Severe combined immunodeficiency (SCID) is a heterogeneous group of disorders associated with early death due to opportunistic infection. Stem cell transplant (SCT) is now considered the standard of care for SCID because it represents the only hope of cure, and as techniques have improved it is increasingly a consideration for children with less severe primary immunodeficiencies (PIDs). Despite its being available in South Africa, to date only a handful of transplants have been performed. Major limiting factors are a lack of awareness of both the condition and the possibility of cure by means of SCT. Despite a relative paucity of matched sibling donors and limited access to umbilical cord blood stem cells, most patients can be transplanted from a haploidentical maternal donor. Age at transplant is an important prognostic factor and patients with SCID should be transplanted as early as possible. A family history of death in infancy due to severe or recurrent infection or the development of Bacille Calmette-Guérin (BCG) infection should prompt early consideration of a PID, since delays in diagnosis and transplant preparation frequently lead to complications which compromise the chances of successful SCT.

The purpose of this article is to give the primary paediatrician and the immunologist insight into the practicalities and pitfalls of SCT for PID. We hope to encourage prompt and efficient referral of patients for transplant and to foster effective shared care of these patients.

INTRODUCTION

Severe combined immunodeficiency (SCID) is a heterogeneous group of disorders associated with lymphopenia, absent production of T cells, and even B cells and natural killer (NK) cells, that if undetected leads to death from opportunistic infections. These disorders are caused by mutations of at least 13 genes. Following the description of the human leucocyte antigen (HLA) system, there was considerable interest in treating these patients with allogeneic stem cell transplantation (SCT), which proved to be curative. The first successful SCT was performed in a 5-month-old child with SCID in Minneapolis in 1968, and by 2008 more than 1 500 transplants had been performed worldwide for SCID and other primary immunodeficiency disorders (PIDs). Despite making up a relatively small proportion of the total number of allogeneic SCTs, many innovations have been pioneered in these patients, and many of the biological insights now widely applied to allogeneic SCT were first identified in transplantation for SCID. SCT remains the only curative therapy for many PIDs and it is clearly indicated for SCID as patients face death within the first few years of life. As techniques have improved it is increasingly a consideration for children with longer, but still limited, life expectancy.

While only a handful of transplants have been performed in South Africa for this indication to date, the modality is accessible to all patients regardless of socioeconomic status. The major limiting factor is awareness of the condition and the possibility of cure. Even when there is awareness of what can be done for PID, delays in diagnosis and transplant preparation frequently lead to complications which compromise the chances of successful SCT, or rule the procedure out completely. A family history of death from infection in infancy or the development of Bacille Calmette-Guérin (BCG) infection should raise suspicion of PID. Severe lymphopenia requires investigation at a specialised immunology laboratory to confirm severely affected T-cell function.

WHO BENEFITS?

Although SCID represents the group of patients for whom SCT is now considered standard care, SCT has also been used successfully for patients with Wiskott-Aldrich syndrome, various T-cell deficiency syndromes (such as Omenn syndrome and CD40-ligand deficiency), phagocytic disorders (such as agranulocytosis and chronic granulomatous disease) and haemophagocytic syndromes.

WHEN TO TRANSPLANT?

The simple answer is as soon as possible. The ideal time to do SCTs is the neonatal period and early infancy. Analysis of a large European SCID cohort showed that survival after SCT was dependent on a number of factors. Patients transplanted before 6 months of age had a significantly better outcome. Also important was the presence of active infections such as viral pneumonitis before transplantation, with those patients having a significantly poorer outcome (p < 0.0001).

A study from two major UK centres compared the outcomes for 60 patients with SCID diagnosed antenatally or at birth between 1982 and 2010 with those for 48 family members (mostly siblings) previously diagnosed with SCID between 1979 and 2009. The probands had a median age of 143.5 days at diagnosis (range 1-455 days); 35% died before transplant and the overall survival was only 40%. The cohort of relatives screened on the basis of family history had a median age at diagnosis of 0 days (range 0-29); only 1 patient (1.8%) died before transplant and the overall survival was 90%. The improvement in survival was independent of donor source, the conditioning regimen used and the underlying diagnosis. The major distinguishing factor was the condition of the child at the time of transplant. The reasons for this are no doubt the fact that patients diagnosed very early in life...
are able to benefit from prophylactic co-trimoxazole, intravenous immunoglobulin replacement and much improved surveillance for infections leading to early treatment. In South Africa an additional benefit would be the withholding of BCG, since BCGosis is an almost invariable feature of our SCID patients, complicating transplant conditioning and post-transplant care.

**FINDING A DONOR**

HLA-matched grafts from an unaffected matched sibling donor (MSD) remain the preferred source for SCT for PID. Long-term survival rates are reported to be 80-100% with excellent engraftment despite most recipients not receiving a conditioning regimen, rapid immune reconstitution and very little risk of graft-versus-host disease (GvHD). Unfortunately most children with SCID do not have a sibling option.

