ABC of clinical haematology

Bone marrow and stem cell transplantation

Andrew Duncombe

History

Experiments in the 1950s showed that haemopoiesis could be restored in irradiated animals by engraftment of transfused marrow. Attempts to translate this into clinical practice were hindered by immunological problems of transfer between individuals which we now recognise as rejection and graft versus host disease.

With further understanding of the human leucocyte antigen system, rapid clinical progress was made during the 1970s such that bone marrow transplantation soon became an established treatment for some immune deficiency and malignant diseases.

Early animal studies of bone marrow transplantation were translated into clinical practice with understanding of the human leucocyte antigen (HLA) system and immunosuppressive therapy

What is a bone marrow transplant?

Transplantation is the reconstitution of the full haemopoietic system by transfer of the pluripotent cells present in the bone marrow (stem cells). This usually requires prior ablation of the patient's own marrow by intensive chemotherapy or chemoradiotherapy.

The most appropriate generic term for the procedure is haemopoietic transplantation, which may be subdivided according to the donor source and further subdivided into the site of stem cell procurement.

Allogeneic transplantation is when another individual acts as the donor—usually a sibling of the patient, sometimes a normal volunteer. All cases, however, require a full or near HLA match—that is, they should be HLA compatible. Autologous transplantation is when the patient acts as his or her own source of stem cells.

Originally, stem cells were procured from the bone marrow by direct puncture and aspiration of bone marrow and reinfused intravenously, a procedure known as bone marrow transplantation. Recently, it has been shown that stem cells derived from the bone marrow can be liberated into the peripheral blood, where the cells are harvested with a cell separation machine. Transplant operations with this stem cell material are known as peripheral blood stem cell transplantations. Stem cells derived from the bone marrow or peripheral blood may be used in either an allogeneic or an autologous setting.

Transplant terminology.

The aim of haemopoietic transplantation is the elimination of the underlying disease in the recipient, together with full restoration of haemopoietic and immune function

Allogeneic transplantation

Suitability

Owing to the profound toxicity of the transplant procedure potential recipients should be otherwise healthy and aged < 55 years. As bone marrow contains B and T lymphocytes along with macrophages the donor and recipient must be fully or near fully HLA matched to prevent life threatening graft versus host disease or rejection.

This restricts the availability of potential donors. Within the patient's family the greatest chance of a full HLA match is with a sibling. An average recipient in Western countries has about a 1 in 4 chance of having a sibling who is fully HLA matched.

With this restriction in allogeneic transplantation, interest has surrounded the use of normal volunteer donors who show

Indications for allogeneic transplantation

When it is sole chance of cure

- Primary immunodeficiency syndromes
- Aplastic anaemia
- Thalassemia
- Sickle cell disease
- Inborn errors of metabolism
- Chronic myeloid leukaemia

When it is probably better than conventional treatment

- Acute myeloid leukaemia (first or second complete remission)
- Acute lymphoblastic leukaemia (first or second full remission)*
- Myelodysplasia
- Multiple myeloma

*In children, in whom acute lymphoblastic leukaemia is the commonest leukaemia, most will be cured by standard chemotherapy alone, without transplantation (which is reserved for those who relapse)

a close HLA match to the potential recipient. This has been achieved by the establishment of bone marrow registries in which volunteers agree to donate marrow. There are two such registries in Britain—the National Blood Transfusion Service and the Anthony Nolan panels.

Autologous transplantation

Suitability

Less immunological disturbance occurs in autologous than in allogeneic transplantation as the donor and the recipient are the same individual; the stresses on the cardiorespiratory, skin, and mucosal systems, however, are similar. Autologous recipients therefore should still be otherwise healthy but can be aged up to about 70 years.

Indications

These are being continuously evaluated by a number of studies including randomised control trials in many diseases, particularly malignancy. The indications can best be broken down into those in which there is now proved benefit in randomised controlled trials, those in which there is probable benefit, and those in which there is possible benefit.

Although the size of bone marrow registries is increasing, the heterogeneity of the HLA complex means that there is still a shortage of appropriately matched donors for all potential recipients

Indications for autologous transplantation

Proved benefit in randomised controlled trials

- Relapsed non-Hodgkin's lymphoma (intermediate and high grade)
- Acute myeloid leukaemia (first or second complete remission)
- Multiple myeloma

Probable benefit

- Relapsed Hodgkin's disease
- Acute lymphoblastic leukaemia (first or second complete remission)
- Relapsed testicular cancer

Possible benefit

- Chronic myeloid leukaemia
- Disseminated breast cancer
- Disseminated lung cancers
- Other solid tumours
- Severe autoimmune disease

Obtaining the graft

Bone marrow is harvested by puncture of the iliac crests under general anaesthesia. It is aspirated directly from the marrow cavity with marrow biopsy needles.

