Hematopoietic Stem Cell Transplantation: Are we there yet?

*Shalmali Pendse, Anuradha Vaidya
Symbiosis School of Biomedical Sciences,
Symbiosis International University, Lavale, Pune.

INTRODUCTION

➢Hematopoietic Stem Cells (HSCs)

•These are the cells that give rise to all the other blood cells and are derived from the middle germ layer during the development of the embryo i.e. Mesoderm.
•The HSCs have long and short -term regeneration capacities and can commit to myeloid, lymphoid, erythroid and megakaryocyte lineages.
•They have the unique capacity to undergo self-renewal and produce daughter cells that retain stem-cell properties, thereby maintaining a steady state of stem cell pool.
•HSCs repair DNA efficiently, resist apoptosis, and excrete toxic drugs by means of ATP-binding transporters (side population cells).

➢Hematopoietic Stem Cell Transplant (HSCT)

•HSCT refers to a procedure in which HSCs are infused to restore BM function in patients undergoing chemotherapy with or without total body irradiation (TBI).

HSCT is divided into two types on the basis of the transplant donor:

1.Autologous -
In autologous transplantation, the patients own stem cells are preserved and used for transplantation after the conditioning regimen.

2. Allogeneic -
In allogenic transplantation, stem cells from an HLA matched healthy person is transplanted into an immuno-compromised patient.

➢When is HSCT recommended?

A] Leukemia:
•Leukemia represents the most common pediatric malignancy, accounting for approximately 30% of all cancers in children less than 20 years of age.
•During chemotherapy, leukemic patients are treated with drugs like methotrexate by targeting spinal cord. This therapy has higher chances of CNS relapse which can now be overcome by HSCT.
•Allogenic HSCT improves disease free survival. Multiple studies indicate that TBI based allogenic transplant conditioning regimens are associated with lower risk of relapse in comparison to chemotherapy only regimens.

B] Immunocompromised patients:
•Intensive immunosuppression followed by HSCT (CD34 selection) has been proposed or initiated as a therapy for patients with severe autoimmune diseases (SADS) who have poor prognostic features. Before HSCT these patients undergo myeloablative conditioning with TBI with or without immunosuppressive drugs. Till date this therapy shows either stabilization of disease or improvement in the patients suffering from immune mediated diseases.

HISTORICAL PERSPECTIVE

1950's
- Thomas et al first reported the infusion of bone marrow in 1957 to patients who received radiation and chemotherapy.
- During the late 1950s, Thomas et al reported the use of total body irradiation and syngenic transplantation for treatment of leukemia.

1960's
- In the early 1960s a better understanding of human leukocyte antigen typing (HLA) led to the use of allogenic sibling donors for transplantation.
- Emphasis was placed on developments in the areas of histocompatibility, conditioning regimens, and prevention and treatment of graft-versus-host disease (GVHD).

1970's
- Efforts were made to improve supportive care measures such as the use of antibiotics and more effective conditioning regimens.
- By the late 1970s, Thomas et al demonstrated the use of allogenicbone marrow from an HLA identical sibling following administration of total body irradiation and cyclophosphamide.

1980's
- In 1983, The use of a chemotherapy-based preparative regimen of busulfan and high doses of cyclophosphamide was used to replace the use of total body irradiation.
- The use of the stem cell collected from the peripheral blood was introduced in the mid to late 1980s by Kessinger et al. Also the interest of using UCB as a source of stem cells grew in the late 1980's.

1990's
- The use of the unrelated donor as a source of stem cells for transplantation continued to grow because of improved understanding of HLA typing.
- In the late 1990s, non-myeloablative stem cell transplant (NST) was used as an alternative treatment option for hematologic diseases and solid tumors.

21'st century
- Efforts continue to improve the prevention and treatment of GVHD.
- Interest in the use of mesenchymal stem cells for treatment of acute GVHD has been studied and use of extracorpeal photopheresis in treatment of chronic GVHD has been evaluated.
- The use of PBSCs have significantly increased for autologous and allogenic transplantation.

Discovery of markers that minimize GVHD

Sr. No.	Markers	Discoverers	Year
1.	CD34+	Berenson et al	1988, 1991
2.	CD34+ CD38-	Terstappen et al	1991
3.	CD34+ Lin- Thy1+	Baum et al	1992
4.	CD34+ c-kit+	Gunji et al	1993
5.	CD34+ Tie+	Hashiyama et al	1996
6.	CD34+ CD133/AC133+	Yin et al	1997
7.	CD34- Lin- CD133/AC133+ CD7-	Gallacher et al	2000
8.	CD34+ CD38- Lin- Rhodamine123low	McKenzie et al	2007
9.	CD34+ CD38- Lin- CD45RA Rhodamine123low CD49f+	Notta et al	2011

