REVIEW

Haemopoietic stem cell transplantation for genetic disorders

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Stem cell transplantation (SCT) is used to cure or greatly ameliorate a wide variety of genetic diseases, ranging from inherent defects of haemopoietic cell production or function to metabolic diseases mostly affecting solid organs. It ranks as one of the most remarkable therapeutic advances of the past 40 years. Despite rapid technological improvements, however, there are still many short term risks and potential long term toxicities. As a consequence, the rapid emergence of alternative therapies (including new drugs, enzyme and gene therapies), necessitate constant re-evaluation of the risk/benefit ratio for each disease and hence the appropriateness of SCT. This review describes the major aspects of the transplant process, indications for transplantation, outcome statistics, and areas where alternative therapies are becoming available.

DONOR SELECTION AND CELL SOURCE

Major improvements have occurred in tissue typing (especially molecular matching by gene sequencing), cell collection/manipulation, and the development of worldwide donor registries searchable by computer. At the outset, SCT was mostly performed using donor bone marrow from siblings with an identical tissue type. The choice has now widened to include use of peripheral blood stem cells (PBSC) mobilised into the blood of the donor using granulocyte colony stimulating factor (G-CSF), marrow from matched or mismatched family members or unrelated donors and cord blood from siblings or unrelated babies. There is also increasing use of parents who are only half matched for their child's tissue type (haploidentical), and recently even simultaneous use of cord blood units from two babies in larger patients.² This means that transplantation can be performed for the vast majority of candidates, although risks remain substantially higher in the more mismatched transplants. In utero transplantation has a niche role in immunodeficiency diseases.³

CONDITIONING THERAPY

Successful SCT relies on the use of pre-transplant "conditioning therapy" to both eradicate the patient's marrow ("myeloablation": creating space for the incoming donor cells to engraft) and to suppress rejection reactions. In malignant disease the most popular conditioning regime has been a combination of cyclophosphamide and total body irradiation (TBI), although this carries many short and long term side effects. For example, late effects of TBI include endocrine and growth problems, infertility, impaired neuro-psychological function, organ damage, and malignancy.^{4–7} In order to avoid some of these effects, busulfan has historically been substituted for TBI when transplanting genetic diseases. This is generally less effective at producing total marrow ablation and complete donor engraftment (termed complete donor "chimaerism"), but partial chimaerism is often sufficient to cure or massively improve genetic diseases. Unfortunately busulfan carries its own side effects, including veno-occlusive disease (VOD) of the liver, fits, and infertility. Other major side effects of SCT include serious bacterial, fungal, or viral infection, primary graft rejection or later secondary graft failure (where the percentage of donor cells falls progressively, often without perceptible change in

SCT can transform the lives of children with a wide variety of genetic diseases for whom life expectancy or quality of life would otherwise be very poor.¹ However, in many respects this remains a highly experimental therapy. In part, this stems from the relatively short history of the discipline, so that follow up for the vast majority of children surviving after SCT is considerably less than 20 years. There is therefore no data on truly long term follow up into middle age or beyond. This is important: in some multisystem diseases it has taken many years to realise that some organs benefit relatively poorly (for example, bone disease in mucopolysaccharidoses) or that problems may emerge which were never apparent as part of the untreated disease (for example, cerebellar problems in one form of osteopetrosis). Another major factor is technological change, the speed of which makes randomised trials on these diseases—which are individually quite rare—almost impossible to perform.

Most of the diseases treated are of autosomal recessive inheritance and result from reduction or lack of function of enzymes. As there is often considerable redundancy in biological systems it may only be necessary to replace a proportion of diseased cells in order to abolish all symptoms/signs of the disease. In contrast, autosomal dominant diseases may be due to the production of a toxic substance or need very high level production of a protein and so are not amenable to transplantation.

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Abbreviations: GVHD, graft versus host disease; MSD, matched sibling donor; MUD, matched unrelated donor; PCR, polymerase chain reaction; SCID, severe combined immunodeficiency; SCT, stem cell transplantation; TCD, T-cell depletion

Figure 1 PCR amplified segments of microsatellite regions adjacent to genes allow distinction of donor and recipient DNA from marrow or peripheral blood cells. Here white blood cell and T-cell DNA have been analysed in a patient with Fanconi anaemia. After initial full donor engraftment, T-cells were mostly recipient in origin at 18 months post-graft—the probable cause of persistent lymphopenia in this patient.

the blood count), and acute and chronic graft versus host disease (GVHD). In an effort to reduce these side effects, there is now an increasing trend to use “reduced intensity conditioning” (RIC) therapy, with less ablative drugs coupled to more intense immunosuppression. The commonest regimens include melphalan, fludarabine, CAMPATH-1H anti-T-cell antibody, and cyclosporin/mycophenolate mofetil.