Alternative donor sources include bone marrow or stem cells from matched unrelated donors (MUD), mismatched family donors including a haploidentical mismatched source (usually the mother), or umbilical cord blood (UCB) stem cells. Particularly if NK cells in the patient are preserved, such transplants require a conditioning regimen as well as GvHD prophylaxis because the risk of transplant-related complications is considerably higher, and engraftment and immune reconstitution is slower to varying degrees (Table I). MUD SCT seems to represent the best option in the absence of an MSD as results are now almost on a par because of better HLA matching, but the potential time delay in finding a donor is the major drawback. Donor searches can take several months, placing the patient at risk of infections, which apart from being life-threatening can make transplant impossible. UCB transplants are a very attractive option since the graft is immediately available and the potential for GvHD is low even in the face of incomplete HLA-matching. Prior to 1999 SCT for SCID patients in Europe showed a clear difference in outcome based on donor source. MSD and MUD donor transplants in SCID had approximately 90% and 80% 3-year survival rates, respectively, whereas mismatched transplants (predominantly from parental donors) showed a 65% success rate. Mismatched SCTs require intense T-cell depletion and some single-centre studies have reported survival rates in excess of 70% as the technical aspects as well as supportive care have improved substantially. There are a number of techniques for T-cell depletion including immune-magnetic purging of donor T cells with the CliniMax device, the use of antithymocyte globulin and the use of monoclonal antibodies such as alemtuzumab.

Despite delays in engraftment and immune reconstitution and a higher risk of GvHD, haploidentical SCTs may represent the only hope for non-Caucasian patients without MSDs because of poor representation of these HLA types in the local and international stem cell donor registries and cord blood banks. The chances of finding a local donor on the South African Bone Marrow Registry (SAMBR) are small – in June 2012 there were just under 65 000 mostly Caucasian donors on file compared with 20.5 million on 77 international registries (Crookes, personal communication). Current reports suggest that the results for haploidentical SCTs are now comparable to those for UCB SCTs.

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**Table I. Donor sources used in stem cell transplantation for primary immunodeficiency (modified from Cuvelier et al.)**

<table>
<thead>
<tr>
<th>Donor source</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Matched related/sibling donor (bone marrow or peripheral blood)</td>
<td>• Preferred source&lt;br&gt;• Excellent long-term survival&lt;br&gt;• Relatively short period to work-up the donor and obtain the graft (weeks)&lt;br&gt;• Potential for no conditioning regimen or GvHD prophylaxis&lt;br&gt;• Rapid immune reconstitution</td>
<td>• Available in only 15-20% of SCID</td>
</tr>
<tr>
<td>Haploidentical T-cell depleted mismatched related donor (bone marrow or peripheral blood)</td>
<td>• Rapid procurement of stem cells&lt;br&gt;• Motivated donor&lt;br&gt;• T-cell immunity improves in 73%</td>
<td>• Overall lowest long-term survival rates of the different graft options (52-78%)&lt;br&gt;• Particularly poor survival in B-SCID&lt;br&gt;• Technical expertise required for T-cell depletion&lt;br&gt;• Higher rates of non-engraftment leading to second transplant&lt;br&gt;• Delay in T-cell recovery&lt;br&gt;• Poor long-term B-cell immunity with ongoing need for IgG replacement</td>
</tr>
<tr>
<td>Matched unrelated donor (bone marrow or peripheral blood)</td>
<td>• Excellent long-term survival approaching matched related donor transplant&lt;br&gt;• Delay of 2-4 months in working up and acquiring stem cell source&lt;br&gt;• Conditioning and GvHD prophylaxis required</td>
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<td>Umbilical cord blood stem cells</td>
<td>• Greater HLA disparity tolerated&lt;br&gt;• Increasing donor pool&lt;br&gt;• Rapid access to the donor unit (weeks)&lt;br&gt;• Less GvHD than marrow or peripheral blood&lt;br&gt;• Lower risk of latent viral transmission</td>
<td>• Conditioning and GvHD prophylaxis required&lt;br&gt;• Naïvety of lymphocytes against disseminated viral infection&lt;br&gt;• Lack of availability of donor for boost transplant&lt;br&gt;• Potential for slower haematological engraftment</td>
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GvHD – graft-versus-host disease; SCID – severe combined immunodeficiency; HLA - human leukocyte antigen.
HOW DOES IT WORK?

Successful bone marrow transplantation for most forms of SCID requires only the engraftment of donor lymphoid stem cells. Since donor haematopoietic stem cell engraftment is usually not required there is some controversy over whether conditioning with myeloablative agents is necessary in order to overcome graft resistance and achieve complete donor lymphoid and haematopoietic stem cell engraftment. While for MSD SCTs no preparation is required prior to the infusion of stem cells, many centres give conditioning in the form of chemotherapy in unrelated transplants as there is a higher risk of rejecting an incoming graft. Historically, myeloablative therapy with busulfan and cyclophosphamide was used. These agents carry the risk of significant toxicity including mucositis, veno-occlusive disease, and pneumonitis in the post-transplant period, as well as late effects such as infertility and chronic lung disease. The use of reduced-intensity chemotherapy (RIC) conditioning regimens, using agents such as fludarabine, melphalan, and treosulphan at mainly immunosuppressive doses, as well as isotope-labelled anti-CD45 monoclonal antibodies, has meant that patients with liver or lung damage can undergo SCT with relatively few complications; survival in patients undergoing unrelated-donor SCTs improved to 94% in one series versus 53% from historical data for those undergoing myeloablative conditioning.

