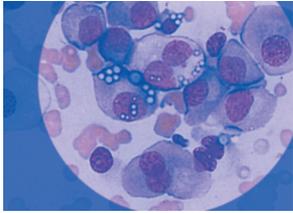


CHAPTER 13



Bone Marrow Transplantation

The idea of rescuing patients by infusing bone marrow after myeloablative chemotherapy or radiotherapy is not a new concept. Animal experiments carried out in the 1950s demonstrated that intravenous infusion of marrow cells could protect against lethal irradiation. Subsequently, successful engraftment was demonstrated in humans. The understanding of the human leucocyte antigen system (HLA) meant that tissue matching between donor and patient was possible and successful bone marrow transplants (BMTs) using matched donors (*allogeneic BMT*) followed in increasing numbers (Fig. 13.1). Overall mortality from the procedure remains high (30%) and this increases with age. Patients over 45 years are often considered too old for this procedure. Patients with certain disorders may benefit from high-dose chemotherapy (myeloablative) and be rescued by infusing their own stored marrow stem cells (*autologous BMT*). Indications for BMT include both malignant and non-malignant disorders (Table 13.1).

Allogeneic bone marrow transplantation

The necessary elements for a successful bone marrow transplant include:

- 1 An HLA-matched donor (Fig. 13.2).
- 2 Immunosuppression (chemotherapy and radiotherapy) prior to marrow infusion to allow engraftment.
- 3 Continuing immunosuppression after infusion to prevent graft-versus-host disease (GVHD).

Donors can be matched siblings or volunteer donors. The chance of any sibling being a

match is one in four whereas the chance of a volunteer being a match is closer to one in 100 000. Most developed countries have registers of donors against which a patient's HLA type can be matched.

The process of allogeneic bone marrow transplantation involves:

1 *High-dose chemotherapy either with or without total body radiotherapy.* This is used to eradicate the neoplastic cells and to allow engraftment of the donor marrow.

2 *Infusion of bone marrow or peripheral blood stem cells.* These are collected directly from the bone marrow of the donor, or by leukapheresis of a donor who has been primed by growth factors such as granulocyte or granulocyte-macrophage colony-stimulating factor (G-CSF, GM-CSF).

3 *Supportive care.* Following high-dose therapy there is inevitably a period of profound marrow suppression which typically lasts 2–3 weeks until the newly infused marrow engrafts. Red cells, platelets and antibiotics are the mainstay of supportive care. Severe mucositis and gastroenteritis often develops and, consequently, many patients require parenteral nutrition during this time.

4 *Prevention of GVHD.* A number of immunosuppressive drugs are used to control the immune component of the donor-derived engrafted marrow. Cyclosporin is the mainstay of this treatment, but other drugs such as methotrexate and prednisolone are frequently used.

Complications of allogeneic BMT

The principal complication of allogeneic BMT is infection. The severe neutropenia that follows

