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HEMATOPOIETIC STEM CELL TRANSPLANTATION: A CORNERSTONE THERAPY FOR BONE MARROW CANCERS

Galaba Yamini Padmasri*[1], Dr. B. Thangabalan[2], Chiruvolulanka Dharmik Ram Teja[3], Sapna Pathak[3], Subhadeep Pratihar[3], Shohida Khatun[3], Pusunuri Pranitha[3], Varshitha Asukolla[3]

[1]*Assistant Professor, SIMS College of Pharmacy.*

[2] *Principal, SIMS College of Pharmacy.*

[3] *Student, SIMS College of Pharmacy.*

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***Corresponding Author: Galaba Yamini Padmasri**
Assistant Professor, SIMS College of Pharmacy.
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ABSTRACT:

Bone marrow cancers involve a mixed group of tumors that are mainly a hematopoietic system problem leading to blood cells production, differentiation, and functioning in a way that is not normal. These cancers consist of leukemia, lymphoma, multiple myeloma, myelodysplastic syndromes, and myeloproliferative disorders, and they are all characterized by the same bad effects on health and life expectancy. Among the different therapeutic approaches to treating these malignancies, the infusion of healthy hematopoietic stem cells known as Hematopoietic Stem Cell Transplantation (HSCT) is considered to be one of the most effective and possibly curative methods. The purpose of this review paper is to present the role of HSCT in bone marrow cancer in a very detailed manner, discussing the classification and pathophysiology of bone marrow tumours, the biological properties of stem cells, and the various methods of transplantation, autologous, allogeneic, and syngeneic HSCT being the main ones. Also, the different types of stem cell sources are explained so that readers can know the characteristics of bone marrow, peripheral blood, and umbilical cord blood as well as their pros and cons. Furthermore, the indications for HSCT, the selection of patients, the conditioning regimens, the transplantation procedures, and post-transplant care are described in detail. Hematopoietic stem cell transplantation (HSCT) is a powerful but complicated treatment option for such patients with significant issues like graft-versus-host disease, severe infections, toxicity to organs, relapse, and long-lasting quality-of-life problems. These issues put a spotlight on the importance of performing thorough patient

evaluation, selecting the right donor, and then providing the best supportive care available. The recent developments in the field of transplantation, such as better HLA matching, reduced-intensity conditioning regimens, mobilization of peripheral blood stem cells using granulocyte colony-stimulating factor, ex vivo stem cell expansion, and using umbilical cord blood as an alternative stem cell source, have all made a huge difference in the outcome of transplants. In addition, emerging molecular and cellular techniques that target tumor cells through purging and immunomodulation make it safer and more effective to use HSCT for patients. In conclusion, HSCT still is a fundamental treatment for bone marrow cancers, as it offers not only a higher chance of survival but also disease control in the long run for selected patients. Research that is continuous and the development of technologies that are advanced are still at refining the methods of transplantation, reducing the complications, and increasing the use of HSCT, which is why it is still a vital part of modern hematologic oncology.

KEYWORDS: Hematopoietic stem cells, Bone marrow cancer, Stem cell transplantation, Leukaemia, Lymphoma, Multiple myeloma.

INTRODUCTION

Bone marrow is a vital hematopoietic organ responsible for the continuous production of red blood cells, white blood cells, and platelets. Bone marrow cancers arise due to uncontrolled proliferation of abnormal blood-forming cells, leading to impaired immune function, anemia, bleeding disorders, and increased susceptibility to infections. Conventional treatment options such as chemotherapy and radiotherapy may destroy malignant cells but also damage normal bone marrow. Hematopoietic Stem Cell Transplantation (HSCT) provides an effective therapeutic strategy by replacing damaged or cancerous bone marrow with healthy stem cells. HSCT has become a standard treatment for several hematological malignancies and inherited blood disorders. Even though autoHCT and alloHCT have been proven to work well, they can only be used for certain patients who are considered "fit." Even with careful selection and improvements in the treatment process, these procedures still carry a high risk of serious complications and deaths. Also, many patients end up having their disease come back after undergoing HCT. Because of these challenges, there is a clear need for new, more effective, and less harmful treatment options. Over the past 20 years, there have been major breakthroughs in creating new therapies for various types of blood cancers.

Hematopoietic stem cell transplant, also known as a bone marrow transplant, is a treatment where healthy hematopoietic stem cells are given to patients whose bone marrow isn't working properly or has been damaged. This procedure offers several advantages. It can help restore the function of the bone marrow. Additionally, depending on the condition being treated, it may help eliminate harmful cancer cells. It can also produce working cells that take the place of faulty ones in conditions such as immune deficiency disorders, hemoglobinopathies, and other similar diseases.

