Hematopoietic Stem Cell Transplantation

Al Hijji I.
Hematology Department, Al Amal Hospital
Hamad Medical Corporation, Doha, Qatar

Abstract:

About 30 years ago bone marrow transplantation was an experimental procedure carried out as a last resort in terminally ill patients. Nowadays hematopoietic stem cell transplantation (HSCT) has become a standard procedure for many severe malignant or non-malignant disorders of the hematopoietic system. It is well known that HSCT is associated with transplant related mortality and morbidity (TRM), the risk of which in allogeneic transplantations can reach 40%; in contrast the risk is less than 5% in autologous transplantation. However, HSCT outcome has been improved significantly over the past decade both in terms of reduced TRM and reduced risk of relapse of the original disease.

Keywords: HSCT, TRM, GHD, RICT and HLA

Introduction:

Hematopoietic stem cells (HSC) are defined by their dual ability to self-replicate and undergo terminal differentiation into erythroid, myeloid, megakaryocytic and lymphoid lineages. This unique feature of HSC has led to hematopoietic stem cell transplantation (HSCT) (1). More than 30 years ago, bone marrow transplantation was an experimental procedure carried out as a last resort in terminally ill patients. Thomas was a pioneer in applying the results from early studies in animals to the treatment of leukemia in people. In 1959, he and his colleagues reported that a patient with end-stage leukemia who was treated with total-body irradiation, followed by infusion of her identical twin’s marrow, had a three-month remission (2).

Allogeneic transplantation became feasible in the early 1960s, after the identification and typing of the major histocompatibility complex in HLA. The genes for HLA are closely linked on chromosome 6 and are inherited as haplotypes. Thus, two siblings have about one chance in four of being HLA identical. In the 1970s, Thomas and colleagues cured some patients who had end-stage leukemia by using marrow from their HLA-identical siblings after ablating the host marrow with total-body irradiation combined with cyclophosphamide (3). Transplantation during the first remission of the leukemia was successful in more than half the patients. The occurrence of Graft V Host Disease (GVHD) reduced the incidence of leukaemic relapse, which suggested that donor lymphocytes can eradicate tumor cells that survive preparative regimens.

So nowadays HSCT is no longer an experimental procedure and it has become a standard procedure for many severe malignant or non-malignant disorders of hematopoietic system (4,5). It is well known that HSCT is associated with transplant related mortality and morbidity (TRM). Risk of TRM in allogeneic transplantation setting can reach up to 40%, in contrast to less than 5% in autologous transplantation. However, HSCT outcome has been improved significantly over the past decade both in terms of reduced TRM and reduced risk of relapse of the original disease (6).

Indications:

HSCT has evolved from an emergency measure in difficult situations to the establishment of a planned procedure that is integrated in the therapeutic plan of many malignancies as well as acquired or congenital disorders of the hematopoietic system. Improvements in HLA matching, prophylaxis and treatment of GVHD, and supportive therapy including prophylactic antimicrobials have enabled the wider application of allogeneic transplantation to more diseases, including some non-malignant conditions such as thalassaemia and inherited metabolic disorders.

On the other hand, autologous transplant allows escalation of cytotoxic treatments and reduces the period of neutropenia after treatment. Therefore it has been introduced for disorders where higher doses of conventional chemotherapy might be expected to eradicate the disease such as neuroblastoma, Non-
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Hodgkin’s lymphoma, Hodgkin’s disease in second remission, certain solid tumors and some autoimmune diseases (5'712'27), (Table 1).

Table 1: Common Indications for HSCT

So the decision on the type of transplant that could be offered depends on many factors including age, underlying disease, stage of the disease, performance status, previous treatment and the presence or absence of other medical illnesses.

HSCT Techniques:

HSCT usually involves the administration of myeloablative doses of chemotherapy with or without irradiation, this is known as a conditioning regimen or high dose therapy (HDT), then it is followed by stem cells infusion, intended to establish hematopoiesis and/or lymphopoiesis.

Allogeneic transplants are hematopoietic stem cells from the bone marrow, peripheral blood, or umbilical cord blood of a healthy donor matched for human leucocyte antigen (HLA) type, who may be a family member or an unrelated volunteer. Autologous transplants are stem cells from the bone marrow or peripheral blood of the patient.

Allogeneic HSCT aims at total replacement of the hematopoiesis system by donor type cells. The patient and the donor should be maximally matched HLA to reduce the risk of TRM. Autologous HSCT is the most common form of stem cells transplantation and is designed to shorten the period of aplasia following HDT (7). (Figure 1).

Figure 1: Stem cell transplantation techniques.