INFECTIOUS COMPLICATIONS

Infection remains one of the greatest challenges in SCT.⁸ Immunodeficient patients often go into transplantation with resident infections. In all patients, bacterial infection is common due to co-existent neutropenia and mucositis induced by the conditioning therapy, and the presence of indwelling central venous catheters. Fungal infection (especially with *Candida* and *Aspergillus* species) is potentially lethal, the latter occurring principally due to inhalation of airborne spores. Viral problems range from nosocomial spread of respiratory pathogens (RSV, influenza, parainfluenza) to reactivation of viruses resident in the patient or donor. Major examples of the latter include cytomegalovirus (CMV), adenovirus, and post-transplant lymphoproliferative disease (PTLD) (due to Epstein Barr virus (EBV)).

The frequency of fungal and viral infection can be reduced by nursing in isolation cubicles with positive pressure ventilation and HEPA filtration. There have been major advances in prophylactic therapy including the use of aciclovir to prevent herpes infections, fluconazole and

itraconazole to prevent fungal infections, ciprofloxacin to reduce Gram negative bacterial infections, and cotrimoxazole to combat *Pneumocystis*. Viral reactivation can be monitored accurately in blood by quantitative PCR analyses, allowing careful pre-emptive use of toxic antiviral drugs before viral disease becomes established. These assays have allowed radical reductions in the frequency of CMV disease by guiding early introduction of ganciclovir or foscarnet (although viral reactivation remains common). Similar approaches are now being used to assess EBV reactivation and introduction of the anti-B-cell antibody Rituximab to prevent cases of PTLT. There remain no reliably effective drugs against adenovirus or parainfluenza.

Technological advances include specific selection of anti-viral T-cells which can attack virally infected cells but carry a low risk of producing GVHD,⁹ the use of new antifungal drugs (for example, caspofungin, voriconazole), and mobilisation of granulocytes from volunteer donors by G-CSF and dexamethasone.¹⁰ Future strategies may also rely on immunisation of donors against common viruses.

GRAFT VERSUS HOST DISEASE

Immunosuppressive drugs (for example, cyclosporin A, mycophenolate mofetil, tacrolimus) are given to most patients for 3–12 months after SCT and then gradually withdrawn. The main aim of these is to prevent the allogeneic recognition of patient tissue by donor T-cells; if this occurs in the first three months after transplant it can result in acute GVHD. This affects the skin, gut, or liver (in descending frequency, either alone or in combination), manifesting as rashes, diarrhoea, and liver dysfunction in degree varying from mild and transient to therapy resistant and life threatening.¹¹ Management of GVHD necessitates further immunosuppression with steroids and other agents which are both toxic and increase the risk of infective death. Patients with moderate/severe acute GVHD often go on to develop chronic GVHD, which resembles a severe autoimmune disease. In its extensive form, chronic GVHD is one of the most undesirable and serious complications of SCT.

During the 1990s, T-cell depletion (TCD) procedures were introduced widely. These involved either direct killing or removal of T-cells from the graft, or selection of blood progenitor cells (expressing the CD34 protein) using magnetic beads conjugated to antibodies which recognise these proteins. TCD dramatically reduced rates of GVHD, but at the price of increased infections and more frequent graft rejection or mixed chimaerism. RIC conditioning approaches also result in a high frequency of mixed chimaerism due to the less myeloablative drugs/doses used. If mixed or unstable chimaerism is detected, additional donor T-cells can be given at a later stage (termed donor leucocyte infusions (DLI)); this often forces complete donor chimaerism without GVHD by ongoing immune ablation of recipient cells. RIC transplants have transformed the management of some conditions where serious tissue damage is frequent before transplant (for example, liver disease in CD40 ligand deficiency) and is now being much more widely used, especially in immune deficiencies.¹² It is possible that such transplants may completely supplant conventional SCT for genetic diseases, so reducing the risks and widening the potential indications for SCT.