HEMAPOIETIC STEM CELL (HSC)

Hematopoietic stem cells (HSCs) are versatile cells that can renew themselves and develop into all types of blood cells, such as red blood cells, white blood cells, and platelets. These cells are usually recognized by specific markers on their surface like CD3,4 and can be found in:

- Bone marrow
- Peripheral blood (after being mobilized)
- Umbilical cord blood

TYPES OF BONE MARROW

Bone marrow is a soft, sponge-like material inside bones and plays a key role in making blood cells.

It comes in two main forms:

1. **Red bone marrow**: This type is active in producing blood cells and is mainly found in flat bones and long bones in children and adults.
2. **Yellow bone marrow**: This type contains a lot of fat and can change back into red bone marrow if needed.

HISTORY AND EVOLUTION:

Hematopoietic stem cell transplantation (HPSCT) was first tested in humans in the 1950s. This idea came from studies done in mice, which showed that giving healthy bone marrow cells to a mouse with a weakened bone marrow could help restore its function. These studies soon led to the first successful human bone marrow transplant in 1957 in New York, where it was used to treat acute leukemia in identical twins. The doctor who did this, E. Donnell Thomas[1], continued to research bone marrow transplants and later won the Nobel Prize for Physiology and Medicine for his work. The first successful allogeneic bone marrow transplant was done in 1968 in Minnesota for a child with severe combined immunodeficiency syndrome. Since then, both allogeneic and autologous stem cell transplants have become more common in the United States and around the world. According to the Center for International Blood and Marrow Transplant Research (CIBMTR), more than 8,000 allogeneic transplants were done in the US in 2016, and there were even more autologous transplants. Over time, the number of autologous transplants has consistently been higher than allogeneic ones.

TYPES OF HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT):

There are mainly three types of HSCT:

1. **Based On Donor Type**

a) **Autologous Stem Cell Transplantation**: The patient's own stem cells are collected, stored, and then given back to them after they receive high-dose chemotherapy. No risk of graft-versus-host disease (GVHD).

Commonly used in Multiple myeloma, Lymphomas, Solid tumors (selected cases)

Advantages: Lower complications, faster recovery

Disadvantages: Risk of reinfusing malignant cells

b) **Allogeneic HSCT**: Stem cells are collected from a donor, who can be a relative or someone unrelated, as long as their tissue type matches the patient's. It Offers graft-versus-tumor effect. Risk of GVHD is present.

Indications: Leukemias
Myelodysplastic syndromes
Aplastic anemia
Inherited blood disorders

c) **Syngeneic HSCT**: Stem cells are taken from an identical twin. No GVHD and minimal rejection. Rare due to limited availability.

d) **Haploidentical Stem Cell Transplantation Donor** is a partially matched family member (usually parent or sibling). Increasingly used due to donor availability. Requires intensive immunosuppression.

2. **Based on Source of Stem Cells**

a) **Bone Marrow Transplantation (BMT)**: Stem cells collected directly from bone marrow. Lower chronic GVHD risk.

b) **Peripheral Blood Stem Cell Transplantation (PBSCT):** Stem Cell mobilized into blood and collected by apheresis. Faster engraftment**.**

c) **Umbilical Cord Blood Transplantation:** Stem cells obtained from umbilical cord blood. Less stringent HLA matching required. Slower engraftment.

3. Based on Conditioning Regimen

a) **Myeloablative Transplantation:** High-dose chemotherapy ± radiation. Completely destroys bone marrow.

2. Reduced-Intensity Conditioning (RIC) / Mini-Transplant: Lower doses of chemotherapy. Suitable for elderly or fragile patients

TYPES OF BONE MARROW CANCERS:

Bone marrow cancers are malignancies that originate in the bone marrow or primarily affect bone marrow–derived cells. The main types of bone marrow cancer are:

1. **Leukemias**: These are cancers that impact the blood-forming cells in the bone marrow, causing the body to make unhealthy blood cells. There are different types, such as

- AML (Acute Myeloid Leukemia)
- ALL (Acute Lymphoblastic Leukemia)
- CML (Chronic Myeloid Leukemia)
- CML (Chronic Myelogenous Leukemia)

2. Lymphomas: These cancers begin in the cells of the immune system and often affect the lymph nodes and other tissues. The main types are

- Hodgkin's Lymphoma
- Non-Hodgkin's Lymphoma

3. Multiple Myeloma: This is a type of cancer that affects plasma cells in the bone marrow. It can cause bone damage, anemia, and problems with the kidney

4. Aplastic Anemia*: This is a rare condition where the bone marrow stops producing enough blood cells. It can happen due to autoimmune disorders, exposure to toxins, or infections.

