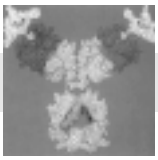

Stem-Cell Transplantation for Primary Immunodeficiencies

Bella Bielorai MD, Hana Golan MD, Gideon Rechavi MD PhD and Amos Toren MD

Department of Pediatric Hematology-Oncology and Bone Marrow Transplantation, Sheba Medical Center, Tel Hashomer, Israel
Affiliated to Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

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Primary immunodeficiency diseases represent a heterogeneous group of inherited disorders of the immune system. Classically these disorders are classified into T lymphocytes, B lymphocytes, phagocytic cells, and complement deficiency. Since the first bone marrow transplantation in 1968 for severe combined immunodeficiency [1], much progress has been made with regard to the molecular understanding and therapeutic options of these diseases. There are three major therapeutic approaches. The first is enzymatic therapy that is given to patients with adenosine deaminase-deficient SCID, representing only about 15% of all SCID patients [2]. This is a life-long replacement therapy and not a curative modality. The second is gene therapy, which so far has been successfully used in only four patients with X-linked SCID [3] and with questionable efficacy in ADA-deficient patients [4]. The third is stem-cell transplantation, which has become the most common treatment in these disorders. Both gene therapy and stem-cell transplantation are aimed at long-term curative treatment.

In this review we will focus on the different approaches used according to the various types of PID (SCID versus non-SCID), the sources of stem cells for the graft (bone marrow, peripheral blood, umbilical cord blood), the manipulations done on the graft (unmodified versus T cell-depleted), and the potential donors (matched sibling, haploidentical family member, unrelated).

Primary immunodeficiency diseases

During the last decade the molecular basis of most of the phenotypes of PID was unraveled. This was accompanied by increased understanding of the molecules that play a role in the normal processes of lymphocytes and myeloid development. There are several ways to classify PID. One classification is based on the type of cell involved (for example T cells, B cells, or phagocytic cells). Another possibility is to classify these disorders according to the underlying mechanism (lymphocyte development, antigen presentation, DNA repair, immunoglobulin class switch) [5]. A complete description of all the enzymatic molecular defects responsible for these diseases is beyond the scope of this review.

SID = severe combined immunodeficiency
ADA = adenosine deaminase
PID = primary immunodeficiency disease

A more practical classification in the setting of stem-cell transplantation is to divide these disorders according to the severity of the disease, namely SCID (absence of functional T cells) and non-SCID (some residual immune function). The various immunodeficiency disorders are shown in Table 1.

Principles of stem-cell transplantation

Allogeneic stem-cell transplantation is the transfer of self-replicating cells expressing the cell surface glycoprotein CD34, which can give rise to all mature blood cells – including T and B lymphocytes –

Table 1. Primary immunodeficiencies curable by stem-cell transplantation

I. Immunodeficiency of the lymphoid system
Severe combined immunodeficiency (SCID)
T-B+SCID
• X-linked (γ-chain deficiency
• Autosomal-recessive (jak3 deficiency, IL-7Rα deficiency)
T-B-SCID
• 1. Autosomal-recessive (Rag1/Rag2 deficiency)
• 2. T-B-SCID associated with increased cellular radiosensitivity (Artemis deficiency)
• Adenosine deaminase deficiency
• Reticular dysgenesis
Non-SCID immunodeficiency
• Omenn syndrome
• Purine nucleoside phosphorylase deficiency
• HLA-class II deficiency
• Cartilage hair hypoplasia
• Wiscott-Aldrich syndrome
• X-linked hyper-IgM syndrome (CD40 ligand deficiency)
• Autosomal-recessive hyper-IgM syndrome (activation-induced deaminase AID)
• X-linked lymphoproliferative syndrome
• Autoimmune lymphoproliferative syndrome (as deficiency, caspase 10)
II. Immunodeficiency of the phagocytic system
• Severe congenital neutropenia
• Leukocyte adhesion deficiency type I (CD18 β2 integrin deficiency)
• Chronic granulomatous disease (CGD X-linked & autosomal-recessive)
• Chediak-Higashi syndrome
• Familial hemophagocytic syndrome
• Immunodeficiency with partial albinism (Griscelli syndrome)

when transplanted from a healthy donor. In malignant disorders, the conditioning regimen is myeloablative since it is directed at eliminating all malignant cells, and also provides immunosuppression to allow acceptance of donor stem cells and the immune system.