Haematologists performing bone marrow harvest.

Needles for bone marrow harvesting.

Up to a litre of marrow may be needed to provide sufficient stem cells for transplantation. The procedure is well tolerated, requiring only simple analgesia postoperatively. Serious complications are rare.

In peripheral blood stem cell transplantations, stem cells are mobilised into the blood by single agent chemotherapy or a haemopoietic growth factor (for example, granulocyte colony stimulating factor), or both. When the white blood count rises after 7-12 days, the individual is connected to a cell separation machine, blood is drawn off and spun in a centrifuge, and stem cells are harvested while the remaining blood elements are returned to the patient. The procedure takes 2-4 hours and is well tolerated.

Peripheral blood stem cell transplantation is gradually replacing bone marrow transplantation as the procedure of choice as no general anaesthesia is needed, engraftment is more rapid with earlier discharge from hospital, and the procedure is cheaper.

Extracorporeal cell separation device for collection of peripheral blood stem cells, showing inlet and outlet intravenous lines; collected stem cell product is in bag above machine.

Transplantation procedures

Allogeneic transplantation

The recipient is treated with high dose chemotherapy or chemoradiotherapy to ablate the bone marrow (conditioning). On the day after the treatment has ended, bone marrow or peripheral blood stem cells are harvested from the donor, and the transplant is performed by infusing the stem cells intravenously. After a period of severe myelosuppression lasting 7-21 days, engraftment of the transplanted material takes place. Full engraftment may not be complete for several months.

Autologous transplantation

The recipient, while in disease remission, undergoes a bone marrow or peripheral blood stem cell harvest. The stem cells are processed and frozen in liquid nitrogen. The recipient then starts conditioning. One day after the conditioning has ended, the stem cell product is thawed and infused intravenously. The bags are thawed rapidly by transfer directly from a liquid nitrogen container into water at 37-43°C. The product is infused intravenously rapidly through an indwelling central line. Myelosuppression and engraftment follow as described above.

One major procedural difference between allogeneic and autologous transplantation is the requirement for immunosuppression in allografts to prevent graft versus host disease and rejection. This is achieved with combinations of cyclosporin A and methotrexate or with in vitro or in vivo depletion of T cells using monoclonal antibodies.

Transplantation procedures.

Procedural complications

Early complications

Allogeneic and autologous procedures are associated with considerable morbidity and mortality. Overall, transplant related mortality for autologous recipients is 5-20%, for recipients of sibling HLA matched allografts 20-30%, and for recipients of allografts from volunteer, unrelated donors up to 45%.

Nausea and vomiting from chemoradiotherapy is controllable with drugs, but the widespread mucosal damage to the gastrointestinal tract causes mucositis, which can be more difficult to control. Oral ulceration, buccal desquamation, oesophagitis, gastritis, abdominal pain, and diarrhoea may all be features.

The severe myelosuppression after the transplant, together with immune dysfunction from delayed reconstitution or graft versus host disease, predisposes to a wide variety of potentially fatal infections with bacterial (Gram positive and negative), viral, fungal, and atypical organisms. Prophylactic antibiotics may reduce their incidence, but astute surveillance and prompt intervention with intravenous antibiotics are mandatory.

Infection with the herpes simplex virus or the herpes zoster virus is common, and infection with the herpes zoster virus in particular may present with fulminant extensive lesions.

The most feared viral infection after allografting, however, is caused by cytomegalovirus. This may give rise to fulminant cytomegalovirus pneumonitis, which still has a high mortality despite newer antiviral drugs.

Fungal infections with candida species are common, and disseminated aspergillus infection is particularly serious. Preventive measures include the use of broad spectrum antifungal agents prophylactically and the use of air filtration in positive pressure isolation cubicles for patients throughout transplant.