Apart from UCB transplants, donor stem cells can be sourced from either peripheral blood (by apheresis via a large-bore intravenous catheter, a process akin to haemodialysis) or bone marrow (by direct aspiration under anaesthetic). Our practice is to use peripheral blood stem cells in most instances but there are circumstances, notably graft failure, where bone marrow is preferred. After processing and storage the stem cells are infused via a central line into the peripheral blood of the recipient. Haematopoietic engraftment occurs between 14 and 28 days after stem cell infusion and the patient remains in protective reverse isolation until the white cell count has recovered sufficiently to provide innate immunity against bacterial infections. Engraftment is followed by immune reconstitution of T cells and B cells. Unmanipulated grafts contain mature memory T cells which expand early providing immediate T-cell immunity until progenitor T cells have time to mature. This decreases the risk of opportunistic viral infections but may increase the risk of acute GvHD, and this is the rationale for T-cell depleting mismatched and haploidentical grafts. Post-transplant use of cyclosporine and immunodepletion of grafts leads to a delay in T-cell recovery of 3-6 months and increased risk of infections.

Acute GvHD is characterised by T-cell-mediated damage to the skin, the liver and the gastrointestinal tract, while chronic GvHD can affect almost any organ. Both GvHD and the long immune reconstitution times associated with alternative donor transplants put recipients at risk for opportunistic viral infections (especially respiratory pathogens), cytomegalovirus (CMV) reactivation, adenovirus and Epstein-Barr virus (EBV)-related lymphoproliferative disease. It is reassuring that while a UK study of 111 children with PID who underwent SCT showed a high rate of admission to intensive care for invasive ventilation (35%), the survival was good provided inotropes and renal replacement therapy were not needed.

PREPARING THE PATIENT

Metabolic supportive care is the cornerstone of transplant preparation. PID patients should not receive BCG vaccination, and where the diagnosis is suspected on the basis of a previously identified sibling, the BCG must be withheld until PID is ruled out. Unfortunately public health considerations preclude a policy of withholding BCG in all neonates. If the patient has received a BCG one should rule out BCGosis, as well as excluding Mycobacterium tuberculosis and active infection with CMV and EBV. Thereafter regular surveillance by polymerase chain reaction (PCR) for CMV and EBV is critical, and the patient should be started on prophylactic co-trimoxazole, and intravenous immunoglobulin supplementation. All patients should be given filtered blood products. Patients with a T-cell abnormality are at risk of transfusion-induced GvHD, which has a high fatality rate, and must in addition receive irradiated blood products. If the primary paediatrician and the immunologist believe that bone marrow transplantation is indicated, they should:

- Tissue-type the patient and any full siblings as soon as possible after diagnosis. In the event that there are no siblings, inform the SABMR that you will be looking for an MUD (stem cell or cord blood) so that the patient’s typing can be done to a high resolution.
- Discuss the patient with a paediatric transplant centre as soon as possible (the SABMR will make the tissue-typing results available to them).
- Optimise the patient’s clinical condition. Ideally the patient should be free of active BCGosis and CMV, well-nourished and free of organ failure. Keep in mind that it may not be possible to clear a BCGosis.

WHAT HAPPENS AFTER STEM CELL TRANSPLANT?

Most patients receive GvHD prophylaxis in the form of cyclosporin which must continue for at least 3 months post-SCT. During this period they will require ongoing immunoglobulin supplementation (either stabilised human serum (SHS) which is what we prefer, or intravenous immunoglobulins), as well as co-trimoxazole prophylaxis and CMV prophylaxis with valacyclovir. CMV surveillance (viral load measured by quantitative PCR or the pp65 assay) allows the detection of preclinical CMV reactivation which must be treated with gancyclovir. This period may be extended if GvHD develops, and families must be prepared for a prolonged stay away from home when they embark on SCT for PID.

Vaccination must be delayed for 12 months from the time of HLA-matched SCT and 18 months for alternative donor SCTs. A post-SCT vaccine schedule will be made available by the transplant centre. All household contacts should be immunised against influenza, and sibling infants and toddlers against measles, varicella and rotavirus. Oral polio vaccine should be avoided in favour of inactivated polio because viral excretion continues for 4-6 weeks post vaccination. The potential for graft failure, acute and chronic GvHD and late effects mandates shared care between the primary physician, the immunologist and the transplant centre.

SCT for PID is truly a team sport.

Declaration of conflict of interest

The authors declare no conflict of interest.

REFERENCES


