Bone marrow transplant for children—a cure for sickle cell disease

Bone marrow transplant (BMT) offers a cure for sickle cell disease and experience is increasing relating to outcome and problems. Sickle cell disease is a family of recessively inherited β-globin disorders, of which sickle cell anaemia (SS) is generally the most severe. The severity of the disease is very variable, not only from patient to patient but also in any single person over time.1 Our knowledge respecting the disease has advanced since the initiation of the collaborative study of BMT for SS from Seattle, USA, and the definition of UK criteria for BMT by the British Paediatric Haematology Forum (BPHF), a subcommittee of the British Society for Haematology. It is, therefore, timely to review the role of BMT in sickle cell disease.

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Clinical perspective

Reactions to divorce and marital strife produce the same range of symptoms and behavioural phenomena as other forms of stress in childhood, and are frequently a factor even when not overtly part of the presenting problem. The children who present to child mental health services specifically for help with reactions to marital strife or divorce are a selected sample, including those whose parents are especially concerned for their welfare, those whose parents are seeking support in disputes over custody and access, and children who cause concern to parents, schools, social workers, and doctors because of severe reactions. These may take the form of a child’s chronic anger with one parent, refusal to accept a step-parent, clinging behaviour, excessive anxiety about arguments, fears of violence or loss, low self esteem and fears of abandonment, insecurity about personal identity in adolescence related to a lost or absent parent. Often the children referred are at the heart of battles over access in which there is no such thing as safe neutrality. In such instances, every aspect of their lives may be invaded by partisan considerations, whether it be school, or medical or psychological treatment, and the child and family mental health services may be unable to help until a reduction in the level of conflict makes effective intervention possible.

A variety of interventions (family, group, individual, parental, cognitive, behavioural, psychodynamic) is possible depending on need, patient preferences, and local resources. Interventions probably have the best chance of success when the consent of both parents is obtained, and where feasible goals are set which relate to the alleviation of the presenting problems. It is also helpful if treatment can be constituted as an area of intervention distinct from legal proceedings. This allows the potential for exploration which is usually impossible where either parents or children are determined to use treatment to force a particular outcome.

Bone marrow transplant for sickle cell disease—an update

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Criteria for selection

Despite the radical suggestion that any SS child with an HLA compatible sibling should be transplanted in infancy,2 which we do not support, we believe that our
BPHF criteria should stand for British children (see list below). It is important that children with moderate or severe pre-existing organ damage should not be transplanted as their morbidity and mortality may be unacceptably high, underlining the importance of a thorough pre-BMT work up. This must include a detailed neurological assessment, by clinical examination, magnetic resonance parenchymal imaging, and angiography, as well as neuropsychometric studies, to identify children with severe damage. Such children should be excluded from BMT due to the high anticipated risk of fatal neurological events.

**BPHF criteria for selection of sickle cell disease patients for BMT**

**Acceptance**
1. Informed family (including patient) consent
2. < 16 years + HLA matched sibling
3. (i) Sickle cell disease related neurological deficit, cerebrovascular accident, or subarachnoid haemorrhage; (ii) > 2 episodes acute sickle chest syndrome and stage I chronic sickle lung disease; (iii) recurrent severe and debilitating pain due to sickle cell disease
4. Problems respecting future medical care

**Exclusions**
1. Donor with a 'major' haemoglobinopathy
2. One or more of the following conditions: Karnofsky performance < 70%
3. Major intellectual impairment
4. Portal fibrosis: moderate and accurate
5. Renal impairment (glomerular filtration rate < 30% predicted)
6. Stage III and IV sickle lung disease
7. Cardiomyopathy
8. HIV infection

The Seattle collaborative study group are now finalising a collaborative study of BMT for adults, up to 33 years of age, with sickle cell disease, the criteria for which are moderate, but not severe, chronic organ damage (central nervous system, renal, lung), avascular necrosis of multiple joints, and recurrent severe painful crisis (> 3 episodes/year for three consecutive years). We support the designation of a limited number of centres for BMT in adults with sickle cell disease, in the UK and Europe, as a part of the Seattle collaborative study.