### Allograft Procedure

**Recipient**
- Conditioning (Chemotherapy or Chemoradiotherapy)
- Harrowing of bone marrow or peripheral blood
- Severe myelosuppression as conditioning takes effects
- Engraftment: Neutrophils > 0.5 x 10^9/L Platelets > 20 x 10^9/L

**Donor**
- Conditioning (Chemotherapy or Chemoradiotherapy)
- Harvesting of bone marrow or peripheral blood
- Processing and cryopreservation
- Conditioning (Chemotherapy or Chemoradiotherapy)
- Transportation of thawed stem cells
- Severe myelosuppression as conditioning takes effect
- Engraftment: Neutrophils > 0.5 x 10^9/L Platelets > 20 x 10^9/L

### Autologous Procedure

**Recipient (in Disease Remission)**
- Harvesting of bone marrow or peripheral blood
- Conditioning (Chemotherapy or Chemoradiotherapy)
- Transportation of stem cells
- Severe myelosuppression as conditioning takes effect
- Engraftment: Neutrophils > 0.5 x 10^9/L Platelets > 20 x 10^9/L

**Recipient**
- Conditioning (Chemotherapy or Chemoradiotherapy)
- Harrowing of bone marrow or peripheral blood
- Severe myelosuppression as conditioning takes effects
- Engraftment: Neutrophils > 0.5 x 10^9/L Platelets > 20 x 10^9/L

### Table 1: Common Indications for HSCT

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<th>Allogeneic Transplantation</th>
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<tr>
<td>Non-Hodgkin lymphoma</td>
<td>AML</td>
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<tr>
<td>(at time of relapse)</td>
<td>Non-Hodgkin lymphoma (high risk especially with low grade)</td>
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<tr>
<td>Hodgkin disease</td>
<td>Hodgkin disease (high risk)</td>
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<tr>
<td>(at time of relapse)</td>
<td>Acute lympho-blastic leukemia (ALL)</td>
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<tr>
<td>Acute myeloid leukemia (AML)</td>
<td>Chronic myeloid leukemia (CML) (now a days the decision is becoming more difficult due to the introduction of Imatinib)</td>
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<tr>
<td>(the outcome is almost the same as Chemotherapy)</td>
<td>Myelodysplastic syndromes</td>
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<tr>
<td>Medulloblastoma</td>
<td>Multiple myeloma (still experimental)</td>
</tr>
<tr>
<td>Germ-cell tumors</td>
<td>Chronic Lymphocytic Leukemia (CLL)</td>
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<tr>
<td>Combined immunodeficiency</td>
<td>Thalassemia major</td>
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<td>Thalassemia major</td>
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Improvements in HSCT:

The lack of suitable HLA-matched donors has limited the use of allogeneic transplants due to the high risk of life-threatening complications associated with the procedure when immunological identity between donor and recipient is not present. Because of this and the toxicities associated with transplant, many researches have been focused to find other sources of stem cells, reduce the toxicity and to improve the outcome.

Stem Cell Sources:

Bone marrow was the first source of hematopoietic stem cells. During the early 1980s it was noted that marrow stem cells circulated in peripheral blood in small numbers in normal controls but in greater numbers in patients recovering from neutropenia induced by chemotherapy. Stem cell yields increased further if the patient was given bone marrow growth factor during the recovery period. With this technique, called peripheral blood stem cells transplantation (PBSCT), sufficient cells can usually be harvested from the peripheral blood over 2-3 days to safely perform an autologous transplantation. It was quickly noted that patients receiving this type of transplant recovered their peripheral blood counts more rapidly than did patients given transplants of cryo-preserved autologous bone marrow. The other advantages are that the procedure of mobilization does not need an operating theatre and peripheral blood probably has less tumor contamination compare to bone marrow.

Despite an increase in T-cells of mobilized peripheral stem cells, the incidence of acute GVHD in allogeneic HSCT is the same as that complicating the bone marrow transplant. However, chronic GVHD incidence in patients undergoing allogeneic PBSCT may be increased when compared with recipients of conventional bone marrow harvests (Table 2).

Overall this has altered the practice of clinical transplantation in the last 15 years. As a consequence more than 90% of autologous transplants are now performed using progenitors harvested from the peripheral blood rather than the bone marrow and mobilized progenitors are also increasingly used in allogeneic transplantation\(^{(8,9,10)}\).

Another source of stem cells is umbilical cord blood (UCB), which has been rapidly established as an alternative to bone marrow for allogeneic related and unrelated HSCT. Despite the fact that the number of functional hematopoietic stem cells in a cord blood unit is 10 times less than a bone marrow graft, their proliferative capacity is superior to that of cells in adult bone marrow or peripheral blood (Table 3). The association with GVHD is small, the allowance of a wider HLA disparity between grafts and recipients and the relatively easy collection procedure has permitted an enormous expansion of the donor pool and representation of ethnic minorities. It has been found that UCB is associated with low transmission rates of infections and genetic diseases although this is still controversial. The disadvantage of UCB is that, due to the dose of cells, it is usually suitable only for children and it is associated with a delayed hematopoietic recovery\(^{(11,12)}\). The use of additional grafts from different donors may improve engraftment. This strategy can be applied for adults who do not have matched donor and are in need of allogeneic transplant\(^{(13)}\).

