can be used as a platform for directed therapies like:
- Dendritic cell/NK cell immune therapy
- Vehicle for cancer vaccine delivery
- Use of specifically generated cytotoxic T cell lymphocyte responses
  These therapies can then be used against malignancy and against infection.

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**Stem Cell Uses:**

![Figure 11: Potential uses of Stem Cell](image)

At present stem cells are an accepted form of treatment only in bone marrow disorders.

- All other forms of stem cell treatment are currently experimental.

**Developing Applications Of Stem Cells:**

- Induction of solid organ graft tolerance, In living donor solid organ transplants of
liver and kidney

- Pancreatic islet cell transplants (still experimental)

Transplanted marrow lymphocytes tolerate patient and recognize transplanted organ as “self”. This helps in induction of tolerance and avoidance of rejection.

**Developing Applications Of Stem Cells In Heart Disease:**

- Heart muscle damaged by coronary heart disease or viral injury can be treated by injection of stem cells into the area of the dead heart muscle, this regenerates viable muscle. The injection of stem cells promotes formation of new blood vessels in the injured heart muscle. Further trials are ongoing, to see if intracoronary or intravenous purified stem cell populations can be given during cardiac catheterization.

**Conclusions:**

- Stem cells can be derived from adult, cord blood and eventually embryonic stem cells
- Stem cell transplantation can both support highly intensive chemotherapy and promote highly effective immune therapy
- Recent advances in stem cell transplantation allow therapy more tailored to disease and patient
- Improved supportive care measures expand transplant to more patients
- Expanded applications capitalizing on stem cell plasticity are feasible

**Personal experience:**

- Worked in Jaslok Hospital for 6 years in Medical Oncology and Stem Cell Transplants.
- The only major transplant centre in Mumbai at that time.
- Performed over 150 transplants during this period.
- Success rate greater than 85%.

**International Experience:**

- Worked as a visiting transplant physician and member of the faculty at the Seattle Cancer Care Alliance.
- The largest and first bone marrow and stem cell transplant in the world.
- Worked with the leading transplant physicians of the world.
- Performed over 50 bone marrow and stem cell transplants.
- Specially trained in unrelated donor, umbilical, mismatched and haploidentical transplants.
\textbf{Indian Bone Marrow Registry:}

- Located in Tata Memorial Hospital
- Connected to various international registries
- Source of stem cells for pts without sibling matches
- Bone marrow donors are desperately needed to increase the possibility of obtaining a match.

\textbf{BIBLIOGRAPHY:}