In PID the goal of stem-cell transplantation is to provide normal cells of hematopoietic origin capable of producing the normal components of the immune system. Hence, myeloablation that is directed at effacement of the malignant cells is not always necessary and only immunosuppressive therapy is required for the engraftment of stem cells in the host bone marrow. In SCID patients no immunosuppression is needed because there is no graft rejection capability. In other forms of PID, some combination of myelosuppressive and myeloablative treatment is needed to allow engraftment and complete immune reconstitution, according to the type of donor used and the immunologic potency that is harbored by the host. The beneficial effect of the conditioning regimen is counterbalanced by increased short and long-term toxicity, especially in this patient population that is already subject to complications of infection. In recent years it has been shown that the engraftment of donor cells is possible with less intense conditioning regimens based mainly on immunosuppression, thus reducing the toxicity associated with high dose chemoradiotherapy. These non-myeloablative regimens seem to be an attractive approach for children with immunodeficiency disorders in which reduced conditioning may be sufficient to establish host tolerance to the donor immune cells responsible for immune reconstitution.

Sources of stem cells

There are three potential major sources of stem cells. The first, the traditional source, is the bone marrow. The second is mobilized peripheral blood. During the past 10 years there has been increased use of peripheral blood as the source of stem cells. Hematopoietic growth factors, such as granulocyte colony-stimulating factor, can be used to mobilize stem cells from the bone marrow into the peripheral circulation. Using leukopheresis, many of these cells can be collected from the peripheral blood, obviating the need for general anesthesia and shortening the time required for engraftment.

A third potential source of stem cells is umbilical cord blood, which can be collected at the time of delivery and contains a rich population of primitive hematopoietic stem cells as compared to bone marrow. Other approaches, such as the use of stem cells isolated from fetal liver, were tried but are still considered highly experimental.

Donor selection

The ideal donor is a sibling who shares with the host identical human leukocyte antigen class I and class II loci. Unfortunately only 25–30% of patients have an identical donor within the family, necessitating an alternative donor. An emerging alternative is the use of unrelated donors who are classified according to their HLA typing in worldwide registries. Until recently it was expected that the search for an appropriate donor, activation, and confirmatory tests would take 4–6 months on average. However it has been shown that the process can be accelerated in some urgent cases.

An important alternative for a donor in cases with no matched family or unrelated donor was demonstrated by Reizner et al. [6] in their pioneering transplantation of a SCID patient from a haploidentical family donor [6]. Almost every SCT candidate has a family member who is haploidentical (matched for only three of the six HLA loci). The major problem with these transplantations is the high rate of graft rejection and of graft versus host disease. These difficulties were resolved in recent years by meticulous T cell depletion by CD34-positive selection, which is currently being practiced in all transplantation centers, and by the large number of stem cells transfused with the graft that overcame the HLA barrier (the megadose concept) [7]. This was made possible by the use of G-CSF mobilized peripheral blood that enables collection of a much higher number of stem cells as compared to bone marrow.

The main advantage of the haploidentical transplants is that the donors are available immediately, something that has to be taken into consideration when an urgent transplant is needed for an infected SCID patient [Figure1].

Transplacentally acquired maternal T lymphocytes

The transplacental passage of maternal leukocytes to the fetal circulation during pregnancy is common, however it is the SCID patient who has no capacity to reject these cells. Maternal T cells can be detected in about 30–40% of SCID patients [8]. The significance of the existence of such cells has yet to be defined. Usually there is no immunologic advantage of the engrafted

