

## Review Article

# Haematopoietic stem cell transplantation: Current status

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### ABSTRACT

Haematopoietic stem cell transplantation (HSCT) is now an established treatment for a number of non-malignant and malignant conditions. Bone marrow- or peripheral blood-derived allogeneic SCT from an HLA-identical sibling or matched unrelated donor cures more than half the patients with severe aplastic anaemia, thalassaemia major, congenital immunodeficiency diseases and genetic metabolic disorders. Among the malignant conditions, acute and chronic leukaemia, multiple myeloma, Hodgkin and non-Hodgkin lymphoma, and high risk neuroblastoma are important conditions that can be treated by HSCT. The major morbidities associated with HSCT are regimen-related toxicities, development of acute or chronic graft-versus-host disease (GVHD), failure of engraftment of the bone marrow and complications related to the immunodeficiency that occurs in the post-transplant period. Peripheral blood stem cells are now being used as an alternative to bone marrow stem cells for allogeneic HSCT and exclusively for autologous HSCT. Reduced intensity conditioning for allogeneic HSCT has resulted in a lower frequency and severity of GVHD and risk of infections. This has resulted in allogeneic HSCT being done in older patients and for those with co-morbid conditions. Patients with low grade Hodgkin and non-Hodgkin lymphoma, chronic lymphocytic leukaemia and multiple myeloma appear to benefit more with this approach. Prevention of acute GVHD while maintaining the graft-versus-tumour effect and close monitoring of the kinetics of chimerism hold promise for improving the outcome of those receiving reduced intensity allogeneic HSCT. In recipients of autologous HSCT, identification of patients at increased risk for relapse and use of agents (interferon, interleukin-2) post-transplant to augment the graft-versus-tumour effect are possible areas of further research.

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### INTRODUCTION

Bone marrow transplantation (BMT) refers to intravenous infusion of haematopoietic progenitor cells to re-establish haematopoiesis in a patient with a defective or damaged bone marrow (BM).<sup>1</sup> The haematopoietic progenitor (stem) cells can be obtained either from a genetically identical twin (syngeneic) or from an HLA-identical matched sibling or matched unrelated donor (allogeneic) or from the patient's own (autologous) BM or peripheral blood

(PB). A number of benign and malignant diseases can be treated by allogeneic and autologous haematopoietic stem cell transplantation (HSCT; Table I).<sup>2</sup>

### HLA TYPING

Accurate HLA typing is essential for patients receiving allogeneic HSCT. An HLA-identical donor is one that matches the recipient's HLA antigens: HLA-A, HLA-B, HLA-C, HLA-DR, HLA-DQ (also called a 10/10 match). The probability of finding an HLA match in the family (from a sibling) is about 25%–35%. By searching international databases, which contain more than 10 million potential volunteer stem cell donors,<sup>3</sup> a matched unrelated donor can be found for an additional 50%–80% of patients, depending upon the ethnic group. For patients of Asian origin, the probability is low, mainly because of the small number of volunteer donors of Asian origin in these registries.

TABLE I. Indications for bone marrow/blood stem cell transplantation\*

Condition	Allogeneic	Autologous
<i>Non-malignant</i>		
Severe aplastic anaemia	+	–
Fanconi anaemia	+	–
Beta thalassaemia	+	–
Sickle cell anaemia	+	–
Chronic granulomatous diseases	+	–
Immunodeficiency diseases		
Severe combined	+	–
Wiskott–Aldrich syndrome	+	–
Chediak–Higashi disease	+	–
Inborn errors of metabolism	+	–
Autoimmune diseases	+†	+†
<i>Malignant</i>		
Chronic myeloid leukaemia	+	+†
Acute myeloblastic leukaemia	+	+
Acute lymphoblastic leukaemia	+‡	–
Myelodysplastic syndrome	+	+†
Chronic lymphocytic leukaemia	+†	+†
Hodgkin disease	+†	+
Non-Hodgkin lymphoma	+†	+
Multiple myeloma	±	+†
Germ cell tumours of testis	–	+†
Neuroblastoma	–	+
Other childhood tumours	–	+†
Breast cancer	–	+†
Cancer ovary	–	+†
Renal cell cancer	+†	–

\* Adapted from Bedi *et al.*<sup>2</sup> † currently experimental, definite evidence of benefit is awaited from randomized trials ‡ indicated only in select cases

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DNA-based methods have now replaced serology for HLA typing. These methods use polymerase chain reaction (PCR) amplification of specific HLA genes from genomic DNA. Sequencing-based typing or sequence-specific oligonucleotide probe hybridization (SSOPH) has allowed identification of an HLA allele. This is critical for selecting an unrelated donor. Accurate matching by molecular methods is associated with reduced post-transplant complications such as graft rejection, and acute and chronic graft-versus-host disease (GVHD).<sup>4</sup>

If multiple donors are available, then the choice is based upon the donor's blood group (ABO type), age, transfusion history and cytomegalovirus (CMV) status; for women donors, parity is also a consideration. In general, the results of allografting with HLA-identical sibling donors are superior to those with matched unrelated donors. Matching for natural killer cell immunoglobulin receptors (KIR) which recognize HLA-class I molecules may have an important role in haplo-identical or mismatched HSCT.<sup>5</sup>

### SOURCES OF STEM CELLS

Stem cells can be obtained from the BM, PB or umbilical cord blood (UCB). Traditionally, BM has been used as a source of stem cells for allogeneic HSCT. Results from randomized studies have provided evidence that PB stem cells can be used without an increased risk of acute GVHD. However, the risk of chronic GVHD is increased with the use of PB stem cells.<sup>6</sup> The Centre for International Blood and Marrow Transplant Research (CIBMTR) data from 1997 to 2004 suggest that in adults >20 years of age, >60% of allogeneic HSCTs were done using PB stem cells while for those <20 years of age, >60% were done using BM stem cells.<sup>7</sup>

UCB is a rich source of primitive stem cells that are able to produce long term, re-populating haematopoietic stem cells *in vivo*. The major advantage of UCB stem cells is the relative immaturity of the immune system at birth, resulting in a much lower risk of acute GVHD. The other advantages are easy procurement, no risk to donors, reduced risk of transmitting infections, immediate availability of cryopreserved units and acceptable partial HLA mismatches. One of the drawbacks of UCB stem cells is the higher primary graft failure (10%–20%) and delayed myeloid recovery, which is primarily due to a smaller number of stem cells in UCB grafts.<sup>8</sup> Till 2002, >6000 HSCTs had been done worldwide, mostly in children, using allogeneic HLA-matched sibling or matched unrelated UCB for both benign and malignant conditions.<sup>7,8</sup> For this purpose, a number of UC blood banks have been set up in North America, Europe and Japan. Due to the limited yield of stem cells from a single UCB donor, these have been used mainly for children weighing up to 25 kg. In adults, the use of double UCB donor stem cells can overcome the problem of an inadequate number of stem cells.<sup>9</sup>