5. Myelodysplastic Syndromes (MDS): These are disorders where the bone marrow doesn't make enough healthy blood cells. This can lead to issues like anemia, frequent infections, and bleeding.

6. Inherited Blood Disorders:

- Thalassemia: This is a genetic condition that affects how the body makes hemoglobin, leading to anemia and other complications.
- Sickle Cell Disease: This is a genetic condition where the hemoglobin in red blood cells becomes abnormal, causing painful episodes, anemia, and damaged to organs.

7. Myeloproliferative Neoplasms (MPNs): Conditions characterized by overproduction of blood cells in the bone marrow.

Types: Polycythemia vera

Essential thrombocythemia

Primary myelofibrosis

Chronic myeloid leukemia (CML)

8. Autoimmune Diseases:

- Scleroderma: This condition happens when the immune system attacks the connective tissue, resulting in thickening and hardening of the skin and internal organs.
- Lupus (SLE): This is an autoimmune disease that can affect many parts of the body, including the skin, joints, kidneys, and other organs.

HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) PROCESS:

1. Pre-treatment:

Intensive chemotherapy and/or radiation annihilate cancerous cells and dampen the immune response.

Sets the stage for the arrival of new stem cells.

2. Stem Cell Delivery:

Healthy stem cells are administered via a central line or vein.

The cells journey to the bone marrow to commence the generation of new blood cells.

3. Cell Integration:

The implanted stem cells begin to thrive and generate new blood cells.

Generally, takes 2-4 weeks for proper integration to take place

PATHOPHYSIOLOGY:

Genetic / Environmental Factors
(Radiation, chemicals, mutations)

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Mutation in Hematopoietic Stem Cells

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Uncontrolled Cell Proliferation

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Bone Marrow Cancer

(Leukemia / Lymphoma / Multiple Myeloma)

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Infiltration of Bone Marrow by Malignant Cells

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Suppression of Normal Hematopoiesis

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Decreased RBC (Anemia)	Decreased WBC (Infections)	Decreased Platelets (Bleeding)

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▼

Bone Marrow Failure

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▼

High-Dose Chemotherapy / Radiotherapy

|

▼

Destruction of Cancer Cells

+ Bone Marrow Ablation

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Hematopoietic Stem Cell Transplantation

(Autologous / Allogeneic)

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Stem Cell Engraftment in Bone Marrow

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Restoration of Normal Blood Cell Production

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Improved Immunity & Clinical Recovery

MECHANISM OF ACTION OF HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

Transplantation of hematopoietic stem cells is a treatment that involves extensive biological and immunological processes that eventually leads to the complete cessation of the malignant process by restoring the bone marrow function.

1. Myeloablation and Tumor Cell Eradication

The patient undergoes pre-transplant chemotherapy with very high doses of radiotherapy. The conditioning treatment kills the rapidly dividing tumor cells located in the bone marrow. At the same time, it destroys the defective or diseased bone marrow of the patient and makes room for the healthy stem cells to be implanted.

2. Immunosuppression and Prevention of Rejection

The conditioning regimen also causes immune system suppression in the recipient of the transplant. This is a crucial step for the transplanted stem cells not to be rejected, particularly for allogeneic HSCT. The lessness of immune activity permits the donor stem cells to coexist, multiply, and settle in the recipient's bone marrow.

3. Homing and Engraftment of Stem Cells

Once the hematopoietic stem cells are infused into the blood, they move along the bloodstream and specifically find their way to the bone marrow. At that point, they are already attached to the stroma cells and have started the en-grafting process. If the engraftment is successful, the resulting bone marrow will be functional and capable of producing all types of blood cells.

4. Reconstitution of Hematopoiesis

When, the stem cells are transplanted, they get differentiated into erythroid, myeloid, and lymphoid progenitor cells. This re-establishment of blood cell production includes the production of red blood cells, white blood cells, and platelets, thereby reversing anemia, providing immunity, and stopping bleeding created by either the failure of the bone marrow or the malignancy.

5. Graft-vs-Tumor (GVT) Effect

In an allogeneic HSCT (Hematopoietic Stem Cell Transplantation), the donor's immune cells identify the remaining cancerous cells in the patient's body as foreign and attack them. This immune response against cancer, called Graft vs Tumor or Graft vs Leukemia, greatly decreases the chance of cancer reoccurring and allows for a chance of being cured or going into a long-term remission.

