Introduction

Stem cell transplantation (SCT) is a life saving procedure for a number of malignant and non-malignant life threatening diseases. More than 40,000 SCTs are being performed annually worldwide. In India, progress has been slow and the number of transplants performed till now is around 500. The procedure itself has many technical variations according to the primary disease, age of the patient, facilities available, and experience of the centre. In India, the larger transplant centres are: Tata Memorial Hospital, Mumbai; Christian Medical College, Vellore; AIIMS, New Delhi; Apollo Cancer Hospital, Chennai; Army Hospital R&R, New Delhi; SGPGI, Lucknow; Cancer Institute (WIA), Chennai. Some of the other hospitals which have also started the procedure or are in the process of establishing the facility are: Apollo Hospital, Hyderabad; Rajiv Gandhi Cancer Institute, New Delhi; Command Hospital (SC), Pune; Cancer Care Trust Hospital, Indore; PGIMER, Chandigarh. The cost varies from Rs 6 to 15 lacs per procedure. The majority of patients who have undergone SCT will lead productive lives in their own towns and any complications will have to be managed initially by the local physicians.

Terminology

The following terms are often used in relation to SCT: Allogeneic – when the donor is another individual, related or unrelated; Syngeneic – when an identical twin is the donor; Autologous – when the patient’s own stem cells are used for the transplant. The source of stem cells used is another form of classification of SCT and the terms used are: Bone marrow transplant (BMT) – when stem cells are derived from the bone marrow; Peripheral blood stem cell transplant (PBSCT) – when stem cells are collected from the blood; Cord blood transplant (CBT) – when stem cells are derived from cord/placental blood.

Indications for SCT

The indications for haematopoietic stem cell transplantation can be conveniently divided into two groups: (a) Malignant disorders – like leukaemias, lymphomas, multiple myeloma, and solid tumors, like breast cancer, testicular cancer. In all these indications, the cure or palliation is by the high doses of chemotherapy or radiation therapy, while the transplant serves to rescue the patient from the myelotoxic effects of the anti-cancer therapy. In allogeneic type of transplants, there is an additional immunological advantage of graft versus cancer effect, which contributes to the disease relief. (b) Non-malignant diseases – like thalassaemia, aplastic anaemia, Gaucher's disease, etc. In these conditions, the abnormal marrow is deliberately destroyed and replaced by the healthy donor marrow. In this setting, autologous transplantation cannot be effective for obvious reasons.

Allogeneic BMT

For an allogeneic BMT, an HLA identical sibling is the ideal donor and has to be identical in the HLA-A, B, DR loci. In spite of HLA identity, there is always variation in the minor histocompatibility loci. These antigenic differences lead to graft rejection or graft versus host disease (GVHD) unless immunosuppression is used. In the rare event of an identical twin being available, both donor and recipient are perfectly matched both for HLA and non-HLA genes. It is also possible to have a successful transplant using a partially matched sibling as a donor, or an unrelated HLA identical donor, but the complications of graft versus host
disease and graft rejection increase\(^3\). Most centres in India are not conducting any unrelated BMTs. Unlike majority of other organ transplants, in bone marrow transplantation ABO blood group compatibility is not essential\(^4\). After successful BMT, the blood group of the recipient will also change.

### Procedure of allogeneic BMT

The actual BMT is technically not complicated. The donor’s marrow is harvested by repeated aspiration from the posterior and anterior iliac crests, under general or spinal anaesthesia\(^5\). Usually two operators function simultaneously, and aspirate small aliquots of marrow, through bone marrow aspiration or biopsy needles. The marrow is collected in a bag with anticoagulant. The number of marrow cells or total nucleated cells (TNC) required for successful engraftment is estimated to be at least 2 to 3 \(\times 10^8\) per kg of recipient’s body weight\(^6\). In practice, the volume of marrow to be harvested is dictated by the weight of the recipient and the maximum volume which can be safely harvested is 20 ml per kg of the donor’s weight or around a litre for an adult. The procedure is safe for the donor, apart from the risk of anaesthesia and temporary soreness at the site of aspiration. A surrogate marker for stem cells is CD34. In \(10^8\) marrow cells, around 1 to 3 \(\times 10^6\) CD34\(^+\) cells are present. Usually the donor’s marrow is harvested on the day the marrow is to be transplanted but it can be cryopreserved if necessary\(^7\). Bone marrow is transfused through the veins and the donor marrow cells home into the recipient’s marrow space and start engrafting. Engraftment is considered established when the peripheral neutrophil count reaches 500/cu mm on 3 successive days.