### HARVESTING STEM CELLS

#### *Bone marrow*

The BM is usually harvested under general anaesthesia by repeated aspiration from the posterior iliac crest and is well tolerated. In case of difficulty in obtaining an adequate number of stem cells, BM can be harvested from the anterior iliac crest or sternum. In allogeneic HSCT with major ABO incompatibility between the donor and recipient, it is necessary to remove mature erythrocytes from the graft to avoid a haemolytic transfusion reaction.<sup>1</sup>

#### *Peripheral blood*

PB stem cells have to be mobilized from the BM. This is done by giving the donor granulocyte colony-stimulating factor (G-CSF)

in a dose of 5 µg/kg/day in 2 divided doses subcutaneously for 4–5 days. On day 5–6, PB stem cells are collected by leukapheresis using an apheresis (cell separator) machine. A PB-stem cell harvest contains substantially more CD34+ cells and 10 times more lymphocytes than a BM harvest. The recovery of neutrophil and platelet numbers is quicker in recipients of PB-derived allogeneic stem cells than in those receiving BM. Neither anaesthesia nor hospitalization is required for the donor. Currently, PB stem cells are used for autologous HSCT. Once harvested, the PB stem cells are cryopreserved at –80 °C using 7.5% dimethyl sulphoxide (DMSO) or liquid nitrogen.<sup>10</sup> The patient is then administered high dose chemotherapy (HDCT). Depending upon the half-life of the chemotherapeutic drugs used, the PB stem cells can be re-infused either after 24 hours (melphalan) or a longer interval (5–7 days). The primary concern with autologous HSCT is relapse due to re-infusion of malignant cells along with progenitor cells. Various methods including *in vitro* treatment with chemotherapeutic drugs or monoclonal antibodies have been used to remove the contaminating tumour cells (purging). Retrospective analyses suggest that purging leads to decreased rates of relapse in patients with acute myeloblastic leukaemia (AML) and non-Hodgkin lymphoma (NHL).<sup>11</sup>

#### *Umbilical cord*

UCB stem cells can be harvested at the time of elective delivery by clamping the cord and nicking the umbilical vein at the newborn's first cry. We use normal blood bags for collecting UCB. The median volume collected is 100 ml (range 60–140 ml).<sup>8</sup> Once harvested, samples are sent to determine cell counts and for culture. The UCB is then cryopreserved in liquid nitrogen till further use.

#### *Number of stem cells*

The precise number of BM (nucleated cells) or PB stem cells (mononuclear cells) required is not known. In practice, for BM, approximately  $3 \times 10^8$  nucleated cells/kg of the recipient's body weight and for PB  $5 \times 10^8$  mononuclear cells/kg or  $2\text{--}5 \times 10^6$ /kg CD34+ cells (marker for stem cells) are harvested.<sup>2</sup> For UCB stem cells, usually a dose of  $>2\text{--}5 \times 10^7$ /kg nucleated cells or  $2\text{--}5 \times 10^5$ /kg CD34+ cells is considered adequate.<sup>8</sup>

### RECIPIENT AND DONOR EVALUATION

Potential recipients of HSCT are evaluated for the underlying disease and for any major organ dysfunction. This includes assessment of cardiac, renal, lung and liver function. Evaluation for viral infections (hepatitis B and C, CMV, etc.) is also done. Patients with moderate to severe major organ dysfunction or those with active infection are at high risk for transplant-related complications or reactivation of infection and are not suitable for HSCT. Children with  $\beta$ -thalassaemia and a high iron load are given desferrioxamine infusion before and after HSCT.

Donor evaluation includes a detailed general physical examination, haemoglobin, blood cell counts, liver and renal functions, chest X-ray and serology for viral infections (hepatitis B and C, CMV). For a BM harvest, a pre-anaesthetic check up is done. Both for the patient and donor, counselling by a BMT coordinator and psychologist is helpful to allay fears or apprehensions about the donation, stay in the hospital and issues related to the transplant.<sup>12</sup> We insert a central venous line (Hickman catheter) in all recipients 10 days prior to the procedure. This facilitates the administration of chemotherapeutic drugs and antibiotics, parenteral alimentation and

transfusion of blood products in the post-transplant period. A comparison of various sources of stem cells for allogeneic transplant<sup>12</sup> is given in Table II.

#### PREPARATORY REGIMEN

Prior to HSCT, the patient's own BM is destroyed by giving HDCT with or without total body irradiation (TBI). This is done to (i) eradicate the malignant cells (cytoreduction), (ii) provide immunosuppression so as to prevent rejection and allow the normal BM to grow (engraft) in a patient with aplastic anaemia or destroy a dysfunctional BM such as in a patient with beta-thalassaemia, and (iii) possibly to create space (niche) within the BM microenvironment to allow engraftment of donor stem cells.<sup>1,12</sup> For autologous transplantation immunosuppression is not required and the preparatory regimen is used to provide maximum dose intensity with a goal of eradicating the malignancy.

Earlier, most patients were given cyclophosphamide and TBI (Cy-TBI) as the preparatory regimen. Fractionation of TBI (total dose 1200–1500 cGy) was used to reduce toxicity to the normal tissues. A combination of busulphan (4 mg/kg/day × 4 days; total 16 mg/kg) and cyclophosphamide (60 mg/kg/day × 2 days; total 120 mg/kg; Bu-Cy2) is effective for allogeneic and autologous HSCT, and has been popular in the past two decades. Four randomized studies have compared Cy-TBI v. Bu-Cy2 for conditioning prior to HSCT for leukaemia.<sup>13</sup> At a mean follow up of >7 years among patients with chronic myeloid leukaemia (CML), there was no significant difference in the overall or disease-free survival (DFS) between the 2 regimens. The projected 10-year survival estimates were 65% for Bu-Cy2 and 63% for Cy-TBI. For patients with AML, the projected 10-year survival

estimates were 51% for Bu-Cy2 and 63% for Cy-TBI. An analysis of complications revealed an increased risk of cataract in patients with CML who received Cy-TBI and an increased risk of irreversible alopecia in patients who received Bu-Cy2.<sup>13</sup> Oral busulphan is erratically absorbed, particularly in children, and the recent availability of intravenous busulphan overcomes this problem.<sup>14</sup> The Cy-TBI regimen is preferred by many centres for acute leukaemia while the Bu-Cy2 regimen is preferred for CML.

