Science, medicine, and the future: Stem cell transplantation

A L Lennard and G H Jackson

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Science, medicine, and the future

Stem cell transplantation

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A L Lennard, G H Jackson

Stem cell transplantation is a generic term covering several different techniques (see fig 1). Allogeneic transplants are haemopoietic stem cells from the bone marrow, peripheral blood, or umbilical cord blood of a healthy donor matched for HLA type, who may be a family member or an unrelated volunteer. Autologous transplants are stem cells from the patient's own bone marrow or peripheral blood.

Allogeneic transplantation was first used to treat congenital immune deficiencies, bone marrow failure, and haematological malignancies and is now used routinely for some non-malignant conditions such as thalassaemia. Autologous transplantation was introduced to rescue the bone marrow of patients due to undergo high dose chemotherapy, and it is now increasingly written into protocols for the primary treatment of solid tumours such as breast cancer and neuroblastoma. Autologous transplantation is also used experimentally to treat difficult autoimmune conditions such as systemic sclerosis and as a vehicle for gene therapy. Knowledge of stem cell transplantation techniques and their clinical application is therefore becoming essential for increasing numbers of medical specialists.

Probable future developments

- Growth of stem cells in the laboratory, enabling wider use of cord blood donations in adults
- Improved techniques to "clean up" autologous stem cell transplants in cancer patients to prevent contamination with tumour cells
- Expansion of indications for transplantation, such as various solid tumours and severe autoimmune conditions
- Expansion of mini-transplant protocols—less intensive chemotherapy or chemoradiotherapy followed by planned infusions of donor lymphocytes as well as stem cells in order to "mop up" remaining tumour cells
- Increased use of donors not matched for HLA type

Department of Haematology, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP
A L Lennard *senior lecturer*
G H Jackson *consultant haematologist*
Correspondence to: A L Lennard A.L.LENNARD@ncl.ac.uk

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Methods

Our review is based on current haematological textbooks, review articles in major haematological journals, and information from recent meetings of learned societies such as the American Society of Haematology and the European Bone Marrow Transplant Society. This review reflects our personal perspectives and is not meant to cover every likely use or possible advance within this rapidly expanding field.

Stem cell transplantation techniques

The first successful bone marrow transplant in humans was performed between identical twins. With a greater understanding of the HLA system, it became possible to perform bone marrow transplants between siblings who were fully HLA identical. Transplantation is widely used for treating congenital bone marrow disorders and malignant haematological diseases. Today, over 350 centres in Europe are performing more than 18 000 bone marrow transplants a year. Centres may report their transplants to the European Bone Marrow Transplant Registry, which periodically publishes outcome data. The European Bone Marrow Transplant Group is currently establishing a system of voluntary accreditation for transplant centres. Given the governments' emphasis on clinical governance issues, most centres are likely to seek early accreditation.

Donor availability

The major factor limiting the number of allogeneic transplants performed is availability of donors.

Sibling donors

We know from population based studies that only 20%-25% of patients eligible for allogeneic transplantation will have suitable sibling donors.[1]

Matched unrelated donors

To make transplants available to a greater number of eligible patients, registries of volunteer bone marrow donors have been developed. These can provide transplant physicians with stem cells from unrelated but matched donors. There are now over 6 million donors registered on national donor panels worldwide.

Transplants from unrelated volunteers are associated with higher morbidity and mortality than transplants from matched siblings, but outcomes are

