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HAEMATOPOIETIC STEM CELL TRANSPLANTATION, FROM ITS EARLY STAGES TO TILL DATE

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Abstract:

Formation or development of a new cell or an entire human being requires an actively diving cell, which we refer as Stem Cell. By discovering the potency of a stem cell in forming new cells, tissues & organs, the thought of application or use of stem cells in treating various irreversible tissue/ organ damages came out. Different stem cells are responsible in producing different tissues/ organs. With the advent that the stem cells do exist in the adults & can be extracted specifically, various stem cell transplantations took over in treating lethal diseases like cancer, diabetes, etc. The process of stem cell therapy & its applications in various fields of medical sciences is lot to be known. The current study provides a detailed glance on various aspects of one of the majorly studied/ known stem cell transplantations, Haematopoietic Stem Cell Transplantation.

Key Words: *Haematopoietic stem cell transplantation; Stem Cells; Irreversible tissue/ organ damage; Autologous S.C.T.; Allogenic S.C.T.; Bone Marrow Transplantation; Peripheral Blood Stem Cell Transplantation; Immuno-phenotyping; Stem Cell Mobilisation.*

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INTRODUCTION:

An active stem cell is found in foetus or in an infant body/ blood in more number but becomes inactive as a person grows older & the number of actively dividing cells also decreases. Due to which, tissue or organ damage cannot be reversed by native body homeostasis resulting in disease prognosis. However, most of the diseases are curable & can be treated successfully with various available treatment options. Stem cell transplantation is one such procedure to combat lethal diseases like cancers, myelomas, sclerosis, diabetes, neurodegenerative disorders, etc.

Stem cell transplantation is a procedure in which actively dividing stem cells are extracted from the patient or from the donor and are injected into the patient body intravenously to replace inactive or damaged stem cells, so that the damaged tissue/ or organ is repaired by the newly produced cells of engrafted stem cells. Before stem cell transplantation, the patient is given with high dose chemo therapy or radiation to prepare the body for transplantation and reduce chances of rejection.

Now we are in the decade or age of Stem Cell biology [(2)]. With the proof that stem cells exist in the haematopoietic system, several tissue specific stem cells and progenitor cells isolation are made possible and is achieved. The most unique and important property of Stem Cells, being self- renewable, impacted their use and application in the regenerative medicine to cure several lethal diseases like Anaemia, Diabetes and even Cancer [(2)]. Among all the Stem cells, haematopoietic stem cells are the earlier stem cells used clinically and most widely used to treat haematological diseases like blood cancers, anemia, thalassemia, etc.

Types Of Stem Cell Transplantation

There are majorly 2 types of stem cell transplantation. They are:

1. Autologous Transplantation
2. Allogenic Transplantation

1. AUTOLOGOUS TRANSPLANTATION

In this, own stem cells are collected and are engrafted into the body after high dose chemo- or radiotherapy. Stem cells may be collected from bone marrow or blood stream. As the cells are very native to the body, there are less chances of the cells getting rejected. Graft versus Host Disease is also not expected in this case. Parallelly, the desired effect of Graft versus Cancer effect is also not seen, as the native cells has already failed in combating the cancer cells for which the disease is seen. Despite the above reason, the autologous stem cell transplantation is done to replace the lost cells of the body, due to disease progression.

2. ALLOGENIC TRANSPLANTATION

In this, the stem cells are collected from a donor and are transplanted. As these are non-native cells, the recipient can present with rejection syndrome. To minimise the chances of rejection, HLA typing (Human Leukocyte Antigen- typing) is done before transplantation to ensure that the stem cells match the native cell type of the recipient.

Depending on the matching level it can be of

- Matched Allogenic Transplantation (complete matching) or
- Haplo- Identical Matched Allogenic Transplantation (half of the typing is matched).

Depending on the donor, it can be of

- Matched Sibling Allogenic if the donor is a sibling,
- Matched Unrelated Donor (MUD) if the donor is unrelated,
- Matched Related Donor (MRD) if the donor is a relative like uncle, aunt or any of the blood relative.

Allogenic have both the pros and cons. Pros being that it precipitates Graft versus Cancer effect and helps in fighting the cancer. It also adds up new immune capabilities to the recipient. Cons include it can precipitate Graft versus Host Disease for which the immune system of the recipient is to be silenced by giving immune suppresants which the patient may need to continue throughout life which in turn could increase the risk of infections[24].