For non-malignant conditions such as severe aplastic anaemia, a combination of cyclophosphamide and antithymocyte globulin (ATG) has a lower risk of rejection. Similarly, for beta-thalassaemia, a combination of busulphan and cyclophosphamide with or without ATG is used.

The same regimens have been used for autologous HSCT. For patients with myeloma, high dose melphalan (200 mg/m<sup>2</sup>) is currently the standard.<sup>15</sup> For patients with Hodgkin and NHL, a combination of carmustine (BCNU), etoposide, cytosine arabinoside and melphalan (BEAM) or a combination of BCNU, cyclophosphamide and etoposide (CBV) is used. For solid tumours, a combination of carboplatinum and etoposide with or without cyclophosphamide or ifosfamide is used. More recently, monoclonal antibodies (Rituxan or Compath) have also been combined with chemotherapy as part of the preparatory regimen for NHL.

#### Non-myeloablative or reduced intensity regimens

During the past decade, for allogeneic HSCT, the focus has shifted from a combination of myeloablation and immunosuppression to only immunosuppression (non-myeloablative, less intensive or reduced intensity). The initial experience with these regimens suggests a reduction in mucositis and a lower risk of acute and chronic GVHD,<sup>16</sup> resulting in older patients (41–45 years of age) and those with co-morbid conditions being able to undergo HSCT. Most of these regimens use a combination of fludarabine, busulphan and ATG; fludarabine, cytosine arabinoside and idarubicin (FLAG-Ida); fludarabine and cytosine arabinoside; fludarabine and TBI (200 cGy); or fludarabine and melphalan. Reduced intensity regimens are suitable for patients with Hodgkin lymphoma, myelodysplastic syndrome, multiple myeloma, low grade NHL and chronic lymphocytic leukaemia.<sup>16</sup>

#### STEM CELL INFUSION

After completion of the preparatory regimen, there is a 24–48-hour period (called rest period) prior to infusion of the stem cells. For patients undergoing autologous HSCT or UCB transplant, the stem cells are removed from the deep freezer, thawed at room temperature in a water bath and reinfused into the patient. Some patients may experience nausea, dizziness or a suffocating feeling—all side-effects related to the use of DMSO for cryopreservation of stem cells. These patients require strict isolation after infusion (transplantation) of the stem cells. Most centres use prophylactic antibiotics (quinolones—ciprofloxacin), antifungals (oral fluconazole or itraconazole) and antiviral drugs (acyclovir for sibling or ganciclovir for unrelated donor or high risk patient). Allogeneic HSCT recipients also receive acute GVHD prophylaxis with methotrexate and cyclosporin.

#### COMPLICATIONS

In addition to severe and prolonged myelosuppression, regimen-related toxicity, GVHD, CMV pneumonitis and relapse are the main complications seen after HSCT (Table III).

TABLE II. Comparison of stem cell sources for allogeneic transplantation\*

Allogeneic stem cell transplantation	Advantages	Disadvantages
Sibling	HLA match 6/6, 5/6 Available to 25%–30% of recipients GVL effect +	Acute GVHD 20%–40% Graft rejection 2%–5% Relapse risk 10%–20% 100-day TRM 8%–14%
Matched unrelated donor	HLA match 6/6 Available through BM donor registry to 50%–80% of recipients GVL effect ++	Acute GVHD 20%–50% Graft failure 5%–10% Increased risk of viral infections Relapse risk low <10% 100-day TRM 10%–20%
Umbilical cord	HLA match 3/6 to 6/6 Available through banks GVL effect +	Generally done in patients weighing ≤25 kg No chance of second infusion in case of graft failure or donor lymphocyte infusion for relapse Acute GVHD 10%–20% Slow engraftment Graft failure 10%–20% 100-day TRM <10%
Syngeneic	Identical twin Available in 1% Immunosuppression not required No GVL effect	No acute GVHD High risk of relapse 100-day TRM <5%

\* Adapted from Forman<sup>12</sup> GVHD graft-versus-host disease  
GVL graft-versus-leukaemia effect  
TRM transplant-related mortality (data from Pasquini<sup>7</sup>)

TABLE III. Complications following bone marrow transplantation

<i>Acute</i>	
Infection	
Acute graft-versus-host disease	
Graft rejection	
<i>Regimen-related complications</i>	
Gastrointestinal: Nausea/vomiting, diarrhoea, mucositis	
Pulmonary and cardiac	
Haemorrhagic cystitis	
Veno-occlusive disease	
<i>Late</i>	
Chronic graft-versus-host disease	
Relapse	
Sterility	
Cataract	
Secondary leukaemia	

TABLE IV. Organisms causing infections after haematopoietic stem cell transplants

Organism	Early (day 0–30)	Middle (day 31–120)	Late (>day 120)
Bacteria	<i>Streptococcus</i>	<i>Nocardia</i>	<i>Streptococcus pneumoniae</i>
	<i>Staphylococcus</i>		<i>Haemophilus influenzae</i>
	Gram-negative rods		
Virus	Herpes simplex	Cytomegalovirus	Varicella zoster
Fungus	<i>Candida</i>	<i>Candida</i>	—
	<i>Aspergillus</i>	<i>Aspergillus</i>	
Parasite	—	<i>Pneumocystis carinii</i>	<i>Pneumocystis carinii</i>
	—	<i>Toxoplasma gondii</i>	<i>Toxoplasma gondii</i>

### Infections

Infections can be divided into three categories based on the time of their occurrence after transplant (Table IV). In the first 30 days, most bacterial infections are due to chemotherapy-induced neutropenia. Fungal infections tend to occur during the first 3–4 months after HSCT but may occur later if immunosuppressive therapy is continued for chronic GVHD. The commonly encountered organisms include *Candida albicans*, *Candida tropicalis* and *Aspergillus*.