6. Re-educating the Immune System

The process of HSCT generates a completely new immune system from stem cells provided by the donor. This newly generated immune system aids the patient's body in fighting off infections better than the previous immune system, as well as assists in some autoimmune diseases in normalizing the immune response.

7. Correcting Genetic and Functional Deficiencies

For patients with inherited blood disorders, HSCT allows for the replacement of abnormal hematologic cells with healthy stem cells. The abnormal production of hemoglobin or a malfunctioning immune system will be corrected for many years, potentially curing patients and not just treating symptoms.

COMPLICATIONS OF HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

1. Graft-versus-host disease Management:

Steroids (prednisone) are first-line for acute GVHD. Calcineurin inhibitors (cyclosporine, tacrolimus) + methotrexate-prophylaxis

RATG (rabbit anti-thymocyte globulin) or ATG in high-risk cases

Monitoring of skin, gut, and liver for manifestations of GVHD

Confirming the diagnosis through biopsy [12]

2. Infection Prophylaxis

Bacterial: fluoroquinolones, cephalosporins

Fungus Medications: azoles include fluconazole and echinocandins

Viral: acyclovir for HSV/VZV, ganciclovir for CMV

PJP prophylaxis with TMP-SMX [13]

3. Prevent Organ Damage

Liver: Monitor LFTs, VOD may be managed with defibrotide

Kidney: dose adjustment of drugs, follow creatinine

Heart: echo, ECG monitoring for cardiotoxicity

RECENT ADVANCES IN HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

1. **New FDA-approved treatments:** ibrutinib, ruxolitinib, belumosudil, and axatilimab-csfr for chronic GVHD, targeting different mechanisms like BTK inhibition, JAK1/JAK2 inhibition, and ROCK2 pathway modulation.
2. **Enhanced strategies for prevention:** post-transplant cyclophosphamide protocols and antibody-based approaches have reduced the incidence of severe GVHD.
3. **Biomarker-driven strategies:** Identify high-risk patients for personalized treatment, reduce organ injury, and adverse effects related to GVHD.
4. **Ruxolitinib for GVHD:** effective in the treatment of steroid-refractoriness of acute and chronic GVHD, associated with improved response rates and symptom burden.
5. **Belumosudil for cGVHD:** highly promising in heavily pretreated populations, with overall response rates of approximately 70% Recent advances in HSCT have involved new FDA-approved therapies, including ibrutinib, ruxolitinib, Belumosudil, and axatilimab-csfr for chronic GVHD, targeting various mechanisms, such as BTK inhibition, JAK1/JAK2 inhibition, and modulation of the ROCK2 pathway.
6. **Combination Therapy:** Axalimab used in combination with ruxolitinib and/or belumosudil showed promising results in severe, treatment-resistant chronic GVHD.

ADVANTAGES OF HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) IN BONE MARROW CANCER:

1. Curative Potential

HSCT made it to the list of a limited number of treatments that can cure some forms of bone marrow cancer, particularly acute leukemias. With the help of healthy stem cells, the diseased marrow is replaced and the source of the cancerous blood cells has been eliminated.

2. Allows High-Dose Chemotherapy/Radiotherapy

Very high doses of chemotherapy or radiation are usually required to get rid of the malignant cells completely. These huge doses would destroy the bone marrow, but HSCT helps to keep the marrow alive and, therefore, allows the doctors to treat cancer with more aggressive and effective methods.

3. Graft-Versus-Cancer Effect (Allogeneic HSCT)

In the case of allogeneic transplantation, the donor's immune cells see the tiny leftovers of the cancer as foreign and attack them. One of the reasons the tumor is less severe is that the immune system has taken control, so there are fewer relapse cases and better survival rates over the long term.

4. Replacement of Defective Marrow HSCT restores normal hematopoiesis, leading to:

Improved hemoglobin levels.

Reduced risk of bleeding (platelet recovery).

Enhanced immune defense against infections.

5. Useful in the Herbalist or High-Risk Disease

Patients with poor prognostic factors or relapse disease are often the same ones that standard therapy has no effect on. HSCT comes as a more radical and final treatment option for high-risk cases.

6. Autologous HSCT Benefits

The use of the patient's own stem cells:

Eliminates the risk of graft-versus-host disease.

Results in fewer immunological complications.

Allows quicker and easier engraftment and recovery.

This is a common practice in cases of multiple myeloma and lymphomas.

7. Improved Long-Term Survival

Donor matching levels (HLA typing), conditioning regimens, and advance supportive care are all factors that contributed to better transplant success, thus leading to a better survival rate and quality of life in patients who are able to receive this treatment.