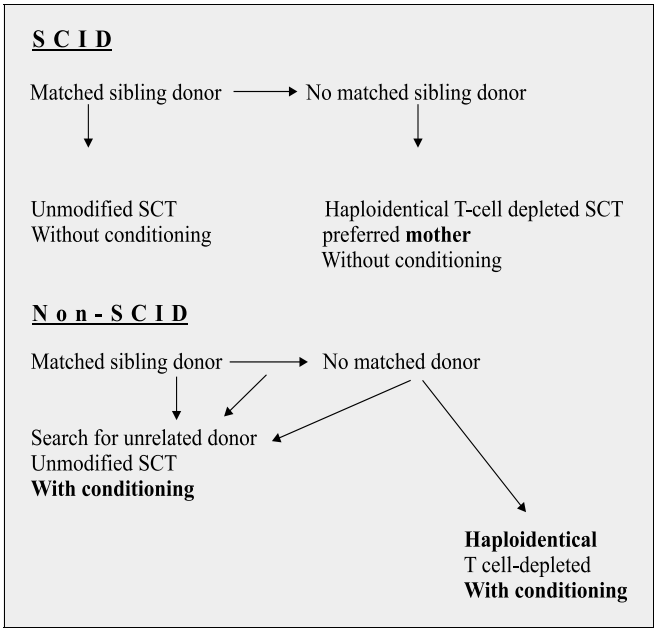

Figure 1. Donor selection for primary immunodeficiencies

HLA = human leukocyte antigen
SCT = stem-cell transplantation
G-CSF = granulocyte colony-stimulating factor

maternal T cells to the SCID patient. They may sometimes cause clinical signs of GVHD even before stem-cell transplantation. These signs are usually prominent in the skin when the maternal transplanted cells are CD4 cells, whereas only subtle or no signs of GVHD develop when maternal T cells are predominantly CD8+ [9]. They can complicate the transplant course if a donor other than the mother is used. In the absence of conditioning (no eradication of maternal cells) there is always a potential for graft versus graft reaction: T cells in the graft react against the previously engrafted maternal T cells. In the setting of haploidentical transplantation without conditioning, usage of the father as a donor is associated with a high incidence of rejection whereas usage of the mother is associated with an earlier than usual immune reconstitution [10].

SCT for SCID

SCT has been more widely applied and more successfully used in infants with SCID than in other PID. More than 600 patients have been reported in the European and American medical literature [11–14]. Three-quarters of them were transplanted from haploidentical donors with a success rate of 50–60% (however not all of them were T cell-depleted as practiced today), and a quarter of the patients were transplanted from matched siblings with a success rate of 80%. The reported matched unrelated transplants are sparse.

Buckley et al. [15] reported a smaller group of 85 children transplanted at Duke University Medical School between 1982 and 1998. Only 12 of these SCID patients had HLA-identical donors and all of them survived with functional grafts. Fifty-six of the 73 patients (77%) who received a haploidentical transplant are alive. Although the group was smaller, these better results may represent a better outcome due to better supportive care and lower mortality from infections.

The time to development of initial T cell immune function following HLA-identical stem-cell graft is usually 2 weeks since it is based on the presence of mature T cells in the graft. In haploidentical transplantation, 90–120 days on average are required for stem cells to mature in the recipient's thymus, hence the period of vulnerability to infection is much longer in recipients of a T cell-depleted graft. B cell function develops much more slowly, averaging 2–2.5 years for normalization in some patients and never in others. The most common way to divide the patients with SCID is according to the existence B cells (B+ SCID) or lack of B cells (B- cells). It is noteworthy that B+ SCID patients have a better outcome and engraftment than B- SCID patients [16]. The explanation for the poor engraftment in B- SCID is not fully understood and could be related to the presence of natural killer cells that are capable of graft rejection. In addition, the occurrence of post-transplant B cell lymphoproliferative disease occurs in this type of transplantation, whereas it does not in unfractionated HLA-identical grafts [17,18].

A recent study has shown that SCT for SCID performed in the neonatal period has an excellent outcome with a 95% success rate [19].

GVHD = graft vs. host disease

In *utero* transplantation

Availability of early prenatal diagnosis for several PID offers the option of *in utero* treatment. There has been limited experience with this technique and the procedure carries the risk of fetal wastage. Usually, paternal CD34 are infused intraperitoneally during the first half of gestation in non-SCID patients, or even later in SCID patients where no immunologic system develops and hence there is no rejection capacity [20,21]. The benefits of *in utero* transplantation over immediate postnatal transplantation in settings where parents do not want pregnancy interruption have to be carefully assessed. *In utero* transplantation reduces the risk of infectious complications. On the other hand, early postnatal haploidentical transplantation in SCID has been successful in more than 92% of cases [22], making it difficult to justify such a risk to the fetus.