CHIMAERISM

Donor/recipient chimaerism can now be monitored accurately and quickly in most patients by PCR methods (fig 1). One of the most fascinating aspects of SCT is the level of donor chimaerism which can cure a given disease.¹³ Partial chimaerism will cure most blood diseases, although the level

Table 1 Red cell and platelet disorders treated by SCT	
Disorder	Indications
Red cell disorders	
Thalassaemia major	MSD: routine MUD/cord donors: developmental or pilot studies undertaken in specialist units
Sickle cell disease	MSD: when severe complications present MSD/MUD/cord
Congenital erythropoietic porphyria (CEP, Gunther's disease)	
Congenital dyserythropoietic anaemia (CDA) types I and II	Severely affected patients only
Hereditary sideroblastic anaemia	Severely affected patients only
Pyruvate kinase deficiency	Severely affected patients only
Platelet disorders	
Glanzmann's thrombasthenia	Severely affected patients only

MSD, matched sibling donor; MUD, matched unrelated donor.

Box 1: Immunodeficiency diseases treated by SCT

Major severe combined immunodeficiency (SCID) syndromes

- SCID without B- or T-cells
- SCID with B-cells
- ADA deficient SCID

Non-SCID immunodeficiency diseases

- T-cell immunodeficiencies
  - Omenn’s syndrome
  - Purine nucleoside phosphorylase deficiency
  - Major histocompatibility complex class II deficiency
- Wiskott-Aldrich syndrome
- CD40 ligand deficiency (X-linked hyper-IgM syndrome)
- Phagocyte disorders
  - Agranulocytosis
  - Leucocyte adhesion deficiency
  - Chronic granulomatous disease
- X-linked lymphoproliferative disease

Box 2: Other haematological conditions treatable by SCT

Bone marrow failure/cytopenic conditions

- Pancytopenia
  - Fanconi anaemia
  - Shwachman-Diamond syndrome
  - Dyskeratosis congenita
- Red cell aplasia
  - Diamond-Blackfan anaemia
- Neutropenia
  - Severe congenital neutropenia
- Thrombocytopenia
  - Congenital amegakaryocytic thrombocytopenia

Disorders of phagocytic cells operating in solid organs

- Haemophagocytic conditions
  - Haemophagocytic lymphohistiocytosis
  - Chediak-Higashi syndrome
  - Griscelli syndrome type 2 (due to RAB27A mutations)
- Malignant infantile osteopetrosis

required varies depending on the disease treated. In some conditions, for example Fanconi anaemia and thalassaemia major, it is common to see mixed chimaerism in the early months after the transplant followed by spontaneous improvement of chimaerism to 100% donor. This implies a competitive advantage for the normal cells and may be an important clue as to whether gene therapy can be successful in these conditions in the future.

In many matched transplants for immunodeficiency, little or no conditioning therapy has been used since graft rejection is rare due to lack of T-cell function. As a consequence, many patients engraft exclusively with donor T-cells but these coexist with progenitor cells, myeloid cells, and B-cells largely of recipient origin. Defective B-cell function means that patients often need intravenous immunoglobulin infusions for many years after transplantation.

In metabolic diseases controversy remains as to (a) whether homozygous donors with normal enzyme levels produce superior outcome over carrier siblings/other relatives (who usually have 50% normal enzyme levels), and (b) whether mixed chimaerism is important since this lowers the proportion of donor cells and so reduces the amount of enzyme available.

CLASSES OF DISEASE TREATED

SCT acts in one of three ways in treating genetic diseases:

- By directly replacing diseased marrow or blood cells operating within the blood system
- By replacing phagocytic cells of the monocyte/macrophage lineage which operate in solid organs; for example, osteoclasts in osteopetrosis, macrophages and histiocytes in haemophagocytic conditions
- By acting as a source of indwelling enzyme therapy in metabolic diseases.

Genetic diseases treated by SCT are listed in detail in the tables and boxes. In the descriptive section which follows, these are grouped according to the above categories.

Table 2 Recommended indications for SCT in metabolic diseases (EBMT, 2004)

Disease	SCT
Adrenoleukodystrophy (ALD)	R
Aspartylglucosaminuria	D
Batten disease (neuronal ceroid lipofuscinosis, NCL)	D
Fucosidosis	D
Gaucher’s disease, types I and III	D
Globoid cell leukodystrophy (GLD)	
Infantile GLD (Krabbe)	D
Later onset GLD	CRP
α-Mannosidosis	CRP
Metachromatic leukodystrophy (MLD)	
Late infant MLD (pre-symptomatic only)	D
Juvenile and adult onset MLD	CRP
Mucopolidosis, type II (I-cell disease)	D
Mucopolysaccharidosis	
Type I: Hurler’s syndrome (not in Scheie or Hurler/Scheie)	R
MPS type IV: Maroteaux-Lamy syndrome (severe form)	CRP
MPS type VII: Sly syndrome	CRP
MPS types II, III, and IV: Hunter’s, Sanfilippo’s, and Morquio	C
GM1 and GM2 gangliosidosis	C
Niemann-Pick disease types A and C	C

R, routine in selected patients; CRP, to be undertaken in approved clinical research protocols; D, developmental or pilot studies undertaken in specialist units; C, contraindicated.