**Access to transplant**
The British patients so far transplanted in the three centres designated by the BPHF (Hammersmith, Birmingham Children's, and Manchester Children's Hospitals) came from their own and two other clinics. These centres were chosen because of their interest and dual expertise in the management of both sickle cell disease and BMT: By concentrating and sharing experience in these centres we expect to optimise patient outcome. We, and others, estimate 10% of all SS children fulfil the BPHF criteria of whom only about one in five will have a donor, so supportive care for sickle cell disease, including analgesia and fluids, will remain the mainstay of treatment. Review of the 1992 census data, and the β-gene frequency, suggests there are between 50 and 100 SS children in the UK who have not been referred for BMT. This low level of referral for BMT has also raised concern in the American collaborative study who found a wide variation of SS patients (0.9–36%) meeting the entry requirements for BMT, reported from 22 collaborating centres (M Walters, K Sullivan, personal communication). We need to develop strategies to improve access for BMT in sickle cell disease including increased awareness by both physicians and patients.

**Conditioning regimens**

Most patients with sickle cell disease have received conditioning with a combination of oral busulphan, usually 14–16 mg/kg, and intravenous cyclophosphamide, usually 200 mg/kg. Several groups also give 'antilymphocyte' treatment with antilymphocyte globulin, or Campath, before transplant in order to reduce the risk of graft rejection. In Belgium, in their first cohort, only those aged over 12 years were also given thoracoabdominal radiation.

**Results of BMT for sickle cell disease**

World wide, around 100 children with sickle cell disease have now been treated by BMT with most performed in European centres, particularly in Belgium and France. The indications were similar to the BPHF ones and fell into four major categories: recurrent chest syndrome, stroke, recurrent severe vaso-occlusive crises, and also children returning to Africa.

Overall survival is 90–95%; deaths have been reported in one child out of 42 transplanted in Belgium,

and in two children in the Seattle collaborative study (K Sullivan, M Walters, personal communication). The causes of death were recorded as graft-versus-host disease and intracranial haemorrhage. In the UK, although fewer than 10 children have undergone BMT in the three centres, the results have also been promising.

All the UK patients are well and symptom-free, with a follow up of 12–29 months, although two patients exhibit a small amount of stable mixed chimism ( < 10% host cells).

The majority of children transplanted for sickle cell disease successfully and durably engraft. The rate of graft rejection appears to be around 10–15%, similar to that after BMT for β-thalassaemia, and is accompanied by autologous marrow recovery. Interestingly, several of the patients who have rejected their grafts have developed increased concentrations of fetal haemoglobin (22–33%) in conjunction with autologous reconstitution. They have remained symptom-free after BMT for over two years, presumably related to the high fetal haemoglobin, despite previously severe disease. The mechanism for the high fetal haemoglobin in the setting of BMT rejection is unclear, as it is not, in our experience, seen in rejection after BMT for β-thalassaemia.

The spectrum and rate of complications after BMT in sickle cell disease is, with one important exception (see later), similar to BMT for β-thalassaemia major, despite the inclusion of a majority of children with more severe disease, including stroke and recurrent chest syndrome. Acute graft-versus-host disease occurs in about 40% of patients, but is rarely severe; chronic graft-versus-host disease is rather less common, though at least two patients have died from this complication (K Sullivan, M Walters, personal communication). Aseptic necrosis, erythroblastopenia, and pneumococcal infection have occasionally been seen, but there are insufficient data to evaluate whether these events are occurring more often in sickle cell disease.

The important exception is the occurrence of neurological complications, which have been reported by the Seattle collaborative study to occur in one third of patients with sickle cell disease. Neurological problems in the peri-transplant period appeared to be more common in children with a previous stroke and included seizures, transient ischaemic attacks, hemiplegia, and intracranial haemorrhage, which was fatal in two children. The recognition of
the increased risk led to the introduction of prevention strategies, including maintenance of platelet counts > 50 x 10^9/L, phenytoin prophylaxis, and rigorous control of blood pressure and magnesium, haemoglobin, and cyclosporin concentrations. Since their introduction no further patients have experienced neurological complications.