The risk of *Pneumocystis carinii*-induced interstitial pneumonia may be reduced to <10% by chemoprophylaxis with oral trimethoprim–sulphamethoxazole given 2–3 times per week, starting after engraftment (when the neutrophils are >1000/cmm) and continued for 6–12 months. In patients allergic to sulphamethoxazole, pentamidine (300 mg once a month) by inhalation through a nebulizer can be used. For both allogeneic and autologous HSCT recipients, the risk of bacterial infections diminishes with haematopoietic recovery. However, recovery of humoral and cell-mediated immunity may take 3–12 months. This is important for allogeneic HSCT recipients as they are at risk for viral infections, particularly CMV and Varicella zoster. The risk of CMV infection is particularly high among patients receiving immunosuppressive therapy for GVHD or among matched unrelated recipients.<sup>17</sup> Reactivation of *Mycobacterium tuberculosis* infection can also occur infrequently.<sup>18</sup>

**Mucositis.** Oral mucositis is common in the second week after HSCT. Patients with grade III–IV oral mucositis may need parenteral opioids for pain relief and parenteral alimentation to maintain an adequate calorie intake. Spielberger *et al.* in a

randomized trial reported the use of recombinant human keratinocyte growth factor (pelifermin) to decrease mucosal injury. Both severity (grade III–IV, 63% v. 98%,  $p<0.001$ ) and the median duration of mucositis (6 days v. 9 days,  $p<0.01$ ) were significantly less in the group receiving pelifermin compared with placebo.<sup>19</sup> In another study, the severity of oral mucositis was reduced following administration of amifostine in myeloma patients who underwent autologous HSCT with conditioning using high dose melphalan.<sup>20</sup>

### Pulmonary complications

**Diffuse pulmonary haemorrhage** manifests as dyspnoea (92%), fever (67%), cough (56%), haemoptysis (15%) and hypoxia. Pulmonary infiltrates are seen on chest X-ray and CT scan during the first 30 days after HSCT. This syndrome is probably related to pulmonary injury due to HDCT and is most frequently seen in patients who receive autologous HSCT. The condition seems to respond to corticosteroids.<sup>21</sup>

**Interstitial pneumonitis** is characterized by high fever, pulmonary infiltrates, hypoxia and adult respiratory distress syndrome. It usually occurs during the second and third month after allogeneic HSCT and is often associated with GVHD. It is most frequently caused by CMV infection. Other causes include *Pneumocystis carinii* or non-CMV viral infections, and idiopathic lung disease. Prophylactic acyclovir may reduce CMV infection and pneumonia in seropositive patients. Ganciclovir and high dose immunoglobulin may be beneficial for early or limited CMV infection.<sup>17,21</sup> During the third month or later, some patients may develop progressive pulmonary fibrosis. This syndrome can be related to HDCT with BCNU or can be a complication of chronic GVHD. However, the treatment of this syndrome is generally disappointing.<sup>12</sup>

### Engraftment syndrome

A clinical picture similar to capillary leak syndrome may occur during the second or third week following engraftment. It is characterized by excessive weight gain, ascites and oedema (similar to non-cardiogenic pulmonary oedema) and is associated with kidney and liver abnormalities, suggesting a common injury to multiple organs. The pathogenesis of this disorder is poorly understood; a pivotal contribution by circulating leukocytes is a possibility.<sup>22</sup> Treatment with prophylactic steroids may prevent the engraftment syndrome in autologous HSCT recipients.<sup>23</sup>

### Graft rejection

This occurs in <10% of patients with severe aplastic anaemia compared with 1%–2% in other conditions. Predisposing factors include previous blood transfusions, less intensive preparatory regimens, the use of methotrexate rather than cyclosporin to prevent acute GVHD and the removal of T-cells from the graft. Incorporation of ATG/antilymphocyte globulin (ALG) in the preparatory regimen for severe aplastic anaemia reduces the incidence of graft rejection.<sup>24</sup>

### Haemorrhagic cystitis

This occurs most often following the use of preparatory regimens containing ifosfamide or cyclophosphamide, which cause marked chemical inflammation of the bladder mucosa. Infection with a virus (polyoma BK virus or adenovirus) has also been implicated. Its incidence varies from 7% to 70%. Mild cystitis (grade I, dysuria and microscopic haematuria) is self-limiting and occurs early (during or immediately after conditioning) and can

be prevented with diuresis and 2-mercaptoethane sulphonate (Mesna). However, overt cystitis (grade >II, gross haematuria, clot retention, urinary tract obstruction and impairment of renal function) is clinically more important. This occurs late and has a protracted course requiring regular bladder irrigation and repeated cystoscopy, and is a cause of substantial morbidity.<sup>25</sup> A variety of uroprotective measures including alkaline diuresis, frequent voiding, urethral catheterization and bladder irrigation, and the use of Mesna reduces the risk of haemorrhagic cystitis.<sup>25</sup>

#### *Veno-occlusive disease*

Veno-occlusive disease of the liver is a common regimen-related toxicity characterized by jaundice (serum bilirubin >2 mg/dl), tender hepatomegaly, ascites and unexplained weight gain (>2% of baseline body weight) within 20 days of HSCT.<sup>26</sup> The incidence varies from 15% to 25%, being lower in autologous compared with allogeneic HSCT. The median time of onset is day 8–10 post-transplant (generally before day 21). The course may range from mild, reversible disease to severe disease associated with multiorgan failure with a poor prognosis. It occurs due to injury to the sinusoidal endothelial cells and hepatocytes with subsequent damage to the zone 3 central veins of the hepatic acinus. Early changes include deposition of fibrinogen, factor VIII and fibrin within the venular walls and sinusoids. As the process of venular microthrombosis, fibrin deposition, ischaemia and fibrinogenesis advances, widespread zonal disruption leads to portal hypertension, hepatorenal syndrome, multiorgan failure and death. Patients with elevated transaminases prior to HSCT, and those with persistent fever during the cytoreductive phase are at high risk for developing severe disease.<sup>26</sup> Management of mild/moderate disease requires fluid restriction and diuretics. Treatment of severe disease is unsatisfactory. Therefore, efforts have been directed towards its prevention by using drugs that interrupt the coagulation cascade or those that diminish the influence of thrombogenic factors. Richardson *et al.* reported the use of defibrotide, a single-strand polydeoxyribonucleotide with fibrinolytic, antithrombotic and anti-ischaemic properties. Complete resolution of severe disease was seen in 36% with a 35% survival at day 100.<sup>27</sup> Younger age, autologous HSCT and abnormal portal flow predicted survival whereas busulphan-based conditioning and encephalopathy predicted a worse outcome. Similar results with defibrotide have also been reported in children.<sup>28</sup>

#### *Graft-versus-host disease (GVHD)*

GVHD is the principal cause of morbidity and mortality after allogeneic HSCT. It is characterized by symptoms and signs associated with the skin, gastrointestinal tract and liver. The severity of the condition is graded according to the involvement of these organs.<sup>29</sup> GVHD can be divided into two somewhat distinct clinical entities: acute GVHD when it occurs within 100 days and chronic GVHD when it develops after 100 days of transplant.