Direct replacement of diseased blood/marrow cells

Red cell and platelet disorders

Haemoglobinopathies

Thalassaemia major constitutes the single largest indication for SCT among the genetic diseases, with more than 2300 MSD transplants performed since 1981.^{14–16} In young children, for whom iron overload and HLA sensitisation have not become established, event free survival exceeds 90%. For older patients with significant iron overload, better pre-transplant preparation and modified conditioning regimes are improving survival, although risks of graft failure or toxicity remain high. Recurrent venesection is frequently used to reduce iron overload following transplant and may

result in reversal of early hepatic fibrosis. However, the development of oral iron chelators and the success of rigorous iron chelation are increasing life expectancy. As a result, alternative donor (non-sibling) transplants should only be performed in exceptional circumstances.

By contrast, SCT is relatively rarely employed in sickle cell anaemia, with only approximately 200 transplants having been performed worldwide. In Britain, current guidelines restrict the use of transplant to those with severe SS anaemia aged less than 16 years who have a MSD and severe sickle complications, for example, cerebrovascular accident and recurrent chest syndrome. In three series, event-free survival was 75–84% at 6–11 years post-SCT.¹⁶ Inexplicably, several children who have rejected grafts have subsequently developed increased fetal haemoglobin levels (22–33%) which have rendered them symptom free.

Other red cell and platelet diseases

Small numbers of patients have been transplanted for each of the red cell and platelet defects listed in table 1. SCT is not routine in any of these conditions and is reserved for patients with severe disease refractory to more conventional therapy.

White cell disorders

Severe combined immune deficiency (SCID)

Results for transplant in SCID are remarkable considering the high infective load of many patients going into transplant. The European Blood and Marrow Transplant Group (EBMT) report three year survival with sustained engraftment of 77% for all patients transplanted from 1968 to 1999 from an HLA identical related donor, and 54% after mismatched transplant.¹⁷ The poorest results are seen in patients with absent T- and B-cells but reasonable natural killer cell function (T-B-NK+). Within this data results have steadily improved due to better transplant regimes and supportive care; for some groups survival now exceeds 90%, especially where patients are transplanted before 6 months of age. There are also impressive results from haploidentical transplantation, with 78% long term survival in the largest series and no deaths due to GVHD (although this series lacked T-B-NK+ variants).¹⁸ Increasingly SCID is now classified on a genetic basis and it is becoming clear that some subtypes have better cure rates than others, which will in turn allow better stratification of therapy.¹⁹

Other immunodeficiency diseases

SCT is also employed in a wide variety of other immunodeficiency diseases as detailed in box 1. Results tend to be less good than for SCID, probably because patients tend to present later when significantly infected, for example in Wiskott-Aldrich syndrome where results are best in those transplanted before 5 years.²⁰ Selection of appropriate patients is often difficult. Transplantation would cure a majority of those affected if performed at an early age before onset of significant complications. However, because of the risk of early death with SCT, it is conventional to use more conservative treatments (for example, prophylactic antibiotics, intravenous immunoglobulin), withholding SCT until complications ensue. Unfortunately, this greatly increases the risk of SCT at that stage. An excellent example of this dilemma is provided by chronic granulomatous disease, where prophylactic approaches are improving, but many patients will eventually develop serious infective complications.²¹ At present, SCT in granulocyte disorders remains restricted to patients with significant complications, especially where matched sibling donors are not available.