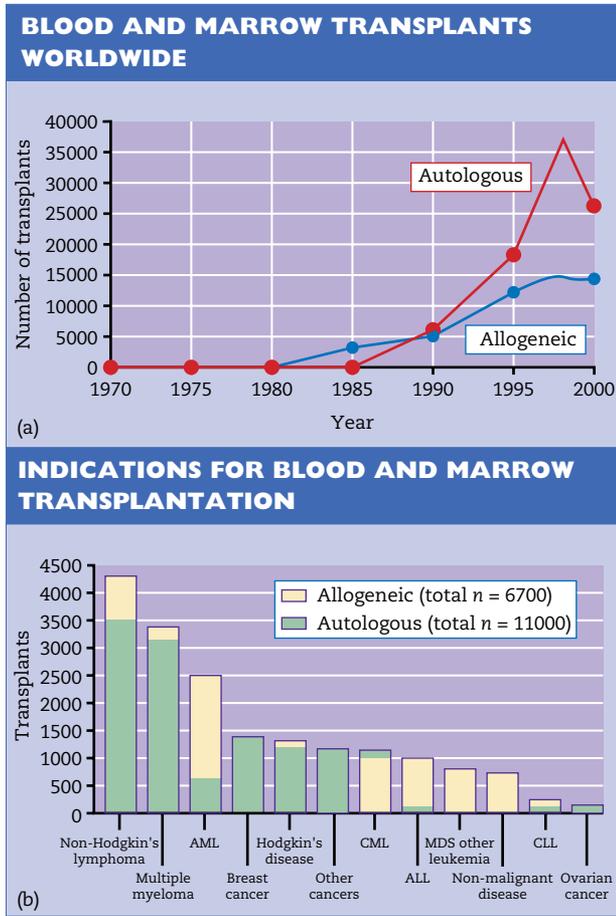


Fig. 13.1 (a) Annual numbers of blood and marrow transplants worldwide 1970–2000. (b) Indications for blood and marrow transplantation in North America in 2000. Courtesy of the IBMT Registry.

Table 13.1 Diseases for which allogeneic and autologous BMT may be considered.

INDICATIONS FOR BMT		
Diseases for which allogeneic and autologous BMT may be considered	Allogeneic BMT	Autologous BMT
<i>Malignant</i>		
Acute leukaemia	+	+
Chronic myeloid leukaemia	+	(+)
Lymphoma (relapsed)	(+)	+
Myeloma	+	+
<i>Non-malignant</i>		
Aplastic anaemia	+	–
Thalassaemia	+	–
Sickle-cell anaemia	+	–

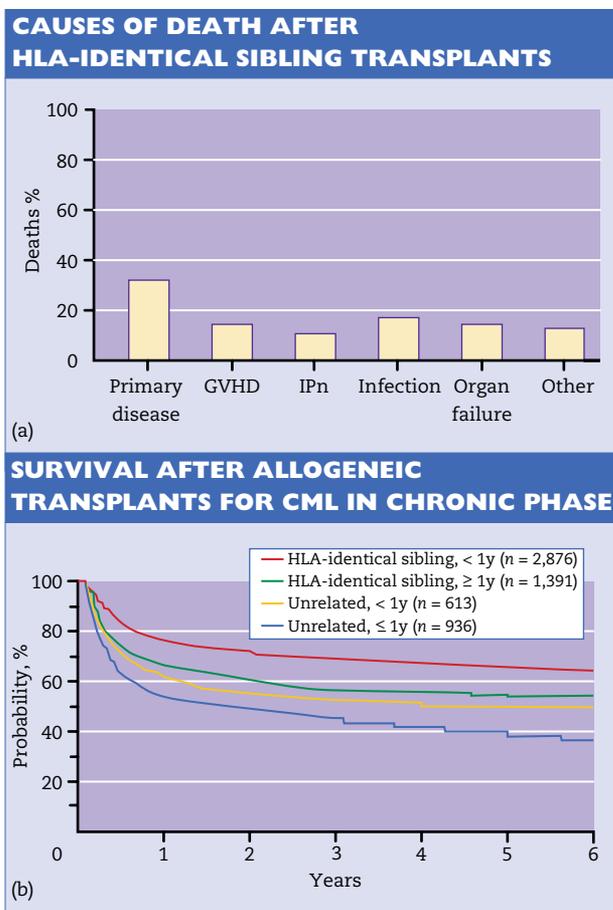


Fig. 13.2 (a) The causes of death after HLA-identical sibling transplants (1994–99). (b) The probability of survival after allogeneic transplants for CML in the chronic phase by donor type and disease duration (1994–99). IPn, interstitial pneumonitis.

high-dose chemotherapy is frequently complicated by Gram-negative infection. Fungal (*Aspergillus* and *Candida* species) and viral (herpes viruses) infections are also found after allogeneic BMT. The use of steroids to control GVHD further increases the risk of fungal infection.

Cytomegalovirus

Cytomegalovirus (CMV) is a cause of morbidity and mortality in BMT patients. Patients may acquire active CMV infection due to the use of seropositive marrow donors, seropositive blood products or the reactivation of latent CMV infection in seropositive patients.

Infection and organ damage is related to viral load, which can be detected in the blood by the polymerase chain reaction (PCR). Interstitial pneumonitis is a serious complication of CMV infection but other organs may be affected, notably, the gastrointestinal tract. The use of CMV seronegative blood products in patients who are not already infected helps to reduce the chance of infection. Prophylactic aciclovir and the use of ganciclovir for treatment has reduced the morbidity and mortality from CMV.