**Long term effects of BMT for sickle cell disease**

We do not yet know the long term effects of BMT in sickle cell disease. The children may experience similar long term problems to children transplanted for other conditions. In addition, it is also essential to assess the impact of BMT on any sickle organ damage that the children with sickle cell disease had previously sustained. It is encouraging that the Belgian group have seen no secondary tumours or leukaemias, with a follow up now of over seven years for some of their patients. There is evidence that splenic reticuloendothelial dysfunction can improve after BMT. In addition, no recurrence of stroke in eight children with a pre-BMT history of stroke has been reported from France, although one patient with pre-BMT transient ischaemia attacks continues to have neurological problems after transplant, reinforcing the importance of keeping these patients under very close review.

**The future of BMT in sickle cell disease**

Improvements in both prevention and treatment of graft-versus-host disease may in future allow BMT using matched unrelated donors to be offered to selected children with sickle cell disease. Unfortunately, the ethnic groups who are at risk are not well represented in the British or international donor panels.

An alternative approach is to transplant cord blood stem cells. Surviving cryopreserved placental stem cell banks have now been established, and are under development in England. Success with children using this strategy, including some with \(\beta\)-thalassaemia major, has been reported. A policy of collection from maternity units with a high proportion of deliveries to women from ethnic minorities should increase the donor pool for patients with sickle cell disease.

More immediately, directed placental blood collections (from mothers with affected children or at risk of having children with sickle cell disease) can also be considered in conjunction with prenatal HLA typing on the fetal sample taken for haemoglobinopathy diagnosis.

The future may be intrauterine BMT or gene therapy. Intrauterine BMT has been attempted, including for \(\beta\)-thalassaemia major, where termination was not acceptable. Although successful engraftment has been described, this approach has not yet resulted in cure of a major haemoglobinopathy. Infusion of haploidential maternal marrow cells early in gestation has been shown to induce fetal tolerance to maternal antigens; this might allow subsequent BMT for sickle cell disease in early childhood using haploidential maternal marrow, thus obviating the need for an HLA identical sibling. Gene therapy, using autologous placental stem cells, as carried out recently for adenosine deaminase deficiency, remains a tantalising prospect for the future.

**Recent developments in sickle cell disease**

The median survival for SS patients in the USA is 44 years, showing that sickle cell disease can no longer be considered a paediatric disease. This survival reflects improvement in both medical care and social environment over the last few decades. With early diagnosis, as a result of neonatal screening and comprehensive care including pneumococcal prophylaxis, the childhood mortality is continuing to fall. So we can confidently expect this prognosis to continue to improve. However, even with present optimal care, we cannot yet eliminate all childhood and young adult deaths. We also know that prognosis in sickle cell disease can be altered by blood transfusion regimens, similar to those used for \(\beta\)-thalassaemia major, with all the same complications.

New pharmacological strategies, such as fetal haemoglobin induction, are under intensive study for the management of the majority of patients with sickle cell disease for whom BMT is not a feasible option. Morbidity, as measured by vaso-occlusive painful crisis, can be significantly reduced by treatment with hydroxyurea. Hydroxyurea has a recognised toxicity including neutropenia, thrombocytopenia, and reversible azospermia. It is also likely to be teratogenic and may, as yet, have unknown, long term sequelae. Studies are in progress in children and early reports suggest growth and development are not affected (M de Montalambert, personal communication). Its main mode of action is thought to be by inducing the production of \(\gamma\)-globulin chains resulting in increased concentrations of fetal haemoglobin that interfere with the gelling (sickling) of the sickle cell haemoglobin. Other fetal haemoglobin inducing agents are also under study, including growth factors, and short chain fatty acids such as butyrate. As with BMT we need to address chronic organ damage, for example, neurological (central nervous system) and chronic sickle lung, can be stopped once started, by fetal haemoglobin induction.