Bone marrow failure syndromes

Although mechanistically very different, these conditions are grouped together since they cause isolated cytopenia(s) or

pancytopenia.¹⁵ Many carry an excess risk of myelodysplasia, acute myeloid leukaemia, or aplasia. The paradigm condition is Fanconi anaemia where defective chromosome repair results in extreme toxicity with conventional conditioning regimes and acceptable transplant results have only been achieved by marked reduction in doses of conditioning therapy. Concerns remain about the long term risk of developing solid tumours, which is already increased in later life in Fanconi anaemia. As one example, patients who develop moderate/severe GVHD have a very high risk of developing squamous carcinoma of the mouth or pharynx.²² As a generalisation, all patients with bone marrow failure conditions show a high incidence of graft failure or complications. While RIC approaches may reduce toxicity, it is imperative that transplantation is only performed by physicians expert in these conditions or after wide consultation.

Replacing phagocytic cells in solid organs

This is the major mechanism of cure in osteopetrosis and haemophagocytic disorders. Osteopetrosis is caused by defective formation or function of osteoclasts.²³ SCT results in gradual replacement of these cells of monocyte/macrophage lineage and normalises bone density within 12 months of transplant (fig 2). Haemophagocytic disorders occur when the mechanisms which control histiocytes are defective.²⁴ Life threatening haemophagocytosis is often triggered by infections in children under the age of 2 years. Transplantation, even with the donor cells at levels as low as 10–20%, can reimpose immune control and hence cure the disease.

Metabolic diseases

This principally applies to lysosomal storage diseases (LSD). In these, enzymes are synthesised in lymphocytes, exported into the plasma, and taken up into cells of the reticuloendothelial system or solid organs, where they are deposited in lysosomes. Replacing bone marrow provides lifelong enzyme therapy, but an important advantage over infused enzyme therapies is that donor cells penetrate the blood-brain barrier and differentiate into microglia, carrying enzyme into the CNS highly effectively.²⁵ It should be stressed that this mechanism cannot be operative in X-linked adrenoleukodystrophy, where progressive CNS deterioration can be prevented if treated at a very early stage of the disease. Enzyme transfer cannot be responsible since the defective ABCD1 transporter protein is membrane bound and aggressive immunosuppression without transplant is ineffective.²⁶

The success of SCT in metabolic diseases is determined particularly by the degree of tissue damage present by the time of transplantation and the rate of progression of the disease. Children with the most severe variants, for example metachromatic leukodystrophy presenting in infancy and type 2 Gaucher's disease, tend to do the least well. Where CNS disease occurs, stabilisation of deterioration will often take 12–18 months (perhaps even longer in more severely affected children with ALD). This places the emphasis on early diagnosis and urgent referral for transplantation.

There is a differential benefit between different organ systems. Thus, in Hurler syndrome, IQ can be stabilised and breathing difficulties, hepatosplenomegaly, facial appearance, corneal clouding, and cardiac deterioration greatly ameliorated, but dysostosis multiplex remains a major factor. In order to preserve maximum mobility, many orthopaedic operations are required.

Gaucher's disease is a good example of a condition where pharmaceutical developments can overcome the need for transplantation. Children with severe forms of type 1 Gaucher's disease respond extremely well to infused enzyme therapy.²⁷ Only those who develop complications (for example, pulmonary) despite this treatment or patients with

Figure 2 Femoral remodelling after successful SCT for malignant infantile osteopetrosis. At presentation the bone is chalky white, lacks cortico-medullary differentiation, and has frayed metaphyses (mimicking rickets). By two years after SCT, bone density is almost normal and remodelling has occurred.

type 3 disease (Norbotnian, chronic neuronopathic, with CNS abnormalities) stand to benefit from transplantation.

Two of the major mysteries in transplantation of LSD are that: (1) transplant rejection is comparatively common in MPS disorders, even from MSD; and (2) some lysosomal storage diseases do not respond at all, for example, Sanfilippo syndrome. The full list of conditions which may benefit and those for whom transplantation is still relatively experimental is given in table 2. It is still not known whether transplants from normal homozygous donors are better in the long term than those from heterozygous carrier donors, who would usually only have 50% of normal enzyme levels.

NEW DIRECTIONS

Despite major advances in the applicability and safety of SCT, substantial risks remain and many patients will be rendered infertile by their conditioning therapy. It is therefore critical to restrict SCT to patients with life threatening disease or complications in whom alternative therapies are not available. Important examples of the latter are the use of enzyme therapies for patients with less aggressive forms of MPS and Gaucher's disease.²⁸ Unfortunately these tend to be extremely expensive: the cost of just one year's therapy for a larger child may equate to the entire cost of an SCT. It is to be hoped that

gene therapy can eventually replace all of these modalities of therapy, especially if lentiviral vectors (based on immunodeficiency viruses) live up to the promise shown in animal models.

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