Introduction

Stem cells have been used in the treatment of hematopoietic disease for more than half a century. Diseased ("bad") stem cells may be replaced with good ones through a process known as hematopoietic stem cell transplantation (HSCT). The earliest attempts began sixty years ago with animal experiments when Lorenz et al demonstrated [1] that mice given lethal doses of radiation could recover if they received bone marrow transplants (BMT). The idea that hematopoietic and immune cells from another individual could exist in harmony with the recipient's cells was reinforced a few years later when Main and Prehn showed that irradiated mice given bone marrow infusions from a specific donor were able to receive skin grafts from the same donor mice [2]. This led to the idea of donor chimerism and immune tolerance. Soon, the knowledge of human leukocyte antigens (HLA) emerged when it was noted that certain antibodies could be formed in sera following childbirth or transfusion that reacted with white cells [3].

The first reported case of BMT was published by Thomas et al in 1959, where a syngeneic twin with terminal leukaemia was irradiated and later infused with marrow from the healthy twin, whereupon there was not only recovery from the low blood counts...
associated with radiation treatment but also transient clearance of leukaemia [4]. Dr Thomas later received the Nobel Prize for this work. The first allogeneic BMT with long term successful outcome was performed in 1968 in a patient with Wiskott Aldrich Syndrome who attained lasting disappearance of all signs of his disease after bone marrow infusion from his sibling [5]. Over the next decade, many more patients with haematological disorders underwent transplantation with sibling donors with improved results. The next major milestone was the use of unrelated donor hematopoietic stem cells in 1979 [6]. This was followed by the first reports of cord blood transplantation and reduced intensity transplantation.

**Procedure and Complications**

HSCT is carried out by first administering a “conditioning” treatment to the patient. This conditioning regimen comprises chemotherapy and/or radiotherapy and serves two purposes. Firstly, it helps to eradicate whatever bone marrow disease the patient has. Secondly, it serves as a strong immunosuppressive to prevent rejection of the donor cells. Following completion of the conditioning regimen, patients will receive an infusion of stem cells from the donor. If the patient serves as his own donor, this is known as an autologous transplant. Otherwise transplants from another individual are known as allogeneic transplants. Such allogeneic stem cells may be obtained from twins (syngeneic), tissue-matched siblings, matched unrelated donors and haploidentical donors. Haploidentical donors are essentially family donors who are only half-matched with the patient and such transplants carry a higher risk.

Besides the risks associated with the chemotherapy and radiotherapy, HSCT is also associated with another complication known as graft versus host disease (GVHD), a phenomenon where donor immune cells attack the patient’s tissues. This syndrome was first observed when Brent, Billingham, Medawar, and their colleagues identified the concept of ‘runt disease’ in mice, which was seen only when the donor cells were of ‘allogeneic’ origin, that is, from someone else who was not a twin [7,8]. Since then, major improvements in understanding HLA and GVHD have resulted in improvements in donor selection and reducing incidence of GVHD.

**Sources of hematopoietic stem cells**

Hematopoietic stem cells (HSCs) for clinical transplantation are currently obtained from the bone marrow, peripheral blood stem cells (PBSC) and umbilical cord blood (UCB). The three different sources have their own unique

<table>
<thead>
<tr>
<th>SOURCE</th>
<th>BMT</th>
<th>PBSCT</th>
<th>UCBT</th>
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</thead>
<tbody>
<tr>
<td><strong>Collection</strong></td>
<td>Need general anaesthesia and invasive procedure - multiple bone marrow aspiration</td>
<td>Relative easy - Donor connected to stem cell harvesting machine through arm veins</td>
<td>Collected from umbilical cord after child birth - Easy</td>
</tr>
<tr>
<td><strong>Dose of stem cells</strong></td>
<td>Low</td>
<td>High</td>
<td>Lowest</td>
</tr>
<tr>
<td><strong>Risk of infection to the recipient from the donor.</strong></td>
<td>Yes - Need stringent testing</td>
<td>Yes - Need stringent testing</td>
<td>Comparably lower - need all the tests still</td>
</tr>
<tr>
<td><strong>Risk to donor</strong></td>
<td>Yes - Risk of general anaesthesia, Pain and discomfort of bone marrow aspiration</td>
<td>Risk from having Growth factor injected prior to collecting stem cells - Bone pains, side effects of connecting to the harvest machine - Low blood pressure etc</td>
<td>None</td>
</tr>
<tr>
<td><strong>Time to count recovery</strong></td>
<td>High (due to low stem cell count)</td>
<td>Low (High stem cell count)</td>
<td>High (Lowest stem cell count of all 3 sources)</td>
</tr>
<tr>
<td><strong>Risk of infection due to prolonged low cell counts prior to recovery</strong></td>
<td>High</td>
<td>Low</td>
<td>Highest of all three</td>
</tr>
<tr>
<td><strong>Risk of GVHD</strong></td>
<td>Low (Due to low T cell count in the stem cell fraction)</td>
<td>High (due to high T cell content in per blood stem cell fraction)</td>
<td>Lowest</td>
</tr>
<tr>
<td><strong>Need for HLA matching</strong></td>
<td>Stringent - best match preferred</td>
<td>Stringent - best match preferred</td>
<td>Less than stringent match allowed</td>
</tr>
</tbody>
</table>
features and these pertain mainly to ease of collection, rapidity of blood count recovery after transplantation and GVHD risk. There has been some shift in the overall preference of stem cell source over the years with more PBSC transplants (PBSCT) and umbilical cord blood transplants (UCBT) being carried out than BMT. Table 1 looks at the relative advantages and disadvantages related to the different stem cell sources.