Graft-versus-host disease

GVHD results from the reaction of donor T

cells against the recipient's tissues; the disorder may be acute or chronic. Prophylactic cyclosporin, a T-cell poison, considerably reduces the incidence and severity of GVHD and is given continuously throughout the post-transplant period. Other drugs such as methotrexate and mycophenolate may be used as alternatives, or in addition to cyclosporin, to prevent GVHD.

Acute GVHD

This may occur during the first 100 days after BMT and chiefly affects the skin, gastrointestinal tract and liver. Skin involvement varies from a mild maculopapular rash to severe desquamation. Gastrointestinal involvement may affect the upper or lower tract. Symptoms include nausea, vomiting or severe watery diarrhoea. Biopsy is usually required to confirm the diagnosis.

T-cell depletion of the donor marrow reduces the risk of GVHD, and some centres routinely deplete donor marrow this way. T-cell depletion is, however, associated with a higher risk of relapse due to a reduction in the graft-versus-leukaemia effect (GVL; see below). Once established, acute GVHD is a serious disorder with a high mortality. Treatment with high-dose steroids can help but many patients with severe GVHD die of infection.

Chronic GVHD

Chronic GVHD is a serious complication of BMT occurring after 100 days in approximately 30–40% of patients. The syndrome is reminiscent of the autoimmune disorder scleroderma and the main manifestations are those of dry eyes, chronic liver disease, weight loss and increased risk of infection. The prognosis is poor.

Graft-versus-leukaemia/lymphoma effect

The suggestion that the lymphocytes from the graft can initiate an immune response against the abnormal cells of the recipient comes from the observation that patients who receive bone marrow stem cells from an identical

twin (and therefore receive a perfectly tissue-matched transplant) have a higher risk of relapse than patients receiving marrow from a matched sibling. Patients receiving a bone marrow transplant for CML often have molecular evidence of persistent leukaemia (the presence of the Philadelphia chromosome) in the immediate post-transplant period but this later disappears. T-cell depletion of the donor marrow is associated with a higher risk of relapse. Donor lymphocyte infusion (DLI) after BMT has been shown to have a powerful antitumour effect and may induce remission after relapse. The understanding of the process of GVL should provide a powerful tool to eradicate malignant disease.

Mini-allograft or reduced-intensity conditioning transplant

A technique has recently been introduced whereby patients receive less ablative chemotherapy. The conditioning regimen is designed to be immunosuppressive enough to allow marrow engraftment but not to eradicate all malignant cells. The lower dose of chemotherapy or radiotherapy reduces the toxicity and therefore the mortality of the procedure. The *mini-allogeneic transplant* or *reduced-intensity conditioning (RIC) transplant*, in which a state of tolerance between patient and donor marrow is achieved, has application to an older age group since allogeneic transplantation is limited to patients under 45–50 years. GVL can be augmented by infusing into the patient lymphocytes collected from the donor in the post-transplant period (DLI) to induce GVHD and thus a GVL. The mortality of this procedure is still in the order of between 10 and 20% in most of the reported series.

Autologous bone marrow transplantation (high-dose therapy)

In autologous BMT, the patient's own marrow stem cells are used to reconstitute the bone marrow after intensive chemotherapy with or

