Introduction

Stem cells are the cells which have the ability to divide (clonogenic ability) and self-renew indefinitely as well as to differentiate into one or more cell types. Adult human stem cells that are intrinsic to various tissues have been described. These cells are capable of maintaining, generating, and replacing terminally differentiated cells within their own specific tissue as a consequence of physiologic cell turnover or tissue damage due to injury. Haematopoietic stem cells that give rise to blood cells and move between bone marrow and peripheral blood are the best-characterised adult stem cells in humans. Mature blood cells are produced continuously by less-differentiated precursors that are in turn descended from more primitive progenitors and, originally, from haematopoietic stem cells. Recent data suggest that adult stem cells generate differentiated cells beyond their own tissue boundaries, a process termed “developmental plasticity”. In fact, a single stem cell can restore the entire lymphohaematopoietic system of a lethally irradiated animal.

Haematopoietic stem-cell transplantation (HSCT) was originally conceived more than 50 years ago as a treatment for injury from irradiation and, later, for cancer. Associated problems needed to be solved before the procedure could be used clinically. HSCT is usually carried out for one of two purposes: (1) to replace an abnormal but nonmalignant lymphohaematopoietic system with one from a normal donor; or (2) to treat malignancy by allowing the administration of higher doses of myelosuppressive therapy than would otherwise be possible. The use of HSCT has been increasing, both because of its efficacy in selected diseases and because of increasing availability of donors.

Types of extrinsic stem cells

Extrinsic stem cells are further classified in two subtypes:

1. Adult stem cells: These stem cells can give rise to specialised cell types of the tissue from which they came (i.e., a heart stem cell can give rise to a functional heart muscle cell). They can be harvested from bone marrow, adipose tissue, and umbilical cord blood.

2. Embryonic stem cells: They are self-renewing (can replicate itself), pluripotent (can form all cell types found in the body) and theoretically is immortal. They are derived from the inner cell mass of developing blastocysts.

Embryonic stem cell versus adult stem cell

<table>
<thead>
<tr>
<th>Embryonic stem cell (ESC)</th>
<th>Adult stem cells (ASC)</th>
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</thead>
<tbody>
<tr>
<td>High malleability</td>
<td>Limited developmental potential</td>
</tr>
<tr>
<td>Potential for undesired development (teratomas)</td>
<td>Better behaved, easier to manage</td>
</tr>
<tr>
<td>Infinite lifespan, unlimited supply</td>
<td>Lose their ability to proliferate or differentiate after a time in culture</td>
</tr>
<tr>
<td>High ethical burden</td>
<td>Less moral ambiguity</td>
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<tr>
<td>Uncertain legal status</td>
<td>Less legal controversy</td>
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</tbody>
</table>

Haematopoietic stem cell transplantation (HSCT)

The transplantation of multipotent haematopoietic stem cells, usually derived from bone marrow, peripheral blood, or umbilical cord blood is called haematopoietic stem cell transplantation. It has a proven role in haematologic malignancies, e.g., multiple myeloma, leukemias, lymphomas, anaemias such as aplastic anaemia, thalassaemia, sickle cell anaemia and germ cell tumour autoimmune disorders such as systemic lupus erythematosus, or amyloidosis.

Types of stem cell transplantation

Allogeneic transplantation: Cell, tissue or organ transplant from one member of a species to a genetically different member of the same species (HLA matched).
Advantages
- No tumour contamination of the graft and no prior marrow injury from chemotherapy (less risk of later myelodysplasia)
- Graft versus tumour effect
- Can be used for patients with marrow involvement by tumour or with bone marrow dysfunction, such as aplastic anaemia, haemoglobinopathies or prior pelvic radiation

Disadvantages
- Dose intensive regimen limited by toxicity (usually limited to patients < age 55)
- Time needed to identify donor if no sibling donor available
- Higher early treatment-related mortality from GVHD (graft versus host disease) and infectious complications (20 - 40%)
- Allogeneic transplant costlier than autologous transplantation (Rs. 500,000 - 100,000 for allogeneic while 300,000 - 500,000 for autologous HSCT in India).

Autologous transplantation: Cell, tissue, or organ transplants from one individual back to the same individual. Such transplants do not induce an immune response and are not rejected.