### Peripheral blood stem cell transplant

In the past few years an increasing number of peripheral blood stem cell transplants (PBSCT) are being performed. The procedure is similar to BMT, except that stem cells are collected from the blood using special cell separators. It is well known that the peripheral blood contains a small percent of circulating stem cells derived from the bone marrow. This number can be increased by administration of colony stimulating factors, like G-CSF and GM-CSF\(^8\), which mobilise stem cells into the peripheral blood. PBSCT can be autologous or allogeneic. For allogeneic donors, administration of colony stimulating factors, like G-CSF and GM-CSF for 4 to 5 days results in a high number of circulating stem cells which can be collected by a cell separator. The procedure requires venous access and takes a few hours. The donor need not be admitted, does not require anaesthesia, and is spared the pain of marrow aspiration\(^9\). For autologous PBSCT, the stem cells are collected in a similar fashion, but chemotherapy is usually given prior to the harvest to reduce the tumour contamination and to yield a higher proportion of stem cells.

### Cord blood stem cell transplantation

Placental blood, which is routinely discarded in clinical practice, is potentially a vast supply of allogeneic foetal haematopoietic stem cells. More than 1,200 placental or cord blood transplantations have been performed till now\(^10\). With sibling donors who matched the recipients’ HLA types completely or partially, transplants of placental haematopoietic cells in children have engrafted without a high risk of graft-versus host disease. It has also been shown that HLA-mismatched placental blood from unrelated donors is an alternative source of stem cells for haematopoietic reconstitution in children\(^11\). Studies now suggest that successful long term engraftment of placental haematopoietic stem cells is possible in some adults who receive relatively small amounts of placental blood\(^12\), but not in the majority\(^13\).

### Practical aspects

#### Conditioning procedure

The standard preparatory regimens given prior to SCT are myeloablative\(^14\). Patients receive extremely high doses of chemotherapy or radiotherapy, or both. The aim is three-fold: (a)
Eradication of malignant cells or of the abnormal clone of cells; (b) Suppression of the immune system of the host (recipient) so that the allograft is not rejected; and (c) Clearing a "physical space" to allow adequate growth of the donor stem cells. This is also toxic to various organs like the liver, lungs, kidneys, gastrointestinal tract, and reproductive system. The mortality as a consequence of this phase may vary from 10-20%. It is likely that in future the high dose preparative regimens used in allogeneic bone marrow and stem cell transplants will be replaced with less toxic therapy leading to a safer transplant procedure.

Supportive care of the patient

(a) Protective isolation : After transplantation of the marrow, it takes about two to three weeks before engraftment occurs. During this period very intensive support is required. Haematopoietic stem cell transplantation is usually done in specially constructed isolation units to prevent exogenous life-threatening infections. Often these units include air handling units with facilities for high energy particulate air (HEPA) filters and/or laminar air flow. Some centres have reported carrying out stem cell transplants without protective isolation or even in outpatient setting, without increase in morbidity or mortality.

(b) Venous access : The transplant process typically involves the use of a long term, silastic, multilumen, flexible catheter for chemotherapy administration, infusion of stem cells, and supportive care management including frequent blood sampling, intravenous antibiotics, blood components, and parenteral nutrition. This is done by inserting a Hickman-Broviac catheter, which is subcutaneously tunnelled and inserted into the superior vena cava.

(c) Early infections : Infection remains an important cause of morbidity and mortality after bone marrow or stem cell transplantation, with bacterial and fungal infections being the predominant cause. Early institution of empirical antibiotics to cover gram-negative and gram-positive bacteria, specially staphylococci, with addition of antifungal drugs like amphotericin if fever persists, is practiced in most centres. Once engraftment takes place, most of these early infections subside.

(d) Blood component support : After conditioning therapy, patients require multiple red cell and platelet transfusions during the 2-4 week period of pancytopenia, till engraftment occurs. Patients are profoundly immunosuppressed and at risk of developing transfusion-associated graft versus host disease after receiving cellular blood products. This is mediated by viable lymphocytes in the blood product, which recognise HLA differences in the host. To prevent this, all cellular blood products should be irradiated prior to transfusion, to inactivate the donor lymphocytes. A gamma-radiation dose of 2,500 cGy is recommended.