HISTORY OF HAEMATOPOIETIC STEM CELL TRANSPLANTATION

Stem cells of adult origin has been used clinically for 40 years in the treatment of haematological neoplasms like leukemia. Earlier, these cells were originally derived from the bone marrow but now-a-days they are derived from the umbilical cord blood [(8)] or peripheral blood stream of an adult. The first human stem cell transplantation (transfusion) was given to a patient with Aplastic Anaemia in 1939 as an attempt to raise leukocyte and platelet count using I.V injection of bone marrow directly [(10)], since the measures to isolate stem cell was not clearly evident that time. It is proven in mouse model that syngeneic marrow transplantation can treat marrow aplasia secondary to radiation in 1950's. In 1956, Barner and collegues published their experiment which demonstrated three major principles of hematopoietic stem cells, they are [(10)]

1. The role of preparative anti-leukemic regimen in hematopoietic stem cells.
2. Ability of newly engrafted immune system to prevent relapse of leukemia.
3. Activity of graft against recipient

The 1st allogenic hematopoietic stem cell transplantation was led by E. Thomas and reported in New England journal of medicine on September 12, 1957 [(9)]. In the mid late 1960's, methods to identify HLA (Human Leukocyte Antigen) in humans was developed, which developed HLA matching criteria for donor and recipient in case of allogenic transplantation. In 1969, E. Donnall Thomas (the pioneer of 1st allogenic hematopoietic stem cell transplantation) started a clinical trial program in SEATTLE for Allogenic Hematopoietic Stem Cell Transplantation which in 1977 reported a registration of 100 patients (54 with AML & 46 with ALL) received transplantation with chemotherapy and radiotherapy. In this trail only 13 out of 100 patients are alive after 1-4.5 years transplantation. Despite of this low success and survival rate, Thomas continued application of hematopoietic stem cells in the early stages of leukemia that ended up reported a cure rate of 50% in 1979 [(10)]. For all these efforts, that laid a strong base for stem cell transplantation, E. DONNALL THOMAS won a Noble prize in 1990 for his discovery of cell transplantations in treatment of diseases.

Discovery and development of HLA matching encouraged the transplantation from unrelated donor. In 1972, International Bone Marrow Transplant Registry (IBMTR) was established, at that point of time only 12 centres are performing about 50 transplantations a year altogether. In 1974, European group for Blood and Marrow Transplantation (EBMT) was established for European collaborations [(10)]. In 1986, first unrelated donor transplantation laid the foundation of National Marrow Donor Program (NMDP) & in 1988 Bone Marrow Donors World Wide (BMDW) was founded [(10)].

In 1982, Allogenic Hematopoietic Stem Cell Transplantation was first used to treat Thalassemia & in 1984 for management of Sickle Cell Disease [(10)]. Currently more than 60,000 transplants are performed annually world-wide [(11)].

PURPOSE OF HAEMATOPOIETIC STEM CELL TRANSPLANT

Any diseases that cause in the reduction of blood cell counts or damage bone marrow can be life threatening, like anaemia, thalassemia, leukocytopenia or blood cancers. Due to disease progression, the body's homeostatic regulations fail to maintain the levels of the reduced blood cells in terms of their production, thus making the patient to get repeated transfusions of blood products as required. Repeated transfusions have several drawbacks of which the major is that the patient will be more susceptible to infections at the site of cannulations or i.v. lines inserted for transfusing the products. To surpass repeated transfusions of various blood products, hematopoietic stem cell transplantation is useful. Due to the fact that the stem cells have ability to differentiate and produce various cell types in large number in less time period whenever required as the normal body homeostatic regulation does, this is considered as a useful measure in treating the diseases or disease conditions where the blood cell count or its function is affected directly or indirectly.