8. Long-Term Remission

Quite a number of patients have been granted durable remission, allowing them to return to near-normal life after recovery.

DISADVANTAGES OF HEMATOPOIETIC STEM CELL TRANSPLANTATION HSCT IN BONE MARROW CANCER

1. High Treatment-Related Mortality

HSCT is a procedure that takes a lot of effort and has the possibility of getting the patient killed because of complications that include to a great extent allogeneic transplants. Severe infections, organ failures, and graft failures are among the main ones.

2. Graft-versus-Host Disease (GVHD)

In allogeneic HSCT, the transplant of immune cells from a donor can cause the patient to experience GVHD in the following ways:

- Acute GVHD (skin, liver, gastrointestinal tract)

- Chronic GVHD (long-term disability, dry eyes, lung and joint problems)

3. Severe Infections

Patients are practically non-existent in immunity for a long period after the operation, which makes them prone to:

- Bacterial infections
- Viral reactivations (CMV, EBV)
- Fungal infections

4. Organ Toxicity

Chemotherapy/radiation of high doses can destroy:

Liver (Veno-occlusive disease), Kidneys, Lungs, Heart

This poses a drawback of HSCT in older patients or those with multiple health problems.

5. Relapse Still Possible

The cancer may come back even after the transplantation has taken place, especially in the case of aggressive or advanced disease. HSCT cannot be taken as a sure cure.

6. Long Recovery Period

The process of getting back to normal after HSCT is slow and can take months or even years, during which time the patient will experience fatigue and weakness and will have to go through frequent hospital visits that will affect their daily life.

7. Limited Donor Availability (Allogeneic HSCT)

Locating a donor who is a perfect match is not always easy, mainly for those patients who do not have siblings or are from underrepresented ethnic groups.

8. Infertility and Endocrine Problems

Conditioning regimens can lead to:

Permanent infertility

Hormonal dysfunction (thyroid, growth hormone issues in children)

9. High Cost

HSCT is a costly treatment that should only be done in specialized centers and that requires long hospital stays and extensive follow-up care, thus making access limited in some regions.

10. Not Suitable for All Patients

HSCT capacity is curtailed as it is restricted to elderly patients or those with severe comorbidities who may not be able to withstand the procedure.

DISCUSSION

Hematopoietic Stem Cell Transplantation is a significant therapeutic procedure for many types of cancers and diseases that affect the bone marrow. This is due to the abnormal growth of blood-making cells in the bone marrow, which causes a decrease in the production of normal blood cells. Both chemotherapy and irradiation are effective in killing cancer cells; however, they can cause damage to the bone marrow as well. Hematopoietic Stem Cell Transplantation reverses this issue by replacing the compromised bone marrow with new stem cells.

The key benefit of HSCT is its capacity to replenish the body with the ability to produce blood cells as well as its immune functions. Specifically, the allogeneic form of HSCT is beneficial because the immune cells derived from the donor can target any cancer cells that may be present due to the graft versus tumor reaction, thus decreasing instances of relapses. The autologous form of HSCT has fewer immune-related risks. It has been successfully applied to multiple myeloma and lymphomas.

Although HSCT offers many advantages, it is fraught with life-threatening complications. Graft-versus-host reaction, infection, tissue damage, and protracted recovery periods are some of the serious concerns associated with HSCT, and this is more so in allogenic HSCT.

Recent advances such as improved HLA matching, reduced-intensity conditioning, better infection control, and new drugs for GVHD management have improved the safety and success of HSCT. Overall, HSCT remains a valuable treatment for bone marrow cancers and continues to improve with ongoing research and clinical advancements.

CONCLUSION

Hematopoietic stem cell transplantation has become an essential therapeutic strategy in the management of bone marrow–associated malignancies, offering outcomes that extend beyond disease control toward long-term remission in selected cases. Its clinical value lies in its ability to re-establish functional hematopoiesis and immune competence following intensive anticancer therapy, addressing both the malignant process and the resultant marrow failure.

Although the procedure carries significant clinical risks, continued improvements in transplant protocols, donor selection, and post-transplant care have progressively reduced treatment-related complications. The integration of novel conditioning approaches, alternative stem cell sources, and immunomodulatory therapies has expanded eligibility and improved tolerability, particularly for patients previously considered unsuitable for transplantation.

Future progress in HSCT is expected to rely on precision-based strategies, including individualized risk assessment, targeted immune interventions, and enhanced supportive care frameworks. These developments are likely to further improve therapeutic outcomes while minimizing adverse effects. As research advances and clinical experience grows, HSCT will remain a pivotal and evolving modality in the comprehensive treatment of bone marrow cancers.

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