Acute GVHD occurs as a result of epithelial cell injury caused by HDCT, activation of donor T lymphocytes by antigens presented by the recipient's dendritic cells and cell death induced by activated T cells, cytokines (tumour necrosis factor- $\alpha$ ) and cells of the innate immune system. HLA disparity between donor and recipient is the major predisposing factor.<sup>30</sup> Prophylaxis with cyclosporin A with or without methotrexate prevents acute GVHD in recipients undergoing allogeneic HSCT. However, 20%–40% of patients will still develop some degree of acute GVHD. It has been shown that natural killer cells, CD4+ and CD25+ T-cells in the stem cell graft

can prevent GVHD without loss of graft-versus-leukaemia (GVL) effect.<sup>31</sup> Treatment for established severe acute GVHD includes high doses of corticosteroids and monoclonal antibodies.<sup>30</sup>

The clinical features of chronic GVHD are similar to those of scleroderma. It is most likely to develop in patients who had acute GVHD and in older patients. Treatment with prednisolone, cyclosporin A or thalidomide improves the long term results of patients with chronic GVHD.<sup>32</sup> Evidence from animal models and clinical trials in patients with leukaemia suggests that GVHD may exert a GVL effect. The most compelling evidence supporting the powerful and potentially curative nature of the GVL effect is the observation that in patients with CML complete and durable remissions can be achieved with transfusion of donor lymphocytes alone.<sup>33</sup>

#### CLINICAL RESULTS: NON-MALIGNANT DISEASES

##### *Severe aplastic anaemia (SAA)*

Allogeneic HSCT is the treatment of choice for patients with severe aplastic anaemia (SAA) who are <40 years of age. However, it must be done soon after onset and before the patients become sensitized by red cell and platelet transfusions. In older patients (40–55 years) and those without a suitable BM donor, immunosuppression (ATG with or without cyclosporin) has become the treatment of choice and >50% of patients survive 15 years after therapy.<sup>24</sup> In the CIBMTR study (1998–2004), among 1737 patients receiving HLA-identical sibling transplant for SAA, the 3-year probabilities of survival were 83% for those <20 years of age and 70% for those >20 years of age. Among 600 recipients of unrelated donor transplants, the corresponding probabilities were 55% and 50%, respectively.<sup>7</sup> There is a small risk of development of solid tumours in recipients of BMT, probably related to the use of TBI for conditioning in the past.<sup>34</sup>

##### *Fanconi anaemia*

Fanconi anaemia, an autosomal recessive disease, is the most common inherited BM failure syndrome. Allogeneic HSCT from an HLA-identical sibling must be considered early in the course of the disease. In the CIBMTR study, among 215 patients transplanted between 1991 and 1997 from matched siblings, the 3-year survival was 72%.<sup>7</sup> Transplants from unrelated donors have been less successful. As patients with Fanconi anaemia are prone to DNA damage because of the sensitivity of non-haematopoietic tissues, pre-transplant conditioning with low dose cyclophosphamide or fludarabine-based protocols is used but not irradiation.<sup>35</sup>

##### *Thalassaemia and sickle cell anaemia*

At present, allogeneic HSCT is the only means of curing  $\beta$ -thalassaemia. It should be considered if an HLA-matched sibling donor is available. The risk is low when the transplant is done at an early age. Lucarelli *et al.* from Italy have reported the results of more than 1000 allogeneic BMT recipients for  $\beta$ -thalassaemia. They used busulphan and cyclophosphamide for conditioning. Patients were categorized according to the presence of risk factors (hepatomegaly, portal fibrosis and poor quality of chelation) to:

Class I: No risk factors

Class II: 1–2 risk factors

Class III: All 3 risk factors.

For patients <16 years of age, the probability of survival in classes I, II and III is 95%, 87% and 89%, respectively. Similarly,

the event-free survival (EFS) in these classes is 90%, 84% and 64%, respectively.<sup>36</sup> In India, the largest experience with transplantation for  $\beta$ -thalassaemia is from the Christian Medical College, Vellore; in 106 patients the EFS was 66% in class I patients ( $n=6$ ), 90% in class II ( $n=30$ ) and 55% in class III ( $n=70$ ) at a median follow up of 26 months (range 2–87 months).<sup>37</sup> Similar results have been reported in 112 patients from Iran.<sup>38</sup>

HSCT has a curative potential for sickle cell disease. More than 200 patients have been transplanted worldwide. Myeloablative regimens have utilized busulphan and cyclophosphamide, with or without ATG. The best results are obtained in children who have HLA-identical sibling donors (EFS 82%) and are transplanted early in the course of the disease.<sup>39</sup>

#### *Immunodeficiency diseases*

A matched sibling donor transplant is the treatment of choice for patients with severe combined immunodeficiency disease, Wiscott–Aldrich syndrome or Chediak–Higashi syndrome. About 74% of patients are cured following HSCT.<sup>40,41</sup>

#### *Inherited metabolic diseases*

The mucopolysaccharidoses are a group of lysosomal storage diseases caused by a deficiency of the enzymes that degrade glycosaminoglycans. Type I mucopolysaccharidosis (Hurler syndrome), an autosomal recessive disorder, is caused by a deficiency of the enzyme  $\alpha$ -L-iduronidase. The first successful BM transplant for Hurler syndrome was reported in 1981. Since then, more than 300 transplants using BM and UCB have been done worldwide.<sup>42</sup> Following successful transplantation, life expectancy is increased, hepatosplenomegaly gets resolved, cardiac disease is stabilized, and there is improvement in the range of motion of joints, airway disease and hearing. The transplant has a minimal effect on the progression of skeletal disease. The effect on the central nervous system may vary from stabilization and prevention of neurological decline to a minimal improvement, depending upon the patient's age at transplant, degree of nervous system involvement and donor status (non-carrier of a pathogenic iduronidase mutation). Overall, results of HSCT are better in children <2 years of age and those with minimal or no central nervous system involvement. Transplant is currently not recommended for types II and III disease. Recently, administration of recombinant enzyme 6–12 weeks before and up to 3 months after HSCT has been proposed as a means of improving engraftment and stabilizing clinical disease before the onset of endogenous enzyme production by the donor cells.<sup>42</sup> Apart from Hurler syndrome, HSCT has been used in the treatment of other inherited metabolic diseases with variable results. Guidelines for the transplant management of these diseases have been published recently.<sup>43</sup>