The radiotherapy or chemotherapy or any diseases that destroy bone marrow cause the loose of Hematopoietic Stem Cells that are present in the bone marrow in mononuclear cells (MNC) and even in peripheral blood in smaller quantities that are very important in homeostatic regulation. In this case, H.S.C.T is used as multimodality or adjuvant therapy to replace those lost blood cells & stem cells [(17)]. H.S.C.T. is also useful in replacing or repairing the damaged tissue or organ i.e., bone marrow in case of bone marrow failure. Myeloablative therapy, termed "high dose therapy" which uses high energy radiations and high dose of chemotherapeutic drugs, is used in some patients that may completely damage bone marrow and whose function can be restored by Hematopoietic Stem Cell Transplantation.

THERAPEUTIC APPLICATIONS OF HAEMATOPOIETIC STEM CELL TRANSPLANTATION

Hematopoietic Stem Cell Transplantation is a highly specialised and unique medical procedure. It has evolved over the last half century from experimental bone marrow transplantation to standard of care for a broad range of patients. Hematopoietic stem cell transplantation can be indicated to treat [(10,11)]:

- Congenital or Acquired disorders of haematopoietic system.
- Chemo-, radio- or Immuno- sensitive malignancies
- Sclerosis (multiple or systemic)
- Crohn's disease
- Solid tumour like sarcoma, neuroblastoma, etc.
- Aplastic anaemia
- Thalassemia
- Myelodysplastic syndrome

- Bone marrow failure syndrome
- Inherited metabolic disorder
- Auto immune disease like AIDS, SLE
- IDDM (TYPE 1 DIABETES MELLITUS)
- Juvenile idiopathic arthritis
- Skin disease

IDENTIFICATION OF HAEMATOPOIETIC STEM CELL

Since HSPC/HSC are found in the heterogenous mixture in Mono Nuclear Cells (MNC) of bone marrow or peripheral blood, it is required to identify H.S.C prior to their extraction. Mono Nuclear cells of bone marrow contains varied type of stem cells like Hematopoietic Stem cells and Progenitor Cells (HSPC), Mesenchymal Stem Cells (MSC), Endothelial Progenitor Cells (EPC), Very Small Embryo Like Stem Cells (VSELS). Establishing the fact that Specific monoclonal antibodies react or interact with specific cell-surface antigens, a way to identify the cell cluster differentiations is made possible. Several cell-surface markers (cell surface antigens) are associated with Mono Nuclear Cells that includes CD-29, CD-34, CD-106, CD-105, CD-133, CD-166, CD-309, etc. Out of all these CD-34+, CD-45+ cell surface antigens represent H.S.C. This allows identification of HSPC's from MNCs through immunophenotyping.

After identification extraction is done in specific conditions that promotes the isolation of HSPC'S alone. Proper and specific culturing media and extraction method need to be established properly for controlled differentiation isolation [(16)].

A minimum dose of 2×10^6 CD-34+ cells/kg body weight is advised for rapid recovery of neutrophils and platelets [(15)].

A higher dose of 4×10^6 CD-34+ cells/kg body weight can be engrafted for even faster hematopoietic recovery [(14)].

EXTRACTION OF STEM CELLS

Stem cell can be extracted from Bone Marrow (BM) the place where they are developed or from Peripheral Blood (PB). If transplantation is done by extracting the stem cells from the former one, it is referred as Bone Marrow Transplantation (B.M.T) and the latter one as Peripheral Blood Stem Cell Transplantation (P.B.S.C.T). Stem cells can also be extracted from umbilical cord blood. Since H.S.P.C. are not present in its original form either in bone marrow of peripheral blood in the required quantity, they need to be isolated from mixture of stem cells present in MNCs of bone marrow [(12)]. Mononuclear cells of Bone Marrow contain varied type of stem cells like Haematopoietic stem & progenitor cells (HSPC) or Haematopoietic Progenitor cells (HPC's), Mesenchymal Stem Cells (MSC), Endothelial Progenitor Cells (EPC), Very Small Embryo Like Stem Cells (VSELS) [(14)]. The availability of stem cells in blood is confirmed by arriving to the fact that, stem cell derived from bone marrow circulates in the blood which are in steady state concentration at their low levels, a limitation for its availability of appropriate quantity in the blood. To overcome this, the MNCs need to be mobilised from bone marrow to peripheral blood.

Extraction of stem cells involves, collection of MNCs and identification and isolation of HSC. Extraction of HSPC either from bone marrow or peripheral blood is constantly getting better by advancing technologies. Initially H.S.C.T. was done by extracting them from Bone Marrow, which is now replaced with Peripheral Blood [(12)].

