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REVIEW ARTICLE

Hematopoietic Stem Cell Transplantation for Primary Immune Deficiency Disorders

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Abstract Hematopoietic stem cell transplantation provides a curative option for children with primary immune deficiency disorders. Increased awareness and rapid diagnosis of these conditions has resulted in early referral and the chance to offer a curative option for affected children. Management of these children involves a multidisciplinary team including infectious disease specialists and intensivists. The use of reduced intensity conditioning chemotherapy, advances in detection and therapy of viral and fungal infections, optimal supportive care and techniques in stem cell processing, including T cell depletion has enabled doctors to transplant children with comorbid conditions and no matched donors. Transplantation for these children has also brought in deep insights into the world of immunology and infectious diseases.

Keywords Primary immune deficiency · Bone marrow transplantation · Reduced intensity conditioning · Haploidentical stem cell transplantation

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) has been a curative option for several primary immune deficiencies (PID) including severe combined immune deficiency (SCID), Wiskott-Aldrich syndrome (WAS), chronic granulomatous disease (CGD), hemophagocytic lymphohistiocytosis (HLH) and many other immunodeficiency disorders for over 47 years [1, 2]. The entire field of hematopoietic stem cell transplantation has progressed and evolved because of the ability to apply new transplant concepts in the treatment of patients with primary immunodeficiency disorders and the majority of innovations in the field of transplantation have been inspired by children with PID. These include the first allogeneic human leukocyte antigen (HLA)-matched sibling bone marrow transplants for severe combined immune deficiency (SCID) and Wiskott Aldrich syndrome (WAS) in 1968 [1, 2], adenosine deaminase deficiency and SCID (ADA-SCID) in 1975 [3], unrelated donor transplant in 1977 [4] and haploidentical related donor transplants in 1983 [5]. In 1981 busulfan and cyclophosphamide were used in the conditioning of patients with WAS. This then became the backbone of myeloablative transplant for other non-malignant disorders like hemoglobinopathies and inborn errors of metabolism [6]. These initial steps have opened the path to accepting HSCT as the treatment of choice in many forms of PID [7–11].

The process of HSCT involves stabilizing the child, identifying a suitable histocompatible donor, conditioning chemotherapy so as to enable the recipient to accept new stem cells, infusion of donor stem cells into the recipient's central vein, providing optimal supportive care for 2 to 3 wk until the new stem cells begin to grow and differentiate and maintain on immunosuppression for about 6 mo to prevent graft rejection and graft *vs.* host disease. PID transplants pose several specific challenges in each of these steps and these will be discussed in detail.

Severe Combined Immune Deficiency (SCID)

SCID is a syndrome of diverse genetic causes characterized by profound deficiencies of T- and B-cell function and, in some

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types, also of NK cells and function. It is proposed that patients who exhibit an absence or a severe reduction of T cells (CD3 + < 300/μL), absence or severe reduction (<10 % of the lower limit) of a proliferative response to phytohemagglutinin, or a maternal lymphocyte engraftment should be defined as having typical SCID. On the basis of data obtained from eleven U.S. newborn screening programs in the general population, Kwan et al. reported an incidence of SCID of 1 in 58, 000 live-births [12]. With initial genetic assessment, mutations in thirteen different genes were found to cause this condition and have been correlated with the phenotype of the disease. In a microarray resequencing of known 240 cases of SCID, a total of 153 distinct mutations were found and 87 (64 %) were found only once in this retrospective cohort.

Since the first successful bone marrow transplant performed in 1968, allogeneic HSCT is the standard treatment for all forms of SCID with over 80 % long term survival when an HLA matched sibling donor is available and the majority of the children survived even in alternate donor transplants [13]. A retrospective study of 240 infants with SCID transplanted between 2000 and 2009 revealed that 5 year survival and T and B cell recovery were more likely in transplants from matched sibling donors than from alternate donors. However, the survival rate was high regardless of donor type among infants who received transplants at 3.5 mo of age or younger (94 %) and among older infants without prior infection (90 %) or with infection that had resolved (82 %). Among actively infected infants without a matched sibling donor, survival was best among recipients of haploidentical T-cell-depleted transplants in the absence of any pre-transplant conditioning. Among survivors, reduced-intensity or myeloablative pre-transplantation conditioning was associated with an increased chance of a CD3+ T-cell count of more than 1000 per cubic millimeter, and recovery of B cell function but did not significantly affect CD4+ T-cell recovery or T cell function. The genetic subtype of SCID affected the quality of CD3+ T-cell recovery but not survival. The study concluded that transplants even from donors other than matched siblings were associated with excellent survival among infants with SCID identified before the onset of infection [14].