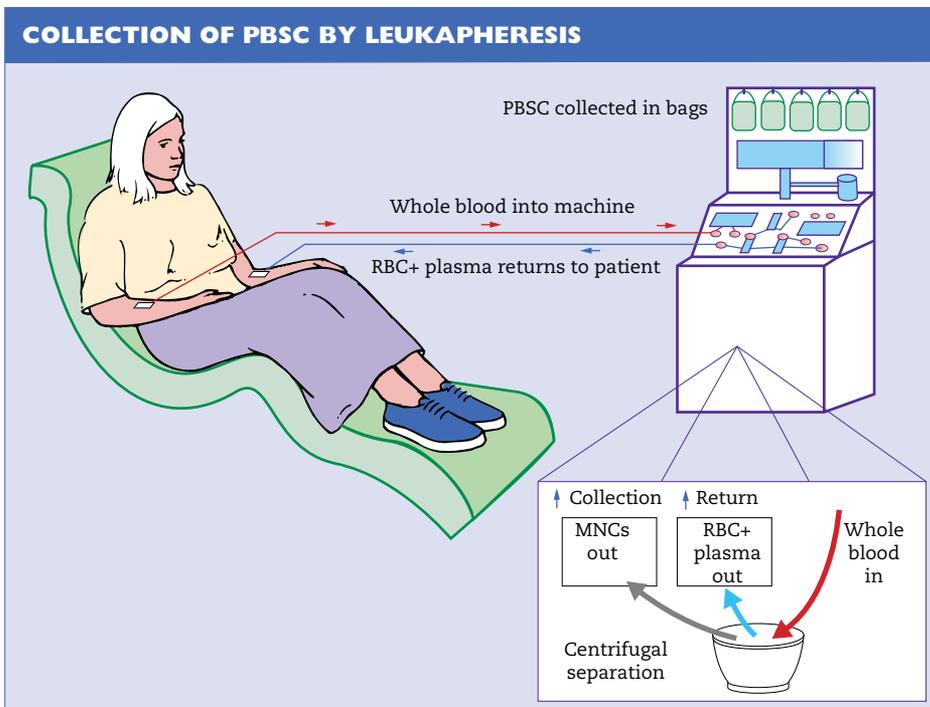


Fig. 13.3 Diagram showing the collection of peripheral blood stem cells using a COBE spectra apheresis machine. MNC, mononuclear cells; PBSC, peripheral blood stem cells.

without radiotherapy. There is therefore no requirement for tissue matching and the risk of GVHD is eliminated.

Chemotherapy or radiotherapy acts by killing a fraction of the tumour. Dose is, however, limited by the myeloablative effects of very high-dose treatment. This can be over-

come by collecting stem cells before high-dose therapy and infusing the stem cells into the patient after intensive conditioning therapy.

There are four phases of high-dose therapy:

- 1 Marrow harvest/peripheral blood stem cell harvest (Fig. 13.3).
- 2 Conditioning therapy.
- 3 Reinfusion of the stem cells.
- 4 Supportive therapy.

Stem cells can either be collected directly by marrow puncture under general anaesthesia or by apheresis. In both cases patients need to be

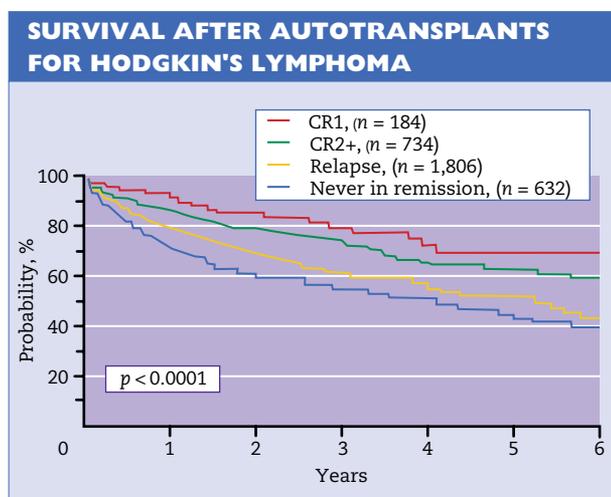


Fig. 13.4 The probability of survival after autotransplants for Hodgkin's disease (1994–99). CR, complete remission.

primed with chemotherapy and granulocyte-stimulating factor (G-CSF).

A serious disadvantage of autologous BMT is the potential for reinfusing malignant cells. Various purging strategies have been tried in an effort to reduce this risk but none have so far been shown to positively affect outcome.

Supportive therapy is very similar to the care given after any intensive chemotherapy.

Blood products — red cells and platelet concentrates — together with antibiotics and nutritional support are the mainstay of therapy at this stage. Most patients will engraft after 2–3 weeks, and some centres use G- or GM-CSF to aid engraftment.

The principal indications for this type of procedure include relapsed Hodgkin's (Fig. 13.4) and non-Hodgkin's lymphoma and myeloma in younger patients.