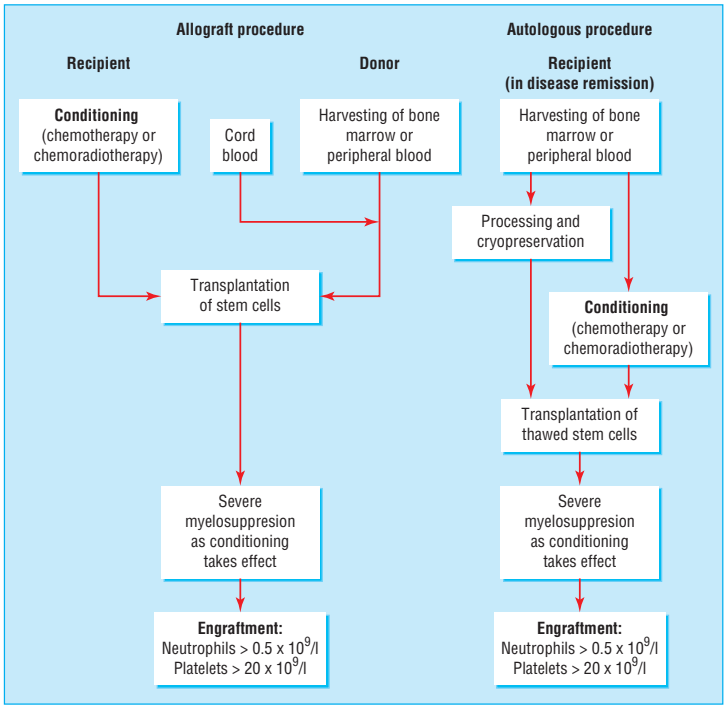


Fig 1 Stem cell transplantation techniques

improving,[2] partly because modern molecular techniques allow closer matching of donors and recipients. Patients with chronic myeloid leukaemia who are considered a good risk for transplantation (aged 20-40, seronegative for cytomegalovirus, in chronic phase, and receive a transplant within one year of diagnosis from a closely matched donor) have outcomes approaching those seen in allogeneic transplants between siblings—that is, over 70% survival at five years.[3]

Patients with common HLA types have a good chance of getting a match, unlike those with rarer HLA types, such as patients from ethnic minorities or those of mixed parentage. It can take many months to locate, test, get the consent of, and pronounce medically fit a suitable volunteer donor, and delays may be critical in patients with acute leukaemia. Their disease may relapse or progress before the search is completed, especially if a search has to be extended outside the country of residence.

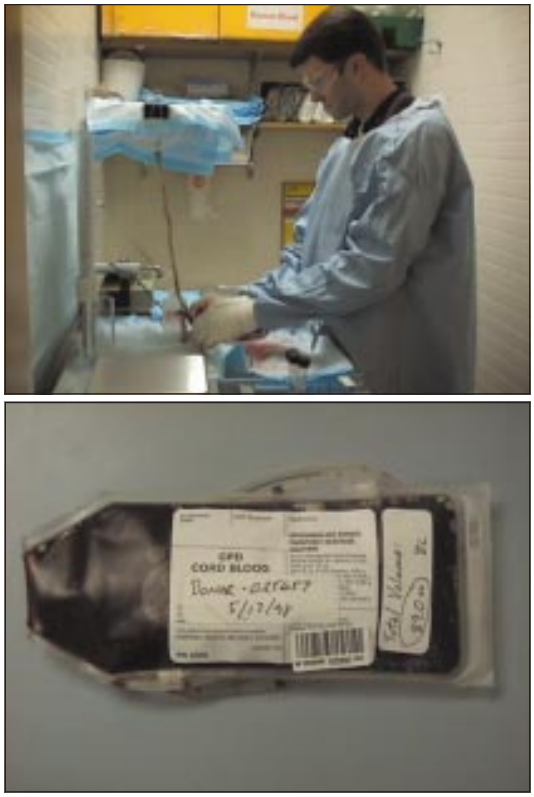
Stem cells from umbilical cord blood

Cord blood from neonates contains substantial numbers of haemopoietic stem cells, which can be harvested at delivery, frozen, and then transplanted to patients who would not otherwise have a donor (fig 2).[4] Thousands of such donations are now stored in special banks worldwide, after cell counts and virological screening tests are performed, and inventories of their HLA types are available to transplant centres. Computer records can be scanned quickly, and donations can be matched with potential recipients without the delays inherent in securing an adult donor. The first cord blood transplant was performed in 1989 by Gluckmann and Broxmeyer, and since then over 700 successful transplants have been made. Such transplants are associated with slightly delayed engraftment but a lower risk of graft versus host disease.[4] Cord blood transplants are usually reserved for children as the calculated stem cell dose in a donation often falls far short of the levels deemed necessary for stem cell engraftment in an adult.