### CLINICAL RESULTS: MALIGNANT DISEASES

#### *Acute myeloblastic leukaemia (AML)*

Following induction chemotherapy 60%–75% of patients with AML achieve complete remission (CR). This is followed by 2–4 cycles of consolidation chemotherapy with high dose cytosine arabinoside (15–18 g/m<sup>2</sup>). Cytogenetic abnormality and time to achieve CR are two important prognostic factors. Patients with favourable cytogenetic findings such as those with (t[15;17], t[8;21], and inv 16 or del 16) have overall 5-year survival rates close to 50% with chemotherapy alone and do not appear to benefit from HSCT. Patients with poor risk cytogenetics such as those with –5/5q–, t(8;21) with del 9q or complex karyotype, inv (3q), abn 11q23, 20q, 21q, del9q, t(6;9), t(9;22), abn 17p, complex

TABLE V. Indications for haematopoietic stem cell transplant (HSCT) in acute myeloid leukaemia (AML)\*

Group	Allogeneic HSCT	Autologous HSCT
<i>AML, in first complete remission</i>		
Good cytogenetics t(8;21); inv 16	Not indicated	Not indicated
Normal cytogenetics	Not indicated	Possibly not indicated
Poor cytogenetics	Indicated	If no match, then indicated
<i>AML, in second complete remission</i>	Indicated	If no match, then indicated
AML relapse	Indicated	Not indicated
Refractory AML	Indicated	Not indicated

\* Adapted from O'Donnell.<sup>44</sup> Autologous HSCT could be considered in AML patients in first complete remission, poor risk category if HLA-matched sibling donor is not available. For patients with normal cytogenetics, allogeneic HSCT should be considered if the patient requires 2 cycles to achieve complete remission.

karyotypes ( $\geq 3$  abnormalities), have poor CR and leukaemia-free survival (LFS) rates with chemotherapy and should be considered for allogeneic HSCT. Many investigators prefer to transplant patients with intermediate risk cytogenetics such as +8, –Y, +6, del(12p, normal karyotype) if an HLA-identical sibling is available. Patients in the second CR or those with an untreated relapse can be cured with allogeneic HSCT with 3-year LFS rates of 22%–30%. About 10%–20% of patients with primary chemorefractory AML can be salvaged with allogeneic HSCT.<sup>44</sup> Guidelines for transplant management in AML are given in Table V.

#### *Acute lymphoblastic leukaemia (ALL)*

About 80% of children with good risk ALL are now cured with standard chemotherapy. Therefore, allogeneic HSCT is usually reserved for (i) children <15 years of age with cytogenetic abnormalities such as t(4;11) and Philadelphia (Ph) chromosome, t(9;22), (ii) children in the second or third remission, and (iii) young adults between 15 and 21 years of age who have a high leukocyte count at diagnosis and have the Ph chromosome. Such patients are considered at high risk for relapse with standard chemotherapy. The best results for allogeneic HSCT in ALL are reported in children and adults in first remission; the LFS is 60% and 52%, respectively.<sup>7</sup> Allogeneic HSCT might also cure a proportion of patients (15%) with ALL in whom remission could not be achieved with conventional chemotherapy. Results with autologous HSCT are not superior to chemotherapy alone in patients with high risk ALL.

For adult patients with Ph+ ALL, early allogeneic HSCT from a sibling donor is the treatment of choice; 27%–65% of patients in first CR achieve long term survival. Survival decreases to 17% and 5% for those undergoing HSCT in the second and third remission, respectively.<sup>7</sup> For Ph+ ALL, the current recommendation is to give induction chemotherapy with imatinib followed by allogeneic HSCT if an HLA-identical match is available.<sup>45,46</sup>

#### *Myelodysplastic syndrome (MDS)*

Allogeneic HSCT is the treatment of choice for patients with International Prognostic Scoring System (IPSS) intermediate-2 and high risk MDS. However, its use is limited because of the higher median age of patients at the time of diagnosis (70 years). For the small number of eligible patients, myeloablative allogeneic HSCT results in long term EFS in 32%–54%. Experience with reduced intensity conditioning HSCT in patients >50 years of age is encouraging. In the CIBMTR study, in 384 patients >50 years

of age who received an HLA-identical sibling HSCT, the 3-year probabilities of survival were 32% and 39% with myeloablative and reduced intensity conditioning, respectively.<sup>7</sup> Autologous HSCT can be considered in selected patients who achieve CR following induction chemotherapy and do not have an HLA-identical donor. In a prospective study by de Witte *et al.*, 36 of 59 patients (61%) without a donor received autologous HSCT in their first CR. The 4-year DFS rates in patients with or without a donor were 31% and 27%, respectively.<sup>47</sup>

#### *Chronic myeloid leukaemia (CML)*

Imatinib mesylate is now the treatment of choice for all newly diagnosed CML patients. It achieves complete cytogenetic response (Ph<sup>-</sup>metaphases) in 50%–75% of patients at 12 months.<sup>48</sup> Currently, allogeneic HSCT is considered for patients (i) who fail to achieve complete haematological remission after 3 months of imatinib therapy, (ii) who fail to achieve complete cytogenetic response after 12–18 months of imatinib therapy, (iii) who relapse after an initial response, and (iv) with advanced disease (accelerated phase/blast crisis). Many investigators also prefer to transplant younger patients (<30 years of age), if an HLA-identical sibling is available. For CML patients in the chronic phase, following allogeneic HSCT, the 5-year LFS is  $\geq 50\%$ .<sup>7</sup> Similar results have been reported from India.<sup>49</sup> In patients with accelerated phase and blast crisis, allogeneic HSCT results in DFS rates of 15%–25% and <15%, respectively.<sup>7</sup>

CML appears to be most susceptible to the GVL effect. Patients who relapse after allogeneic HSCT can be treated successfully using donor lymphocyte infusion (DLI) without pre-transplant conditioning. For patients with molecular or cytogenetic relapse of CML, the CR rate is 85%–90%. These observations have led to the use of non-myeloablative or less intensive allotransplants, especially for patients >45 years of age. Patients may engraft with mixed chimerism which gradually converts to full donor chimerism with the use of DLI. Crawley *et al.* have recently reported the EBMT results of reduced intensity allogeneic HSCT in CML. Among 186 patients (median age 50 years), the 100-day mortality was 6%, and the 3-year overall and progression-free survival rates were 58% and 37%, respectively.<sup>50</sup>