Purging:

As an autograft lacks an anti-tumor effect it might fail for two reasons. Either the chemotherapy fails to eradicate the tumor, leading to eventual relapse, or the graft may be contaminated with tumor cells, which are re-infused and again cause a relapse. To reduce contamination with tumor cells, physicians might attempt to clean up (purge) the transplant by using
monoclonal antibodies directed against the tumor cells, chemotherapeutic agents, or by using peripheral blood stem cells instead of marrow\(^{14}\). However, the overall survival is the same whether purging has been performed or not and most of relapses are due to minimal residual disease which was not eradicated by chemotherapy prior to transplant.

**GVHD:**

GVHD remains the most common complication that occurs after allogeneic HSCT; it usually depends upon age, the source of HSC and the degree of HLA-mismatch between the patient and the donor. It is well-known that GVHD is caused by the activation of lymphocytes derived from the donor, leading to immune damage to the skin, gut, and liver in the recipient. Patients who experience GVHD, however, have a lower risk of developing recurrent disease. This suggests an important anti-tumor effect through donor lymphocytes\(^{15}\).

It has been seen that even with an HLA-matched sibling donor, mild GVHD can occur in half of patients, probably due to a minor mismatched histocompatibility complex. In turn it might lead to a graft-versus-tumor (GVT) effect that benefits the patient by eradicating the residual disease and reducing the chance of relapse.

GVHD can occur early (acute), characterized by loose motions, abnormal liver function, skin rash and can lead to bone marrow failure and severe infections. Also it can occur late (chronic), more than 100 days post transplant, with features similar to autoimmune disorders. Studies have indicated that the addition of cyclosporine to a short course of methotrexate results in improved prevention of acute GVHD. The removal of T-cells from the graft can also prevent acute GVHD but at the cost of graft failure, delayed immunologic recovery and loss of the GVT effect. The standard treatment is immuno-suppressive but, despite this measure, mortality secondary to severe GVHD remains high\(^{16-18}\).

**Histocompatibility:**

The most important factor affecting the outcome of allogeneic transplantation is the quality of the HLA match between donor and recipient. It is known that HLA antigens provoke immune reactions when tissues are grafted from one individual to another. This can cause serious morbidity and even death if there is a major HLA mismatched. The genetic control of these antigens resides on chromosome 6 in a super-gene region known as the major histocompatibility complex (MHC).

In this region, class 1 antigens involve three loci important in transplantation, HLA-A, B, and C while class 2 antigens are governed by HLA-DR, DP, and DQ. Each parent has two HLA haplotype and each child inherits one haplotype from each parent. Thus there is one chance in four that a sibling will be matched with a patient and this has led to searches for unrelated donors.

In the 1990s serologic typing techniques have been replaced by molecular techniques that enable precise characterization of MHC genes. The DNA techniques have improved the outcome of transplant by choosing the most suitable HLA matched donors and have made possible matching of unrelated individuals\(^{19,20,21}\).

**Reduced Intensity Conditioning Transplantation (RICT):**

Current HSCT conditioning regimens are designed to administer the maximally tolerated doses of chemotherapy with or without radiotherapy in an attempt to eradicateresidual disease, ablate host hematopoiesis and immune suppress the recipient to ensure engraftment of donor hematopoietic stem cells. While this approach is curative for many patients, it is associated with ~30-50% TRM. Recent studies suggest that disease control and engraftment of allogeneic HSCT can be achieved following non-ablative doses of chemoradiotherapy. Moreover, in various diseases, the beneficial effects of the allogeneic HSCT result from immune-mediated GVT effect, delivered by donor’s T-cells, and not from the high doses of chemotherapy administered in the preparative regimens.

RICT is generally associated with a decrease in TRM and other complications compared to the conventional HSCT but acute and chronic GVHD remain major complications in high risk and elderly patients\(^{6,13}\). A new strategy has been developed similar to RICT called donor lymphocytes infusion (DLI). Numerous reports have confirmed the anti-tumor effect of DLI. It can result in long-standing remission for relapsed disease post allogeneic HSCT but with risks to the host of marrow suppression and GVHD.

In general the benefits of allogeneic HSCT can be extended potentially to patients who would not be considered candidates for conventional myelo-ablative transplant regimens particularly elderly patients. Therefore, nowadays, RICT is performed to reduce TRM and to allow immune modulation to take place with possibly DLI given three months later to augment the GVT effect particularly if host cells are starting to increase post allogeneic HSCT\(^{23,24}\).

**Infection Prophylaxis:**

Infections are common when HSCT is used but the currently available powerful anti-microbials have improved the out-come of transplant. In addition the development of infection surveillance and the early detection of infection has allowed the use of anti-microbials before full-blown infections in immuno-compromised patients\(^{25,26}\).
Conclusion:

HSCT is a highly complex, cost intensive but powerful therapeutic strategy. It is also an expanding field with additional rapid changes in technology. HSCT requires a complex network of highly trained physicians and nurse specialists with a help of other specialties. The decision making of HSCT represents a challenge for treating physicians, patients and health care agencies. Patients are confronted with immediate risks and late benefits, physicians are challenged to give advice to well informed-patients and health care officials are obliged to provide the needed infrastructure for high tech, high cost medicine. In addition, the introduction and understanding of the new concepts might change the short term outlook for patients or open up the technology to new patient categories.

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