PRESENT SCENARIO

➢ Mesenchymal Stem Cells (MSCs)

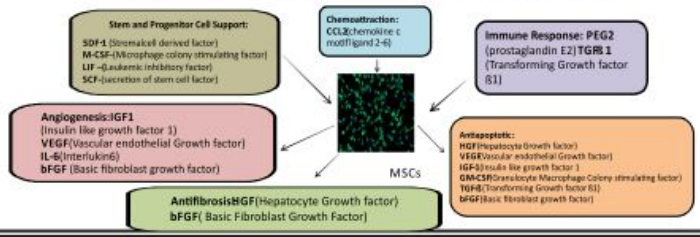
•The first experience with the use of MSC for the GVHD was reported by the Karolinska Transplant Centre which successfully treated a 9-year-old boy suffering prevention of GVHD was reported in 2002 but the first documented observation of their clinical efficacy in steroid-resistant grade IV acute GVHD by using haplo-identical third-party MSCs.
•MSCs act on almost every cell that is responsible for the immune response in our body. They are known to play a very important role in immunosuppression as follows-
1.T cells- The veto like activity of MSCs is responsible for the suppression of T cells. Veto cells refer to a group of lymphoid cells that act as fraudulent APC and specifically inhibit T cell precursor clones that interact with them.
2. Dendritic Cells (DC)- MSCs inhibits the initial differentiation of monocytes to DC by down regulating the expression of certain DC specific markers like CD1a. It is also shown that MSC causes mature DC1 to decrease TNF-α secretion and mature DC2 to increase IL-10 secretion, leading to a state of immunotolerance.
3. Natural Killer cells (NK)- It has been suggested that MSCs down regulate IFN-γ production of IL-2- stimulated NK and suppress the proliferation, cytokine secretion and cytotoxicity of those stimulated by IL-15.
4. B cells- The multilevel intervention model proposed that MSCs affect the proliferation, antibody production and chemo taxis of B cells.
•These immunomodulatory effects of MSCs are responsible for the reduction of GVHD when co-transplanted with HSCs.
•Studies conducted by Le Blanc et al have shown that co-transplantation of MSCs resulted in fast engraftment and 100% donor chimerism, in patients who were re-transplanted for previous graft failure/rejections.
•The BM microenvironment (specialized niche) provided by MSCs is vital to the development, differentiation, and regulation of the lymph hematopoietic system as well as for a successful graft. It comprises different types of cells such as fibroblasts and endothelial cells. •Nowadays, MSCs are used for tissue engineering and skin transplant..

• **Tissue Engineering:**
•The MSCs have been used in preclinical models for tissue engineering of bone, cartilage, muscle, marrow stroma, tendon, fat, and other connective tissues. These tissue-engineered materials show considerable promise for use in rebuilding damaged or diseased mesenchymal tissues.
• Trophic activity of MSCs – Research shows that MSCs secrete certain bioactive molecules that provide a regenerative microenvironment for the HSCs.

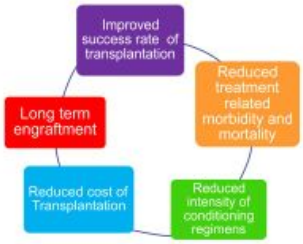
• **Skin transplant:**
•Studies have showed that human MSCs maintain phenotypic attributes and in vitro differentiation plasticity during long term culture.
•Studies have shown that MSCs have been able to accelerate wound healing and clinical studies are ongoing to document their usefulness in the treatment of wounds and grafts.

• **Bone and Cartilage regeneration:**
•As the MSCs have capacity of continuous self renewal as well as differentiation they give rise not only to embryonic bone, but also to the continuous supply of osteogenic cells required for bone remodeling and fracture repair throughout adulthood. Also they are free from ethical concerns, residents of multiple tissues, possess non-immunogenic properties, have injury-seeking capabilities, and can be used as vehicles for bone gene therapy. These characteristics make MSCs safe and promising candidates for use in bone engineering and regeneration.
•In 1974, Friedenstein et al discovered that MSCs regulate osteogenesis and are responsible, for the regenerative capacity of bone tissue and till date using of MSCs for the treatment of disease like osteoporosis is in practice.

Figure- Secreted factors from cultured mesenchymal stem cells



WHAT DOES THE FUTURE HOLD?



•Increasing the rate of success of HSCT.
•Identification and matching of genetic factors such as HLA-C and killer immunoglobulin like receptors (KIRs) improving engraftment potential and reducing GVHD.
•Optimization of the graft versus leukemia effect thereby reducing the chances of relapse of the disease.
•Shift focus from allogenic to autologous transplantation thereby completely eliminating the requirement of HLA matching. To apply this approach it is imperative to specifically identify HSCs and expand them in *in vitro*/*in vivo* without compromising on their stem cell properties or inducing them to become deregulated.

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