(e) Haematopoietic growth factors : Haematopoietic colony stimulating factors (CSF) like G-CSF and GM-CSF are usually administered to patients after infusion of bone marrow or stem cells in order to reduce the duration of neutropenia.

Toxicity related to conditioning

The conventional myeloablative therapy given before infusion of bone marrow causes organ toxicity, in addition to myelotoxicity. The type of organ toxicity seen depends on the drugs used in conditioning.

(a) Veno-occlusive disease (VOD) of the liver: VOD of the liver is a well known complication in SCT patients, responsible for significant morbidity and mortality. This is diagnosed by the presence of at least two of the following features within 30 days of marrow infusion: (a) jaundice, (b) hepatomegaly and right upper quadrant pain, (c) ascites or unexplained weight gain.
(b) Haemorrhagic cystitis : This is characterised by the presence of haematuria, dysuria, and urinary frequency in a patient with sterile urine. A common cause is the use of high dose cyclophosphamide in the conditioning.

(c) Seizures : Drug-induced seizures can occur after high dose busulphan, and in most regimens phenytoin is administered prophylactically along with the drug.

(d) Pulmonary complications : During the early transplant period, pulmonary complications are a major cause of morbidity and mortality. The non-infectious complications include diffuse alveolar haemorrhage, ARDS, idiopathic interstitial pneumonitis.

(e) Skin and mucosal changes : Alopecia, nail changes, and oral mucositis are common after conditioning. Oral mucositis can result in painful ulcers making parenteral nutrition necessary. Intestinal mucosal toxicity with nausea, vomiting, and diarrhoea are also seen frequently.

(f) Permanent sterility : Most SCT patients will become sterile. Sperm banking is an option which may be offered, if required.

Failure of engraftment

Bone marrow graft may get rejected by functional host lymphocytes which survive the conditioning regimen. The incidence is higher in unrelated donor SCT and whenever there is presence of any HLA mismatch. The incidence is higher in those who have less intensive preparative regimes, those who undergo multiple blood transfusions prior to the procedure, presumably as they get sensitised.

Graft versus host disease

In allogeneic SCT patients, a unique complication occurs: Graft versus host disease (GVHD). There are two types of GVHD—acute and chronic. GVHD occurs because of the antigenic differences between the donor and recipient. Even in HLA identical siblings, there are many minor histocompatibility antigens which are not matched. These antigens are perceived as foreign by the donor T cells, which mount an immune response against the recipient cells. It occurs in 30 to 40 percent allogeneic SCTs. It does not occur in identical twins (syngeneic) transplants. It is more severe in unrelated HLA matched transplants, or partially matched related transplants. By nature of its tissue damaging effects and the immunosuppressive treatment given to treat it, affected patients become immunocompromised, and are prone to infections. Severe GVHD is a major cause for morbidity and mortality in SCT patients.

Acute GVHD : This occurs within the first 3 months after transplant. It classically affects three tissues, namely the skin, gut, and liver, and may be accompanied by fever. The severity can be graded according to the extent of skin involvement, degree of hyperbilirubinaemia, and severity of diarrhoea. Majority of patients are put on prophylactic drugs like cyclosporin and methotrexate. A low grade GVHD may be beneficial as the incidence of tumour relapse is less due to a graft versus leukaemia effect.

Chronic GVHD : This develops around 100 days after transplant and often follows acute GVHD but may also develop de novo. Clinically it resembles autoimmune disorders like scleroderma with skin rash, sicca complex, sclerosing bronchiolitis, and hepatic dysfunction. The mortality varies from 20% to 40%. Management is with immunosuppressive agents like cyclosporin, prednisolone, azathioprine, methotrexate, and cyclophosphamide in various combinations. After a year or more, many patients develop self-tolerance, and these drugs can then be tapered off. GVHD is more common in older patients and those with one or more HLA mismatches or unrelated HLA identical transplants. It is one of the reasons that elderly patients do not do well with allogeneic BMT due to severe GVHD. Most centres do not perform allogeneic BMT in patients older than 50 or 60 years.
Tumour relapse

A successful BMT does not always mean that the primary disease is cured. A certain number of patients will relapse from the original malignancy, as the tumour cells survive the chemo/radiotherapy and graft versus tumour effect.