Autologous transplants

Autologous transplantation (using patients as their own donors) is now the most common form of stem cell transplantation. Cryopreservation techniques now allow bone marrow to be stored safely and indefinitely, while the patient undergoes conditioning chemotherapy, without catastrophic loss of stem cells on thawing. Recovery of peripheral blood counts after transplanting cryopreserved marrow previously exposed to chemotherapy was slow, and patients experienced prolonged neutropenia and thrombocytopenia. However, there was no graft versus host disease or prolonged immunosuppression, and the procedure was safer than allogeneic transplantation.

During the early 1980s it was noted that marrow stem cells circulated in the peripheral blood, in small numbers in normal controls but in greater numbers in patients recovering from neutropenia induced by chemotherapy. Stem cell yields increased further if the patient was given bone marrow growth factors such as granulocyte colony stimulating factor during the recovery period. In some patients large numbers of stem cells were found after treatment with the growth factor alone. With this technique, sufficient cells can usually be harvested from the peripheral blood over two to three days to safely perform an autologous transplantation. It was quickly noted that patients receiving this type of transplant recovered their peripheral blood counts more rapidly than did patients given transplants of cryopreserved autologous bone



CAROLINAS CORD BLOOD BANK/DUKE UNIVERSITY

Fig 2 Harvesting of blood from umbilical cord

marrow. Peripheral blood is now the preferred source of autologous stem cells for transplantation in adults.[5 6] In children the choice of peripheral blood or marrow largely depends on the size of the child.

Improving safety and efficacy of stem cell transplantation

Stem cell transplantation is associated with substantial morbidity and (in the allogeneic setting) mortality. Patients may spend considerable periods in hospital and need prolonged convalescence, especially if they are affected by graft versus host disease. However, several advances are associated with an improved outlook for patients and have led to increased interest in stem cell transplantation as a treatment.

Reduced intensity conditioning for allografts

Conventional conditioning regimens for patients with leukaemia are meant to ablate the patient's marrow and all traces of disease before infusion of donor stem cells. However, it is widely recognised that immunocompetent cells in the donation can also help clear the recipient's residual tumour cells—a "graft versus tumour" effect[7 8]—and so it may not always be necessary to completely eradicate the disease with conditioning to achieve a cure. This observation led to experimentation with reduced intensity protocols sometimes followed by immunotherapy (see below). Such non-myeloablative transplants are variously called mini-transplants, low intensity transplants, or "transplant-lite" conditioning. Use of peripheral blood as the source of the stem cells is associated with reduced toxicity, morbidity, and mortality. These techniques are being introduced for older patients, who do not well tolerate conventional, high intensity conditioning and transplantation. It remains to be seen how outcomes will compare with conventional approaches.

Donor lymphocyte infusions

If a malignant haemopoietic condition relapses after an allogeneic transplant, lymphocyte infusions from the original donor can return the patient to remission by exploiting the graft versus tumour effect.[7 8] In chronic myeloid leukaemia such infusions can result in high rates of remission (60-80%).[9] Unfortunately, response rates are lower in other diseases,[9] and treatment may be associated with the development of graft versus host disease.

Improved HLA typing

The most important factor affecting the outcome of allogeneic transplantation is the quality of the HLA match between donor and recipient. New DNA based technologies allow more sophisticated matching and are improving the outcome of this type of transplantation, particularly for unrelated transplants.

Improved supportive care

Improvements in the supportive care of transplant patients have followed development of bone marrow growth factors[10]; new antibiotic, antifungal, and antiviral agents; and better immunosuppressive treatments. Additionally, we are able to detect infections earlier, with better tests for cytomegalovirus[11] and improved imaging techniques for fungal infections.[12]

Purging of transplants

An autograft may fail for two reasons. Either the chemotherapy fails to eradicate the tumour, leading to eventual relapse, or the graft may be contaminated with tumour cells, which are reinfused and again cause relapse. To reduce contamination with tumour cells, practitioners may attempt to clean up (purge) the transplant by using monoclonal antibodies directed against the tumour or by using peripheral blood stem cells instead of marrow. Recent studies, however, have shown that peripheral blood stem cell transplants are not necessarily less contaminated than marrow.[13]

Indications for stem cell transplantation

Indications for stem cell transplantation are constantly changing, partly because of the increasing safety of the procedure. The box shows established and potential indications and is a simplified version of the European bone marrow transplantation guidelines.[14] This is not exhaustive but reflects the current practice of many clinicians performing transplants.