Early complications of transplants

Chemoradiotherapy

- Nausea and vomiting
- Reversible alopecia
- Fatigue
- Dry inflamed skin
- Mucositis
- Veno-occlusive disease

Infections

- Bacterial (Gram negative and positive)
- Viral—herpes zoster virus, cytomegalovirus (particularly pneumonitis)
- Fungi—candida, aspergillus
- Atypical organisms—pneumocystis pneumonia, toxoplasma, mycoplasma, legionella

Acute graft versus host disease (allograft only)

- Rash
- Diarrhoea
- Jaundice

Severe herpes zoster on upper arm after transplant.

Graft versus host disease is classified as acute if occurring within 100 days of transplantation and chronic if occurring after that time. Acute graft versus host disease ranges from a mild self limiting condition to a fatal disorder. The mainstay of treatment remains steroids, but severe disease resistant to steroids is usually fatal. Chronic graft versus host disease is associated with collagen deposition and sclerotic change in the skin, giving a wider distribution of affected organs than the acute disease. Treatment is with combinations of cyclosporin and prednisolone aimed at controlling disease and ameliorating symptoms.

Late complications of transplantation

- Relapse of the original underlying disease
 - Infertility (both sexes)
 - Hypothyroidism
 - Secondary malignancy
 - Late sepsis due to hyposplenism
 - Cataracts (secondary to total body irradiation)
 - Psychological disturbance
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Clinical features of graft versus host disease

Acute

- Skin rash (typically palms and soles)
- Abdominal pain
- Profuse diarrhoea
- Jaundice (intrahepatic cholestasis)

Chronic

- Sclerotic atrophic skin
 - Sicca syndrome
 - Mucosal ulceration
 - Malabsorption syndromes
 - Recurrent chest infections
 - Cholestatic jaundice
 - Joint movement restriction
 - Hyposplenic infections—for example, pneumococcus
 - Myelosuppression
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Follow up treatment and surveillance

For allograft recipients, immunosuppression needs careful monitoring to avoid toxicity. Unlike transplant recipients of solid organs, recipients of haemopoietic transplants do not need lifelong immunosuppression, and cyclosporin is normally discontinued about six months after transplantation. Prophylactic prescription for specific infections is required including penicillin to prevent pneumococcal sepsis secondary to hyposplenism, aciclovir to prevent reactivation of the herpes simplex virus and the herpes zoster virus, and co-trimoxazole or pentamidine to prevent infection with *Pneumocystis carinii*.

Regular haematological follow up is mandatory, and psychological support from the transplant team, family, and friends is vital for readjustment to normal life. Expert counselling and psychiatric input may occasionally be needed.

Despite all the above potential complications most patients return to an active, working life without continuing treatment.

The future

Haemopoietic transplantation is an exciting and rapidly developing field—with the techniques being applied to broader categories of disease, such as autoimmune diseases, as well as being the vehicle for future gene therapy (for example, haemophilia and thalassaemia). The haemopoietic stem cell's property of infinite self renewal makes it an ideal target vehicle for insertion of genes. Candidates include factor VIII gene replacement in haemophilia. The molecular revolution has already resulted in greatly improved DNA matching at the HLA gene loci, which should ensure greater applicability and success of transplants from volunteer unrelated donors. Registration and matching from banks of volunteer donors and umbilical cord donors will be accelerated by the use of the Internet, enabling wider and speedier access of potential grafts to recipients in need.

Some of the photographs were provided by Dr J Treleaven and Mr R Smith.

Andrew Duncombe is consultant haematologist at the Southampton University Hospitals NHS Trust, Southampton.

Cost of haemopoietic transplants

- Haemopoietic transplants score highly on quality of life adjusted years (QALY) analysis, and the cost per QALY is low
 - The cost for each patient will depend on the disease, type of transplant, and particularly on whether complications occur
 - A typical cost for one patient is £15 000-£65 000
 - A successful allogeneic transplant for thalassaemia or primary immunodeficiency will prevent expensive, lifelong alternative supportive treatment
 - The cost of transplantation in malignant disease must be offset against the substantial costs of ongoing alternative chemotherapy
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Future developments in haemopoietic transplantation

- Improved DNA matching techniques for volunteer, unrelated donors
 - Rapid matching on the Internet
 - Umbilical cord blood as transplant source
 - Gene therapy (in haemophilia, haemoglobinopathy, and cystic fibrosis)
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The ABC of clinical haematology is edited by Drew Provan, consultant haematologist and honorary senior lecturer at the Southampton University Hospitals NHS Trust, and Andrew Henson, clinical research fellow, university department of primary care, Royal South Hants Hospital, Southampton.