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Long term outlook in treated congenital heart disease

Without treatment, 85–95% of the 5–10 per 1000 live births affected by congenital heart disease (CHD) will die before adolescence. However, the situation has been transformed by spectacular advances in medical and surgical care during childhood, so that now the majority can expect to survive into adulthood. Echocardiography has become a key diagnostic tool, refinements in surgical procedures and myocardial protection allow longer and more complex operations to be carried out, and transcatheter interventions obviate the need for surgery altogether in some conditions. Further advances can be expected, so that an increasing number of survivors with complex CHD will require continuing expert care into adolescence and adulthood.

This new and growing population of adolescents and adults represent a challenge to the health service. Most adult cardiologists, who in the past might have been comfortable dealing with the small numbers of survivors with relatively simple lesions, do not have the training and experience to manage the very abnormal and complex circulations with which many patients are left, even after their definitive surgical repair. However, paediatricians may also be ill equipped to deal with the acquired medical conditions of adulthood or the psychosocial issues for which these patients require so much assistance. Even patients with ‘simple lesions’ such as aortic coarctation may run into problems without vigilant surveillance: while the risks of recoarctation and aneurysm formation may be appreciated by paediatric cardiologists, the management of their systemic hypertension and acquired premature coronary artery disease may be better managed in the setting of adult cardiology.

It is crucial not only to maintain continuity of high level medical and surgical care, but also to provide feedback about late results in order to improve initial management in infancy and childhood. For example, as a result of such long term follow up information, the favoured surgical approach for transposition is now the arterial switch operation because of the significant late problems that have been encountered in adolescence and adulthood by patients who had undergone interstitial repair.

Surgical needs

Some patients may not need their first operation until adolescence or adulthood, either because a complex lesion, such as Ebstein’s anomaly, was well balanced in early life, or because a simple lesion was missed, or only became haemodynamically significant in later life. This may be the case for atrial septal defect, the dilating aortic root in Marfan’s syndrome, and bicuspid aortic valve disease.

Reoperations, however, are the major surgical need for patients in this age group, some are inevitable, either as part of a staged approach such as in complex pulmonary atresia, or as valvar prostheses and conduits degenerate. Reoperations may also be unexpected and needed as a result of endocarditis, prosthetic valve failure, or thrombosis within an area of low flow, such as across a Fontan conduit. The risks of such surgery are further increased if the patient is haemodynamically compromised or has uncontrolled sepsis. Eventually, if myocardial failure or pulmonary vascular disease develop, transplantation may be the only option.

Operations in these patients are particularly challenging and should not be undertaken by inexperienced surgeons, as previous surgery may make re-entry to the chest difficult, cyanosis increasing bleeding problems and myocardial depression and pulmonary vascular disease adding to the risks of anaesthesia and cardiopulmonary bypass.

Finally, non-cardiac surgery may also represent a danger to the cyanosed patient in whom the severity of complex CHD is not fully appreciated. For example, induction for a general anaesthetic in a patient with Eisenmenger’s syndrome may produce catastrophic vasodilation from which it may not be possible to resuscitate the patient. All too often, the medical records that may guide the surgeon, physician, or anaesthetist are missing because of inappropriate destruction of old notes, adding an avoidable and inexcusable difficulty to these patients’ safe management.

Medical needs

Although some of the more simple conditions may have been definitively corrected in early life, infrequent long term follow up remains important as they may remain at risk of endocarditis or develop complications such as arrhythmia or pulmonary vascular disease in adulthood.

ARRHYTHMIAS AND CONDUCTION DEFECTS

These are the most frequent problems encountered and need to be considered in the context of the patients’ underlying circulation. Some, such as atrioventricular dissociation and accessory pathways in corrected transposition, may develop as a consequence of the cardiac lesion itself; others may arise as a complication of surgery. Atrial arrhythmias are particularly common after atrial surgery, especially in the presence of atrial distention after the Fontan operation.

Understanding the clinical significance and optimal approach to the treatment of an arrhythmia depends on the cardiologist understanding the underlying cardiac defect. If myocardial function is depressed, the onset of arrhythmia or the inappropriate use of negatively ionotropic