Advantages
- No need to identify donor
- No immunosuppression
- Lesser risk of infection
- No GVHD
- Dose intensive therapy can be used for older patients (usually upto age 70)
- Low early treatment related mortality (2 - 5%)

Disadvantages
- Not feasible if peripheral blood is involved
- Possible marrow injury leading to myelodysplasia
- No graft vs host reaction

Indications for bone marrow/blood stem cell transplantation

<table>
<thead>
<tr>
<th>Indications</th>
<th>Allogeneic</th>
<th>Autologous</th>
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</thead>
<tbody>
<tr>
<td>Severe aplastic anaemia</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Beta-thalassaemia</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Fanconi anaemia</td>
<td>+</td>
<td>-</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Sickle cell anaemia</th>
<th>+</th>
<th>-</th>
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<tbody>
<tr>
<td>Immunodeficiency disease</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Severe combined</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Wiskott-Aldrich syndrome</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Chediak-Higashi disease</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Inborn error of metabolism</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Acute myeloblastic leukaemia</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Acute lymphoblastic leukaemia</td>
<td>+</td>
<td>+ (experimental)</td>
</tr>
<tr>
<td>Chronic myeloid leukaemia</td>
<td>+</td>
<td>+ (experimental)</td>
</tr>
<tr>
<td>Chronic lymphoblastic leukaemia</td>
<td>+</td>
<td>+ (experimental)</td>
</tr>
<tr>
<td>Myelodysplastic syndrome</td>
<td>+</td>
<td>+ (experimental)</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>+</td>
<td>(experimental)</td>
</tr>
<tr>
<td>Hodgkin's lymphoma</td>
<td>+</td>
<td>(experimental)</td>
</tr>
<tr>
<td>Non-Hodgkin's lymphoma</td>
<td>+</td>
<td>(experimental)</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>-</td>
<td>+</td>
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<tr>
<td>Germ cell tumour of testis</td>
<td>-</td>
<td>+ (experimental)</td>
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</tbody>
</table>

Harvesting stem cells

Stem cells can be harvested from bone marrow, peripheral blood, and umbilical cord.

Bone marrow

It is done under general anaesthesia by repeated aspiration from posterior iliac crest. It can also be obtained from anterior iliac crest or sternum. In allogeneic haematopoietic stem cell transplantation with major ABO incompatibility between the donor and recipient, mature RBCs are removed from the graft as it avoids haemolytic transfusion reaction1.

Peripheral blood stem cells

Peripheral blood stem cells have to be mobilised from the marrow. It is done by giving the donor G-CSF (5µ/kg/day in 2 divided doses, s.c., for 5 days). On day 5 - 6 after drug administration, peripheral blood stem cells are collected by leucopheresis using an apheresis machine. Peripheral blood stem cells are cryopreserved at -80°C using 7.5% dimethylsulfoxide or liquid nitrogen. Patient is then administered high dose chemotherapy. Peripheral blood stem cells are then infused 24 - 48 hrs later (depending upon half-life of the agents). Primary concern with autologous HSCT is re-infusion of malignant cells along with progenitor cells1,8-11.

Umbilical cord

Umbilical cord blood (UCB) is a rich source of primitive
stem cells. It has certain distinct advantages over other types such as:

- Relative immaturity of immune system at birth → lower risk of acute graft versus host reaction.
- Easy procurement
- No risk to donors
- Reduced risk of transmitting infections
- Immediate availability of cryopreserved unit
- Acceptable partial HLA mismatches

It also has certain shortcomings such as:

- Higher primary graft failure (10 - 20%)
- Delayed myeloid recovery (smaller number of stem cells in UCB)

Due to limited yield of stem cells from a single UCB donor, UCB stem cells from single donor have been in children < 25 kg. weight while in adults – double UCB donor stem cells transplant may be used.

**Pre-transplant issues for all transplant patients**

- Fertility counselling/sperm banking is advised to the patients before chemotherapy administration.
- Well-balanced diet and mild exercise are found to be helpful.
- Smoking is best avoided.
- Counselling about quality of life post-transplant
- Dental examination: dental cavities can be a serious source of infection after transplant. Therefore, these need to be treated before commencing conditioning.
- Bone marrow transplantation is a long process involving unpleasant treatments and side-effects. In some centres, a psychologist is available to help the patient cope and come to terms with this experience.
- Females who have reached puberty are asked to have a pregnancy test as part of routine pre-transplant preparation.

**Transplant process (5 steps)**

1. **Conditioning phase**
   
   The conditioning period typically lasts 7 - 10 days. The purposes is to eliminate malignancy and to provide immune suppression to prevent rejection of new stem cells. It is done by delivery of chemotherapy and/or radiation.