#### *Chronic lymphocytic leukaemia (CLL)*

The median age at presentation of CLL patients is 65 years, 40% are <60 years of age and 12% are <50 years of age. A number of single centre studies have reported the results of autologous HSCT in younger patients with high risk CLL. Treatment-related mortality is low (1%–5%) with CR in 12%–67% of patients. Allogeneic HSCT in CLL is associated with significant morbidity and mortality due to regimen-related toxicity, GVHD and infection.<sup>51</sup> Recently, HSCT with reduced intensity conditioning has also been performed. In the CIBMTR study, among 949 patients who underwent HSCT for CLL, the 3-year probabilities of survival were 77% after autologous HSCT, 50% after allogeneic HSCT with myeloablative conditioning and 53% after HLA-identical sibling HSCT with reduced intensity conditioning.<sup>7</sup> At present, the experience with HSCT is small but it appears that allogeneic HSCT could be considered in selected young patients using reduced intensity conditioning.<sup>52</sup>

#### *Hodgkin lymphoma (HL)*

HDCT supported with autologous HSCT is currently considered the standard of care for relapsed HL or HL refractory to primary chemotherapy. In the CIBMTR study, among 3806 patients receiving autologous HSCT for HL, the 3-year probabilities of

survival were 78%, 68% and 57% for patients in CR, with sensitive relapse or with resistant relapse, respectively.<sup>7</sup> Currently, there is no evidence to suggest that autologous HSCT is superior to conventional chemotherapy for patients with advanced HL responding to frontline therapy.<sup>53</sup> Recently, encouraging results have been reported with reduced intensity allogeneic HSCT in patients with HL and primary refractory disease or patients who relapse after autologous HSCT. The EBMT collected data on 94 patients who received reduced intensity allogeneic HSCT for HL. Nearly 50% had a failed previous autologous HSCT. The 3-year overall, progression-free survival and transplant-related mortality rates were 45%, 35% and 18%, respectively. There appears to be evidence for a GVL effect in these studies.<sup>54</sup> However, at present, allogeneic HSCT for HL must be considered experimental.

#### *Non-Hodgkin lymphoma*

Autologous HSCT is currently recommended for the treatment of patients with intermediate or high grade NHL (diffuse large B cell) who have relapsed and have achieved a second CR or good partial response following salvage chemotherapy. The consensus is that not all patients with aggressive lymphoma benefit when HSCT is incorporated into the frontline treatment. Patients with a high risk International Prognostic Index (IPI) score seem to benefit from HDCT and HSCT as frontline treatment.<sup>55</sup> Most failures after autotransplants are due to relapse. Though the relapse rate is lower with allogeneic HSCT, the beneficial effect is negated by the high transplant-related mortality.

Autologous HSCT is also being done for low grade NHL. In the CIBMTR study, among 2292 patients receiving autologous HSCT for follicular lymphoma between 1996 and 2004, the 3-year probabilities of survival were 73% for chemosensitive and 52% for chemoresistant disease.<sup>7</sup> For low grade lymphoma, a longer follow up is required to assess the curative potential of autologous HSCT.<sup>56</sup> Compared with conventional chemotherapy, autologous HSCT was associated with a significantly superior survival in a randomized study; progression-free and overall survival at 2 years after transplant were 55% and 71%, respectively, compared with 26% and 46%, respectively, for those receiving conventional chemotherapy. These data are highly significant and demonstrate that HSCT provides an important survival benefit to patients of follicular NHL with chemosensitive recurrences and should be considered the treatment of choice in this situation.<sup>57</sup> Recently, rituximab has been used as an *in vivo* purging agent. Pilot studies indicate that rituximab administration eliminates PCR-detectable cells in a significant proportion of haematopoietic cell harvests but may be associated with late neutropenia and serious infections.<sup>58</sup> Relapse rates are low with myeloablative allogeneic transplants, but the risk of transplant-related mortality is high. The results of reduced intensity allogeneic HSCT (which harnesses the GVL effect) are encouraging.<sup>56</sup>

#### *Multiple myeloma*

Initial induction therapy with thalidomide–dexamethasone followed by autologous PB HSCT is now considered the standard treatment for myeloma patients  $\leq 65$  years of age. Data from randomized and non-randomized studies<sup>59</sup> show that autologous HSCT results in a remission rate of 60%–80% including CR in 30%–50%, and prolonged EFS and overall survival. Two studies have suggested that the outcome is superior if HSCT is done early (within 12–18 months of diagnosis).<sup>7,60</sup> In a randomized trial from France, the use of melphalan (200 mg/m<sup>2</sup>) alone for conditioning has been found to be superior to melphalan and TBI.<sup>15</sup>

The French (IFM) group has reported the results of a randomized study comparing single *v.* double autologous HSCT. In this study, 399 previously untreated patients <60 years of age were randomly assigned to receive either a single or double autologous HSCT. Complete or very good partial remission rates were achieved in 42% of single and 50% of double autologous HSCT ( $p=0.10$ ). The probability of overall survival at 7 years was 10% *v.* 20% ( $p=0.03$ ) following single *v.* double transplant, respectively. Patients who achieved <90% response to the first HSCT benefited more from a second HSCT compared with those who achieved CR or very good partial response (>90%).<sup>61</sup>

At our centre 83 patients with myeloma have had autologous HSCT following high dose melphalan. The results of the first 50 patients show that at 30 months, the probability of overall survival and EFS was 62% and 42%, respectively.<sup>62</sup> Chemosensitive disease ( $p<0.008$ ) at the time of transplant and CR post-transplant ( $p<0.0001$ ) were associated with longer survival.<sup>62</sup>

Transplant-related mortality is higher with conventional allogeneic HSCT. Recently, Maloney *et al.* reported promising results using standard autologous HSCT followed by reduced intensity allogeneic HSCT. In 54 patients (including 48% with relapsed or refractory myeloma), the overall survival and EFS at 2 years were 78% and 55%, respectively.<sup>63</sup> Similar observations<sup>16</sup> argue in favour of reduced intensity allogeneic HSCT in young patients with high risk myeloma.<sup>64</sup>

## AUTOLOGOUS TRANSPLANTATION IN SOLID TUMOURS

### *Breast cancer*

Between 1991 and 1999, several studies evaluated the role of HDCT supported by autologous BM or PB HSCT in the treatment of breast cancer (i) with metastasis, (ii) high risk stage II (multiple axillary lymph nodes positive), and (iii) stage III at high risk for relapse. The initial data in non-randomized trials with a short follow up suggested a benefit for HSCT. However, subsequent studies done in North America and Europe and the pooled data by the CIBMTR<sup>7</sup> failed to demonstrate any benefit of HSCT over adjuvant chemotherapy in high risk patients with breast cancer. Even though the risk of relapse was less in the HSCT arm, this did not translate to a survival benefit.<sup>65</sup> The results in patients with metastatic disease indicate that these patients achieve response rates twice as high as those achieved with conventional chemotherapy and many partial responders are converted to complete responders but with insignificant survival benefit.<sup>66</sup> Currently, HSCT for breast cancer remains investigational.