SCT for immunodeficiencies other than SCID

Allogeneic stem transplantation has been found effective for correcting the underlying disorder in immunodeficiencies other than SCID. Diseases that are curable by transplantation are various T cell immunodeficiency syndromes, such as purine nucleoside phosphorylase deficiency, major histocompatibility complex class II deficiency, Wiskott-Aldrich syndrome, among others. Stem-cell transplantation could also offer the correction of a number of inherited phagocytic cell disorders that are otherwise lethal due to the severity of infections. These include the leukocyte adhesion deficiency type I, Chediak-Higashi syndrome, familial hemophagocytic lymphohistiocytosis, and chronic granulomatous disease.

It is estimated that over 400 patients with these various forms of immunodeficiencies have been transplanted worldwide. As more experience with stem-cell transplantation is gained, especially with regard to infection prevention and treatment, a better outcome is achieved. In Europe, the success rate of bone marrow transplants performed since October 1985 was 81.5 vs. 52% before October 1985 [23]. A younger age at transplantation is one of the most important factors for a better outcome. The success rate of transplants performed before the age of 2 years was 79% vs. 48% after age 4. With the advent of methods for identifying molecular defects, patients can be diagnosed at an earlier age, leading to further improvement in transplant outcome. In contrast to SCID patients, those with non-SCID immunodeficiencies have less severe immune dysfunction and this enables them to reject the graft. A conditioning regimen is needed to suppress the residual immune function, which poses the main problem in patients who have already developed infectious complications and end-organ damage due to unacceptable toxicity of the regimen. Non-myeloablative or reduced intensity regimens are being used increasingly in recent years in malignant and non-malignant diseases, with durable engraftment and less toxicity and could serve as an attractive alternative in this patient population.

HLA-identical vs. haploidentical T cell-depleted SCT in non-SCID immunodeficiencies

In contrast to patients with SCID who usually die during infancy, non-SCID patients usually live longer, however they rarely survive to adulthood without stem-cell transplantation. In addition, the

success rate is determined by the clinical status pre-transplant. Many of these patients have latent infections that may exacerbate during or following the conditioning regimen. Therefore, the decision regarding whether or not to transplant during infancy or early childhood is more complicated. Taking these considerations into account, it is generally recommended to transplant earlier if there is a suitable donor. The preferred donor is an HLA-matched sibling. The success rate of stem-cell transplantation differs among the various disorders. HLA-identical sibling transplant has been successful in 88% of patients with Wiscott-Aldrich syndrome [24]. All aspects of the syndrome are corrected by SCT, including eczema, autoimmunity, and the risk of lymphoma as well as thrombocytopenia and the bleeding tendency. Based on the encouraging results, stem-cell transplantation is recommended for patients with Wiscott-Aldrich syndrome and should be performed as early as possible. In contrast, the overall success rate in MHC class II deficiency is lower, with a survival of only 54% [25]. Again, as mentioned earlier, stem-cell transplantation can cure the disease if it is performed before the development of infectious complications. Another disease for which SCT is the only curative treatment is X-linked hyper-immunoglobulin M syndrome. Thus far it has been performed in only a small number of cases and is recommended if an HLA-identical donor is available [26]. The identification of the *SH2D1A/SAP* gene, which is responsible for the X-linked lymphoproliferative syndrome (a syndrome that is characterized by ineffective immune response to Epstein-Barr virus and is otherwise fatal), will help in identifying affected individuals who will benefit from early transplantation before developing overwhelming infection or other life-threatening complications. Satisfactory results have also been achieved with stem-cell transplantation in leukocyte adhesion deficiency type I, a rare disease characterized by defective expression of the β2 integrin subunit of LFA-1, an adhesion molecule involved in leukocyte-endothelial interactions. Its complete absence leads to severe bacterial infections and death within the first years of life.