Few randomised controlled trials provide level 3 evidence based information for or against autologous stem cell transplantation. Such trials are notoriously difficult to perform because of problems in randomising patients between treatment arms of radically different intensity. Exceptions include the Medical Research Council acute myeloid leukaemia 10 trial,[15] where risk of relapse in the transplantation group was 37% compared with 58% in the non-transplantation group. The M D Anderson breast cancer trial showed no advantage for autologous transplantation over high dose chemotherapy,[16] whereas the Intergroupe Français du Myelome trial in patients with multiple myeloma found improved response rates (81% *v* 57%) and probability of event-free five year survival (28% *v* 10%) in patients randomised to receive autologous transplantation after conventional chemotherapy.[17] Results from the Scotland and Newcastle Lymphoma Group trial of autologous stem cell transplantation in patients with Hodgkin's disease[18] are currently being analysed.

More commonly, stem cell transplantation is introduced into patient management because of failure to achieve satisfactory outcomes with standard treatments. Research groups may concentrate on a particular disease to establish the feasibility and outcome of stem cell transplantation. After publication of results some approaches are gradually incorporated into standard clinical practice.

Improvements in HLA matching, treatment of graft versus host disease, and supportive therapy have enabled the wider application of allogeneic transplantation to more diseases, including some non-malignant but severely debilitating conditions such as thalassaemia and inherited metabolic disorders.[19] A greater understanding of permissible mismatches should allow a better choice of unrelated donors and further improve the outcome of transplantation with unrelated donors.

Autologous stem cell transplants allow escalation of cytotoxic treatments and reduce the period of neu-

Indications for stem cell transplantation

Established uses

Allogeneic transplants	*Autologous transplants*
Severe aplastic anaemia	Acute lymphoblastic leukaemia (certain subtypes)
Chronic myeloid leukaemia	Hodgkin's disease in second complete remission
Acute myeloid leukaemia in first complete remission (patient < 50 years old)	Non-Hodgkin's lymphoma in second complete remission
Myelodysplasia (patient < 50 years old)	Multiple myeloma
Acute lymphoblastic leukaemia in first complete remission (certain subtypes)	Solid tumours such as neuroblastoma
Severe congenital immunodeficiency	
Acute myeloid leukaemia and acute lymphoblastic leukaemia in second complete remission	
Thalassaemia	

Emerging uses

Allogeneic transplants	*Autologous transplants*
Multiple myeloma	Autoimmune disorders, such as systemic sclerosis
Sickle cell anaemia	Chronic lymphocytic leukaemia
Osteopetrosis	Acute myeloid leukaemia
Inherited metabolic disorders	Solid tumours, such as breast, ovarian
Hodgkin's disease	Chronic myeloid leukaemia
Non-Hodgkin's lymphoma	Hodgkin's disease in first complete remission
	Non-Hodgkin's lymphoma in first complete remission

Experimental uses

Allogeneic transplants	*Autologous transplants*
Chronic lymphocytic leukaemia	Amyloidosis
Renal cell carcinoma	Other solid tumours
Breast cancer	Juvenile chronic arthritis

tropenia after treatment. They were introduced for disorders where higher doses of conventional chemotherapy might be expected to eradicate the disease—such as neuroblastoma,[20] non-Hodgkin's lymphoma, and Hodgkin's disease in second remission. Improved survival in this last, difficult group of patients[21] led to studies evaluating the merits of autologous transplantation for Hodgkin's disease in first remission and as a means of escalating treatment in solid tumours such as breast and ovarian cancers.

Autologous stem cell transplantation can also be used to "re-educate" the immune system of patients with some autoimmune diseases, such as systemic sclerosis,[22] or to introduce genetically or immunologically modified bone marrow.[23 24]

Future developments

Improvements in harvesting techniques and growth of stem cells in the laboratory will lead to increased safety of autografts and an expanding list of indications. Purging of stem cell transplants may become routine to reduce contamination with tumour cells.