In B.M.T., the bone marrow aspiration is required which is an invasive procedure done under anaesthesia to collect 0.5-1.5 litres of bone marrow. Bone marrow aspiration is a complicated procedure with several side effects like bruising and pain at the site of aspiration, temporary back pain and even swelling and infection that makes the patient to get hospitalized for 2-3 days. As bone marrow aspiration is done under general anaesthesia, the common risks of general anaesthesia are also associated with it. Due to all these limitations, extraction of H.S.P.C from bone marrow has taken a new route and are extracted from peripheral blood. Bone marrow extracted impacts the loose of same in the donor which can be compensated by homeostatic regulation within weeks. The reason for opting BMT despite of its side effects of the injury being caused is the own self-repairing mechanism of the body due to presence of M.S.C.'s that can proliferate and form osteocytes & osteoblasts.

Extraction from Peripheral Blood is initially required with mobilisation of H.S.P.C.'s from Bone Marrow to Peripheral Blood, which is done by injecting drugs-Cytokines such as Granulocyte-Colony-Stimulating Factor (G-CSF) or Plerixafor or combination of both. The combination is usually preferred when G-CSF alone is failed to mobilise the required amount of H.S.P.C.'s to PB. This mobilisation is done 4-5 days prior to the extraction. The extraction is done through a process called Centrifugation using Magnetic Polystyrene Beads coated with monoclonal antibody specific for CD-34+ cell-membrane antigen [(13)].

Whole extraction process completes within 3- 4 hours. Extraction of HSPC from Pb can also be referred to Sem Cell Apheresis, which is done in a single day & the patient need not to be hospitalised for 2-3 days. Studies comparing BMT & PBSCT shows faster haematological recovery in PBSCT than in BMT [(17)].

ADMINISTRATION OF HAEMATOPOIETIC STEM CELL

Administration of identified, isolated & extracted H.S.C.'s is similar to the administration of blood products or normal saline, in which they are given through I.V. that takes approximately 1 hour to completely administer the stem cell product. This is also referred as Engrafting or Transplantation.

For any type of H.S.C.T., conditioning of the therapy is required before administering the Stem Cell product. This conditioning allows the patient for active uptake of engrafts (transplanted Stem Cells). Conditioning is done by giving the patient with high doses of Chemotherapeutic drugs or monoclonal antibodies or even radiation in the form of Total Body Irradiation (TBI). This acts as immune suppressant that increases the chances of transplants to show its effect and minimise its rejection. The conditioning regimen may be a single drug or combination two or three drugs given either orally or intravenously. The conditioning regimen also has anti-cancer activity in which they kill the cancerous cells much before the Stem Cells are engrafted to take anti-cancer activity.

LIMITATIONS OF HAEMATOPOIETIC STEM CELL TRANSPLANTATION

Despite applying modern techniques in treating cancers, the outcome of patients is being poor. This is due to risks or limitations or drawbacks that each and every therapy has. In the same way, even though being novel option, H.S.C.T also holds some limitations.

Allogenic H.S.C.T has a risk of Graft- Versus- Host disease (GVHD) which parallelly benefits by lowering the relapse rate through immune-mediated Grafted Verses Tumour (GVT) effect. To avoid graft rejection and lower GVHD, immuno-suppressants are given. This is called conditioning of the stem cell transplantation which is done using Total Body Irradiating (TBI), Melphalan, Cyclophosphamine, Busulphan, Fludarabine, Etoposide or any combinations. The other limitation of Allogenic H.S.C.T. is low availability of donor stem cells in stem cell banks due to the low counts of donors. In order to decrease the mortality due to GVHD, HLA typing is required, which makes the limitation to get surpassed by finding more appropriate type of stem cells that matches the type of patient and do not precipitate GVHD.

Autologous H.S.C.T. has low rates of mortality as this do not precipitate any GVHD, as the stem cell are taken from the same patient and are engrafted. But relapse of cancer in the patients treated with Autologous H.S.C.T. is considered as its drawback.

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CONSENT FOR PUBLICATION

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AVAILABILITY OF DATA

Not applicable

COMPETING INTERESTS

The author declares that there are no competing interests.

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