Following the improved results with T cell-depleted HLA-haploidentical stem-cell transplantation for SCID, this approach was tried for other immunodeficiencies but with less successful results due to the high rate of graft rejection and infectious complications. This was especially unsuccessful in Wiscott-Aldrich syndrome patients compared to the high success rate with HLA-identical siblings. In sharp contrast to the poor results achieved in the former patients and other immunodeficiencies using a haploidentical donor, a high engraftment rate was observed in patients with LAD-I, possibly due to the defective expression of LFA-1, which has a role in graft rejection [27].

These examples reflect the heterogeneity of the various immunodeficiency disorders and emphasize the need for careful consideration in choosing the appropriate donor for a specific disease.

MHC = major histocompatibility complex
LAD = leukocyte adhesion deficiency

Unrelated SCT for non-SCID immunodeficiencies

Matched unrelated donor is another potential approach for patients with immunodeficiencies in the absence of an HLA-identical sibling. A high rate of success – up to 70% – was reported for patients with Wiskott-Aldrich syndrome, especially if performed before the age of 5 years [28]. Given the poor results with haploidentical donors in Wiskott-Aldrich patients, an unrelated donor is a better alternative considering the limitations involved in finding a suitable donor. Another potential source is unrelated cord blood, which until now has been performed in only a small number of patients.

Non-myeloablative SCT for immunodeficiencies

Chronic granulomatous disease is characterized by impaired microbial killing and susceptibility to life-threatening bacterial and fungal infections, due to mutations in one of the four subunits of the enzyme NADPH oxidase. There is considerable heterogeneity in the clinical course among individuals affected by this disease. Some of them will survive to adulthood with infrequent infections while others will develop severe infections in early childhood. The prognosis of patients with CGD has improved substantially due to prophylactic antibiotic and gamma-interferon. Still, stem-cell transplantation is the only curative treatment if performed early in the course of the disease before severe infections develop. For patients who have already developed severe infections, SCT carries a high risk of morbidity and mortality due to the toxicity of the preparative regimen. A non-myeloablative regimen allows engraftment and reduces toxicity. Nagler et al. [29] from the Hadassah group were the first to report a successful transplant using a non-myeloablative conditioning regimen and donor leukocyte infusion in a patient with chronic granulomatous disease and severe pulmonary disease. Recently, a group of 10 patients with CGD (5 children and 5 adults) were transplanted at the National Institutes of Health, Bethesda, USA, using non-myeloablative conditioning followed by T cell-depleted graft [30]. None of the reported patients died during the transplant period, however despite the reduced toxicity there is still a considerable risk of infectious complications, GVHD and impaired engraftment.

Eight patients with various types of immunodeficiencies underwent bone marrow transplantation from matched related or unrelated donors with non-myeloablative conditioning. All patients had severe organ dysfunction that precluded transplantation with the conventional regimen. All patients were engrafted, and at a median follow-up of 1 year the majority showed immune reconstitution [31]. This limited number of patients indicates that the non-myeloablative approach could be feasible in immunodeficiency disorders, providing adequate immune reconstitution with reduced toxicity.

Summary

Until further improvement in gene therapy is achieved, stem-cell transplantation is still the main option for cure of patients with primary immunodeficiency diseases. Performing the transplant in

CGD = chronic granulomatous disease

early infancy before severe infections and organ damage develop has the highest chance for success. The remarkable progress that has been achieved in understanding these disorders has made it possible to identify most of the genetic abnormalities. This enables an early transplant immediately after birth or even *in utero*.

However, the optimal approach for stem-cell transplantation in children with immunodeficiency has yet to be determined. The non-myeloablative protocols increasingly used in recent years have the potential for immune reconstitution without considerable toxicity, but the experience is still limited.

A better understanding of the specific immune dysfunction and the exact degree of residual immunity may enable the tailoring of the most appropriate conditioning regimen for each patient so that engraftment will be ensured with little morbidity.

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Correspondence: Dr. A. Toren, Dept. of Pediatric Hematology-Oncology and Bone Marrow Transplantation, Sheba Medical Center, Tel Hashomer 52621, Israel.
Phone: (972-3) 530-3037
Fax: (972-3) 530-3031
email: amost@post.tau.ac.il