Because of the perceived relative ease and safety of the PBSC donation, many donors choose to donate PBSC rather than bone marrow. This is especially relevant when the donor is not a sibling, as the prospect of a bone marrow biopsy under general anesthesia is likely to reduce the willingness of an unrelated matched donor. In treatment of certain specific conditions (e.g. aplastic anaemia, a condition whereby the bone marrow stops producing blood cells) however, bone marrow is the preferred stem cell source as it confers a lower risk of GVHD with acceptable rates of blood count recovery. There is growing experience with UCB stem cells, which is the preferred source in pediatric patients in many centers worldwide because of the lower risk of GVHD. In adults, cord blood poses a problem because of the lower stem cell content and the inadequacy to reconstitute a normal sized adult with one unit of cord blood stem. This results in an increased risk of infection as the patients have low cell counts for prolonged periods post transplant. There is increasing experience with using double cord stem cell units harvested from different sources in the same patient with encouraging results.

### Indications for Hematopoietic stem cell transplantation

The indications for HSCT include many cancers and non-malignant diseases. The most common use of HSCT has been for cancer, especially the haematological malignancies like leukaemia, lymphoma and myeloma. Leukemias may be further subdivided into acute myeloid leukemia, acute lymphoblastic leukemia, chronic myeloid leukemia and chronic lymphocytic leukemia. Lymphomas may be subdivided to Hodgkin’s and Non-Hodgkin lymphoma, which may be further subdivided into many varieties of B, T and NK cell lymphoma. Not all patients with these diseases require a transplant and the selection of patients for HSCT depends on various clinical and laboratory prognostic markers.

Besides cancer, many non-malignant genetic diseases may also benefit from transplantation. These include primary immunodeficiencies (like severe combined immune deficiency and Wiskott Aldrich syndrome), bone marrow failure syndromes (like Fanconi Anaemia and Dyskeratosis Congenita), hemoglobinopathies (like thalassaemia major and sickle cell disease), and inherited metabolic diseases (including lysosomal storage diseases like Hurler syndrome). Because of the potential benefit of HSCT for these diseases, accurate diagnosis, early detection and identification of high-risk patients through skilled physicians and specialised laboratories is critical.

Recently, a number of transplants have been performed for patients with autoimmune disease like systemic lupus erythematosus, systemic sclerosis and...
multiple sclerosis. The outcomes of these transplants have been fascinating as many patients have attained long term control of otherwise progressive disorders.

New Frontiers

Stem cells for hematopoietic diseases have been studied, clinically applied and further developed over the last half century. In fact, the application of stem cells in hematopoietic disease is currently the only stem cell type which is used regularly and very successfully in the clinical setting. Scientific advances now allow transplants be carried out even more safely than before. New methods of delivering pre-transplant chemotherapy have reduced the toxicity and increased the efficacy of HSCT. This has allowed us to transplant patients who are older; less medically fit and with more advanced disease. Umbilical cord blood and haploidentical transplants have further increased the number of donors we can choose from. New cellular therapies (like anti-tumor immune cells selected and grown in culture) now also allow us to enhance the anti-cancer effect of donor cells. Mesenchymal stem cell infusions and regulatory T cell infusions have been studied for the treatment of GVHD. Hematopoietic stem cells are also being studied as carriers for gene therapy. The future of HSCT appears to be even more exciting and ever changing.

References


About the Authors

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