2. **Stem cell processing and infusion**

   Infusion – 20 minutes to an hour, varies depending on the volume infused. The stem cells may be processed before infusion, if indicated. Depletion of T-cells can be performed to decrease GVHD. Premedication is done with acetaminophen and diphenhydramine to prevent reaction. It is infused through a central venous line, much like a blood transfusion. Anaphylaxis, volume overload, and rarely a transient GVHD are the major potential complications involved. Stem cell products that have been cryopreserved contain dimethyl sulfoxide (DMSO) as a preservative and potentially can cause renal failure, in addition to the unpleasant smell and taste.

3. **Neutropenic phase**

   During this period (2 - 4 weeks), the patient essentially has no effective immune system. Healing is poor, and the patient is very susceptible to infection. Supportive care and empiric antibiotic therapy are the mainstays of successful passage through this phase.

4. **Engraftment phase**

   During this period (several weeks), the healing process begins with resolution of mucositis and other lesions acquired. In addition, fever begins to subside, and infections often begin to clear. The greatest challenges at this time are management of GVHD and prevention of viral infections (especially CMV).

5. **Post-engraftment phase**

   This period lasts for months to years. Hallmarks of this phase include the gradual development of tolerance, weaning-off of immunosuppression, management of chronic GVHD, and documentation of immune reconstitution.

**Post-transplant care**

**General care**

- Masks are mandatory for these patients.
- Patient has to avoid crowds and public places.
For the first 100 days after transplant, the patient will not return to work or school.

Avoid all contact with animals and their droppings/waste.

Avoid gardening, mowing the lawn, and other activities that stir-up the soil or the ground.

Avoid swimming in lakes, public pools, and sitting in hot tubs.

Stay away from dusty, dirty, moldy things (construction areas, remodelling areas, vacuum cleaner bags, etc.).

Avoid stagnant water (flower vases, vaporisers, dehumidifiers, etc.).

Family members and people in close contact should receive the influenza (flu) vaccine.

Maintain proper hygiene, esp. oral care, skin care.

Sexual activity

Precautions are advised, e.g., barrier method to avoid STD.

Water-based lubricant to combat vaginal dryness (which results because of chemotherapy and radiation).

Notification of communicable diseases like measles, chicken pox, etc., in community.

Avoid contact with children who have received a live immunisation (such as the chicken pox vaccine).

Re-immunisation: The immune system may no longer “remember” its previous exposures to childhood vaccinations. Therefore, the patient will have to be re-immunised with several of the childhood vaccines one to two years after transplant.

Drugs to avoid: Especially aspirin and ibuprofen have to be avoided because of their antiplatelet activity.

Complications following stem cell transplantation

Acute

- Infection
- Graft rejection
- Acute graft versus host reaction
- Regimen related complications
- Gastrointestinal – nausea/vomiting, diarrhoea, mucositis, pulmonary, and cardiac
- Haemorrhagic cystitis
- Veno-occlusive disease

- Chronic graft versus host reaction
- Relapse
- Sterility
- Cataract
- Secondary leukaemia

HSCT in haematological disorders – present scenerio

Severe aplastic anaemia: Treatment of choice in < 40 yrs is allogeneic HSCT. 3 yrs probability of survival is 83% for < 20 years of age, 70% for > 20 years of age. There is a small risk of development of solid organ tumour. Older patients can be managed with ATG ± CSA; 50% survive 15 years after therapy.

Thalassaemia: For children born with severe forms of thalassaemia, chronic transfusions will lead to normal growth and development. However, without aggressive iron chelation, endocrine failure will ensue, and most will die in the second or third decade of life from iron overload. Aggressive iron chelation will prevent or delay these complications. Stem-cell transplantation, if available, is the best treatment option: In young patients, there will be fewer complications than with other treatments, and if transplantation is successful, there is no need for lifelong therapy with transfusion and chelation.

Hodgkin’s lymphoma (HL): Relapsed HL or HL refractory to primary chemotherapy is managed with high-dose chemotherapy (HDCT) + autologous HSCT. 3 yrs probability of survival is 78% for patients in CR (complete remission) and 68% for patients in sensitive relapse and 57% for resistant relapse. Allogenic HSCT for this disease is experimental.

Non-Hodgkin’s lymphoma (NHL): Diffuse large B-cell lymphoma are managed with HDCT + autologous HSCT in case of relapse, in those who have achieved second complete remission and good partial response after salvage chemotherapy. Patient with high risk International Prognostic Index (IPI) score 4 - 5 benefit from HDCT + autologous HSCT.