Late infections

Infections remain a major complication in the post-transplant period. After engraftment, viral infections especially CMV, Herpes simplex, Varicella zoster, Pneumocystis carinii are common. Bacterial infections with encapsulated organisms again predominate after three to six months, akin to infections in post-splenectomised patients.

Autologous SCT

The concept of offering autologous stem cell transplant is to permit administration of very high doses of chemo-radiotherapy which would otherwise be fatal due to myelotoxicity. By first collecting the patient’s marrow or stem cells and cryopreserving them prior to this chemotherapy, these cells are used to ‘rescue’ the patient from the myelotoxicity. The procedure is only indicated for malignancies which are chemo/radiosensitive like leukaemias, lymphomas, multiple myeloma, Ewing’s sarcoma, and gonadal tumors. The marrow must be free of disease at the time of harvesting and should be cryopreserved in liquid nitrogen or electric deep freezers till the time of transplant. The number of autologous transplants being performed now surpasses the number of allogeneic transplants.

PBSCTs have virtually replaced bone marrow for autologous stem cell transplantation. Engraftment takes place more rapidly when peripheral stem cells are used instead of bone marrow cells. This translates in reduced duration of neutropenia, fewer platelet transfusions, and shorter hospital stay. The advantage of autologous transplant over allogeneic transplant is that there is no graft versus host disease, and once engraftment occurs, graft rejection is unlikely. Thus, there is a significant decrease in the complication rate as compared to allo-BMT. However, there is a higher risk of tumour relapse as compared to allogeneic BMT.

In allogeneic SCT, the number of T-cells harvested in PBSC is more than in bone marrow, and there has been a fear that there will be a higher incidence of GVHD. Present data suggests that the incidence of acute GVHD is similar to that occurring after BMT, but evidence on chronic GVHD is controversial. Immune reconstitution may be better with PBSCT as there are more lymphocytes in the graft as compared to marrow. Available data only shows that the results of allogeneic PBSCT are no worse than allo-BMT. Prospective studies comparing the two are in progress. In 1999, of the total autologous transplants performed in Europe, 93% were derived from the peripheral blood. Of all the allogeneic transplants, 55% were BMT and 45% were PBSCT.

Indian spectrum

The facilities for stem cell transplantation in India are increasing, but awareness of its optimal utilisation needs to be improved. The procedure is expensive as a lot of resources are required in the form of supportive therapy. Nevertheless, for those who survive for two years after an allogeneic transplant, the 5-year survival is 89 percent. In terms of cost effectiveness, a SCT performed early is more beneficial than conventional treatment with eventually fatal results. The indications, benefits, and potential complications must be known to all referring physicians.

In India, the largest potential load of patients are those suffering from thalassaemia major. In this condition, allogeneic SCT is the only form of cure, and is clearly cost effective compared to conventional blood transfusions and iron chelation therapy. Christian Medical College, Vellore, has the largest experience in BMT for thalassaemia in the country. Chronic myeloid leukaemia (CML) is
potentially curable with allogeneic SCT, and the cost per added year of life is much less than with drugs like interferon. Tata Memorial Hospital, Mumbai, has performed a large number of SCT in CML. Other diseases likely to benefit are aplastic anaemia, most acute leukaemias, and certain lymphomas. But, for an allogeneic transplant, an HLA donor, ideally a sibling, is essential. Only about 30% patients will have such a donor and be eligible for an allogeneic SCT. The procedure is best tolerated in those less than 20 years of age, while after 40 to 50 years the complication rates increase dramatically. Hence, for those likely to benefit from allogeneic SCT, a search should be made for HLA identical donors early in the course of illness.

For patients who do not have a donor, are elderly, and suffer from a chemosensitive malignancy, an autologous transplant is another option. In multiple myeloma, autologous SCT is now standard therapy, and the maximum number of autologous SCT for myeloma in India have been performed at AIIMS, New Delhi. Recently, a lot of media attention has focused on cord blood transplant, raising false hopes among potential patients that it is simpler than a BMT and does not require HLA matching. It is emphasised that cord blood transplant also requires HLA identity, the time for engraftment is longer than with PBSCT or BMT, and the results are similar to unrelated HLA identical transplants. Moreover, at present there are no unrelated cord blood banks in India. In order to utilise our resources optimally, it is essential to create an awareness of the utility of SCT in India, and to use innovative techniques to make the procedure more affordable.

References
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