Reductions in the intensity of conditioning regimens for allografts will improve safety and increase applicability. Such transplants may be followed by higher relapse rates, but these will be offset by use of graft versus tumour effects by infusion of donor lymphocytes. Techniques that potentially offer a higher cure rate than standard approaches will become suitable for many older patients with haematological conditions and cancer. Improved immunosuppression protocols may allow transplantation across different HLA types.

Ongoing research programmes with potential clinical applications include development of vehicles for gene therapy, tumour specific vaccines, and radionuclide conditioning agents.

Gene therapy—Worldwide, there have now been over 300 phase I and II trials of gene therapy for cancer and monogenic disorders.[23 24] The potential value of such techniques is not in question, but the difficulties of achieving success in clinical settings should not be underestimated; the major barrier is the inability of the inserted gene to reliably reach a sufficient number of target cells.

Tumour specific vaccines to boost patients' immune response to their tumour are now entering clinical trials for non-Hodgkin's lymphoma.[25] More research is needed into the efficacy and optimal use of this immunotherapy.

Radionuclide labelled conditioning agents have been bound to antibodies directed against stem cell antigens is an attempt to target conditioning radiotherapy to bone marrow cells in order to give a higher dose of radiation to the marrow with fewer systemic side effects.[26]

Conclusions

The next five to 10 years will be an exciting time for haematology. Currently, we have patients who might benefit from allogeneic transplantation but who do not have a matched donor. The continued expansion of

cord blood banks should alleviate this problem, especially if the banks can store donations from ethnic minorities in satisfactory numbers. The expansion of stem cell numbers from these small donations by their culture in the laboratory will, if successful, increase the numbers of allogeneic transplants being performed and potentially increase the numbers of patients being cured.

In addition, we see closer collaboration with other medical specialists being necessary to assess the place of autologous transplantation in the treatment of more solid tumours and currently intractable autoimmune conditions.

For further reading we recommend the guide to internet resources for cancer at www.ncl.ac.uk/child-health/guides.

Competing interests: None declared.

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A memorable patient

Treves's young patient

EMG will be 100 years old this month. She is both a friend and a former patient. I first met her as a friend in 1984, and in 1993 I found myself operating on her for gallstones. Laparoscopic surgery had arrived, and so I performed a laparoscopic cholecystectomy. Preoperatively, she mentioned that she had had her appendix removed as a child, and as a routine I asked her the name of the surgeon. "Treves—Frederick Treves," she said.

It turned out that she had had her appendix removed at home in Ealing at the age of 6 (in 1906). Her father was well off and was able to command the services of a surgeon in his home, rather than allowing his child to be taken to the local hospital. At that time, the operation of appendicectomy was still not commonly performed, but it had gained in popularity when Sir Frederick Treves had operated on the Prince of Wales in 1901, the night before his coronation, and drained an appendix abscess that had been brewing for several days. The coronation had to be postponed, but the Prince of Wales survived to be crowned King Edward VII. Treves is also remembered today for his role in studying and looking after "the Elephant Man."

EMG remembers waiting for Treves to arrive, and she remembers a table being taken upstairs to one of the bedrooms for the operation. She then remembers that after the operation she was in bed for three weeks. During that time, she had a day nurse and a night nurse, and her mother was not allowed to see her at all. In fact, her mother peeped through the keyhole one day and when the nurse found out about this she stopped up the hole. EMG remembers having regular dressing changes, and this was a very painful business. The local doctor supervised the dressings, and if EMG behaved herself—that is, she didn't scream the place down—he left a penny on the mantlepiece. After three weeks, she was allowed out in a push chair and had to suffer the taunts of the local children. At about the same time, EMG remembers that another child of her age developed appendicitis and went to the local hospital, but died in hospital.

When I performed EMG's laparoscopic cholecystectomy in 1993, I was able to visualise the caecum and thus see the results of Sir Frederick Treves's handiwork. She has a large incision in the right iliac fossa, which would have been necessary in prerelaxant days to gain access to the appendix.

Michael Lavelle *consultant surgeon, Haywards Heath*