### *Ovarian cancer*

Stiff *et al.* reported the Autologous Blood and Marrow Transplant Registry (ABMTR) outcome data of 421 women who had HSCT at 57 centres between 1989 and 1996.<sup>67</sup> Forty-one per cent of women had platinum-resistant disease at the time of HSCT and in 38% there was residual tumour at least 1 cm in size following primary surgery. For the whole group, 2-year progression-free and overall survival rates were 12% and 35%, respectively. Patients with a high Karnofsky score (90%), non-clear cell histology and platinum-sensitive disease had a better progression-free (22%) and overall survival (55%).<sup>67</sup> Thus, it appears that a small subgroup of patients may benefit from HDCT and autologous HSCT. However, randomized trials in a large number of patients are needed to confirm these observations.

### *Germ cell tumours of the testis*

The prognosis of patients with early stage or in the good and intermediate prognostic subgroup (International Germ Cell Cancer Collaborative Group) is good following standard bleomycin, etoposide and cisplatin (BEP) chemotherapy. However, in patients with disseminated disease or poor risk patients, a 45%–50% long term survival is achieved by standard chemotherapy. HDCT with HSCT has been attempted for patients with poor risk or for those with cisplatin-resistant disease.<sup>68,69</sup> For such patients treatment with high dose carboplatin, etoposide, cyclophosphamide or ifosfamide or paclitaxel with autologous HSCT results in complete response in 30%–50% with DFS (median follow up 24–28 months) in 15%–20% of heavily pretreated patients with cisplatin-resistant germ cell tumours. This represents curative therapy in patients who would otherwise die of their disease. Early intervention with HSCT is associated with reduced haematological toxicity.<sup>70</sup> However, evidence for the superiority of HSCT in germ cell tumours of the testis is awaited from large randomized trials.

### *Paediatric solid tumours*

Approximately 60% of children afflicted with cancer now survive after conventional chemotherapy. Treatment with HDCT and HSCT is reserved mainly for salvage following relapse. In certain childhood cancers (Wilm tumour, germ cell tumours) successful salvage can be achieved by conventional dose second-line chemotherapy. Thus, primary HDCT is reserved for poor risk patients with an expected survival rate of <20% at 3 years with conventional therapy.<sup>71</sup> With the exception of neuroblastoma, there has been no major randomized trial of HSCT compared with conventional chemotherapy alone in advanced childhood solid tumours. Several retrospective analyses have supported the use of HSCT in Ewing sarcoma and in some brain tumours. No evidence of benefit has been reported in rhabdomyosarcoma. Most studies have used PB as a source of stem cells. Data regarding the use of TBI and purging of stem cells are conflicting.<sup>71,72</sup>

Most children with neuroblastoma present with stage IV disease. Despite relatively high chemosensitivity and CR rates (60%), <20% of patients with stage IV disease have a long term survival. A number of randomized and non-randomized studies have reported that myeloablative therapy supported by autologous HSCT for children with stage IV neuroblastoma in first remission results in DFS rates of 20%–40% at 2–4 years. Matthay *et al.* for the Children's Cancer Group have reported the results of a randomized trial. In this study, 434 patients 1–18 years of age with stage IV or high risk stage III ( $n=72$ ) neuroblastoma after primary intensive chemotherapy were randomized to receive myeloablative chemotherapy and TBI followed by purged autologous BMT ( $n=189$ ) or continuation of 3 cycles of intensive chemotherapy ( $n=190$ ). At the end of this treatment, a second randomization was done between maintenance therapy with 13, cis-retinoic acid for 6 months ( $n=130$ ) or no further treatment ( $n=128$ ). Patients in the transplant group had superior EFS (34% *v.* 22%,  $p<0.03$ ) and those who received cis-retinoic acid had a superior outcome compared with no further treatment (46% *v.* 29%,  $p<0.02$ ).<sup>73</sup> Another study from Norway showed no advantage of 13, cis-retinoic acid in EFS post-transplant.<sup>74</sup>

## STEM CELL TRANSPLANTATION IN INDIA

The first BMT was done in 1983 at Tata Memorial Hospital, Mumbai. Subsequently, a number of centres developed BMT programmes. More than 1800 patients have undergone allogeneic and autologous HSCT at these centres (Table VI). The number of

TABLE VI. Bone marrow/stem cell transplantation in India

Centre	First done in year	n	Autologous	Allogeneic	Information up to
Tata Memorial Hospital, Mumbai	1983	330	120	210	November 2006
Christian Medical College, Vellore	1986	771	164	607	November 2006
All India Institute of Medical Sciences, New Delhi	1990	262	180	82	December 2006
Army Hospital (Research and Referral), New Delhi	1998	105	36	69	January 2007
Jaslok Hospital, Mumbai	2002	96	70	26	October 2006
Apollo Hospital, Chennai	1990	114	48	76	November 2006
Sahyadri Hospital, Pune	1990	130	12	118	February 2007
Total		1818	630	1188	

\* Many other centres have also started this activity in the recent past

centres is too few for such a vast country with a large population. Christian Medical College, Vellore has performed more than 350 transplants for beta-thalassaemia. At the All India Institute of Medical Sciences, 100 patients have undergone autologous HSCT for myeloma. Published results from these centres<sup>37,49,62</sup> indicate that it is possible to achieve results similar to international standards. Currently, there is a need for more trained transplant physicians and nurses, and for more transplant centres to cope with the large number of patients who need transplants.

## CONCLUSION

The list of indications for HSCT is growing and ranges from non-malignant to malignant conditions and autoimmune disorders. This progress is a result of better understanding of the biology of HSCT and improved supportive care. The use of reduced intensity conditioning regimens has allowed HSCT to be done in older patients and those with co-morbid conditions. Such transplants require careful monitoring for chimerism in the initial post-transplant period. Recent observations that natural killer cells and CD4+, CD25+ T cells in the stem cell graft can prevent GVHD without loss of the GVL effect are encouraging and could reduce the morbidity and mortality due to acute GVHD.

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