Multiple myeloma (standard of care in patients < 65 yrs of age): Initial induction therapy is given with thalidomide/lenalidomide/bortezomib + dexamethasone followed by autologous PB HSCT and then maintenance therapy using lenalidomide or bortezomib or thalidomide in low dose for 1 year. Outcome is superior if HSCT is performed within 12 - 18 months of diagnosis.

Myelodysplastic syndrome (MDS): It is treatment of choice for patients with IPSS intermediate -2 and high risk MDS.
Chronic myeloid leukaemia (CML): Allogenic HSCT is considered for all patients who fail to achieve remission after 3 months of imatinib therapy, or those who fail to achieve complete cytogenetic remission after 12 - 18 months of imatinib therapy; relapse after initial response and in advanced disease (accelerated phase or blast crisis). LFS (leukaemia free survival) (5 yr) in chronic phase > 50%. DFS (disease free survival) in accelerated phase – 15 - 25%, and in blast crisis < 15% of cases.

Chronic lymphoid leukaemia (CLL): Autologous HSCT is done in young patients with high risk CLL. Allogenic HSCT in CLL is associated with increased failure rates; it is still under research.

Acute lymphoid leukaemia (ALL)

Use of the antileukemic agents together with a stringent application of prognostic factors for risk-directed therapy in clinical trials, has resulted in a steady improvement in treatment outcome in children and adolescents. Unfortunately, the experience with adult ALL has been far less rewarding: reported cure rates seldom exceed 40 per cent. The poor outcome in adult ALL has been variously attributed to an increased frequency of high-risk leukaemia with greater drug resistance, poorer tolerance of and compliance with treatment, reluctance to accept certain temporary toxic effects, and less effective treatment regimens, as compared with childhood ALL. Allogeneic transplantation is the ultimate form of treatment intensification. Among adults with ALL, long-term disease-free survival rates of 30 to 40 per cent have been obtained with the use of chemotherapy, as compared with 45 to 75 per cent with the use of allogeneic transplantation.

Even so, allogeneic transplantation clearly benefits certain very high-risk paediatric and adult patients, such as those with BCR-ABL+ ALL or those with a poor initial response to treatment. The procedure also appears to improve the clinical outcome among adults who have ALL with t(4;11), but whether it is beneficial for infants with the same genotype remains controversial.

HSCT in paediatric solid tumours

Primary HDCT+ HSCT reserved for patients who are poor risk patients with an expected survival rate < 20% at 3 years with conventional therapy.

Stem cell therapy in non-haematological conditions

Stem cell therapy is still under research for its therapeutic potential in the following conditions:

Pulmonology: ARDS, emphysema, lung fibrosis, pulmonary arterial hypertension – endothelial progenitor cells transduced with nitric oxide synthetase, lung cancer – targeting endogenous stem cells with potential.

Neurology: with spinal cord injury, amyotrophic lateral sclerosis (ALS), stroke, traumatic brain injury, and Parkinson’s disease sp.

Endocrinology: Type 1 diabetes.

Hepatology: Liver failure, cirrhosis – it potentially can substitute for organ transplantation.

Peripheral artery disease: Chronic limb ischaemia.

Nephrology: End-stage renal disease.

Umbilical cord banks in India

The following umbilical cord banks are operational in India.

- Life cell
- Public stem cell bank – Jeevan
- Cryosave
- Cord life
- ReeLabs

Stem cell transplantation in India

HSCT is being done at 37 centres in India, e.g.:

- Tata Memorial Hospital, Mumbai, Maharashtra
- Institute Rotary Cancer Hospital, New Delhi
- Adyar Cancer Institute, Chennai, Tamil Nadu
- Apollo Speciality Hospital, Chennai, Tamil Nadu
- Tata Memorial Rural Cancer Project, Barshi, Solapur, Maharashtra
- R and R Army Hospital, New Delhi
- Cancer Care Trust and Research Foundation, Indore, Madhya Pradesh
- Inlaks Hospital, Pune, Maharashtra
- Gujarat Cancer and Research Institute, Ahmedabad, Gujarat
- Sanjay Gandhi Post-Graduate Institute of Medical Sciences, Lucknow, Uttar Pradesh
- Armed Forces Medical College and Command Hospital (SC), Pune, Maharashtra.

Ethical concerns

They are mostly related to embryonic stem cells. Adult stem
cells such as those derived from bone marrow harvested as autologous cells and are generally free of ethical controversy.

References


“A vigorous five-mile walk will do more good for an unhappy but otherwise healthy adult than all the medicine and psychology in the world.”

– PAUL DUDLEY WHITE.