Wiskott Aldrich Syndrome (WAS)

WAS is an X-linked disease due to mutations in the WAS gene causing life-threatening primary immunodeficiency, thrombocytopenia, eczema and a high incidence of autoimmunity and malignancy. The WAS gene provides instructions for making a protein called Wiskott Aldrich Syndrome Protein (WASP) in all blood cells. Lack of any functional WASP results in decreased ability to form immune synapses and leads to immune dysfunction [15]. Currently, HSCT is the only potential curative therapy for WAS [16, 17], and the significant host immunologic barrier mandates the use of conditioning regimen prior to transplantation. CIBMTR/NMDP reported transplant outcomes of 170 boys with WAS where most patients were younger than 5 y (79 %), and received pre-transplantation preparative regimens without radiation (82 %) and had non-T-cell-depleted grafts (77 %). The 5-year probability of survival for all subjects was 70 %. The probabilities differed by donor type with 87 % in patients with HLA-identical sibling donors, 52 % in those with other related donors, and 71 % in those with unrelated donors [18]. A second study reported the results on 194 boys transplanted with 79 matched sibling donors, 91 unrelated donors and 24 unrelated cord blood with improved outcomes after unrelated donor transplant compared with historical experience. The survival of recipients over 5 years was inferior to that in the under 2 y of age at 73.3 *vs*. 91.1 %. Umbilical cord blood transplant recipients had poorer survival as their transplants were associated with a higher risk of post-transplant complications including graft failure, GVHD (Graft *vs*. host disease), autoimmunity or malignancy. Lineage-specific chimerism was unstable in the first year post transplant in 20 % of patients, and mixed chimerism was more frequent among recipients of unrelated donor transplants. Myeloid chimerism of more than 50 % was generally associated with platelet counts above 50,000/ml [19]. In patients with WAS, mixed chimerism appeared to have a detrimental effect on event-free survival after HSCT due to an increased incidence of autoimmunity [20].

Chronic Granulomatous Disease

Chronic granulomatous disease (CGD) was first described in 1954 [21, 22] as recurrent infections occurring in the setting of hypergammaglobulinemia. Intact NADPH oxidase is essential for intracellular killing of microorganisms. Multiple separate proteins contribute to intact NADPH oxidase, mutations in five of which lead to a single syndrome CGD [23]. Originally thought to be an X-linked disease, its recognition in girls in 1968 led to the determination of autosomal recessive forms as well [24]. Individuals who have autosomal recessive forms of CGD may also have other subtle abnormalities, such as vascular disease, diabetes and inflammatory bowel disease [25–27]. Over almost 60 years CGD has evolved from a disease of early fatality to one of effective management with high survival.

Infections of the lung, skin, lymph nodes, and liver are the most frequent first manifestations of CGD. Overwhelming majority of infections in CGD are due *Staphylococcus aureus*, *Burkholderia cepacia* complex, *Serratia marcescens*, Nocardia species, Aspergillus species, Salmonella, severe localized Bacille Calmette Guerin (BCG) and tuberculosis.

Bone marrow transplantation can lead to stable remission of CGD. Conditioning regimens ranging from full

myeloablation to non myeloablative conditioning have lead to the cure of CGD [28, 29]. Even in the setting of refractory fungal infection, bone marrow transplantation has been effective with non-myeloablative transplants being more successful in children with other comorbid features [30, 31]. In patients transplanted with appropriate conditioning regimen before the onset of serious infection, the outcome has been remarkable. With these encouraging results the transplant procedure is being extended for haploidentical grafts following α β T cell depletion with successful outcomes.

Issues in HSCT Specific for PID

The main controversy is related to conditioning – do SCID babies need to receive myeloablative therapy? Conditioning results in complete correction of T cells and B cells whereas non-conditioned child may only have T cell engraftment and continue to require lifelong IVIG replacement therapy. Is myeloablative therapy or reduced intensity treatment better for other PID? Myeloablative therapy increases the chance for complete chimerism but increases the risk of acute morbidity and mortality. Reduced intensity conditioning is less toxic but may lead to mixed chimerism. For some diseases like CGD, mixed chimerism will be adequate to correct the disease. However, mixed chimerism may lead to development of autoimmune diseases in WAS. The optimum conditioning regimen must be evaluated on basis of diagnosis, disease status, co-morbid features and type of donor.

New Developments in the Treatment of PID

The use of haploidentical donors has helped to offer HSCT even to children with no matched donors. Haploidentical transplantation has been specifically used to treat SCID since the 1980's [5]. However, newer techniques are now being used to improve the process of depletion of T cells and reconstruct immunity by being more selective in depletion of α β T cells [32] and depletion of CD19+cells . In a study of T cell depleted haploidentical HSCT, the patients had rapid hematological recovery after transplant with a 22 % risk of GVHD and 27 % chance of graft failure. Optimal conditioning, the use of mega doses of stem cells $>10 \times 10^6$/kg CD34+ cells and residual γ δ T cells and NK cell in the graft with no ongoing immunosuppression have resulted in excellent outcomes in this type of SCID transplant.

Gene Therapy

Gene therapy is an attractive option for many monogenetic diseases [33, 34]. ADA-SCID is the first PID corrected successfully with gene therapy. The clinical trials involved the cessation of polyethylene glycol (PEG)-ADA prior to gene therapy and used a non-myeloablative reduced intensity conditioning regimen consisting of busulfan (4 mg/kg) or melphalan (140 mg/m^2); the trial showed long-term correction of both T and B cell functions [35]. A total of 20 patients, with X-linked SCID received *ex-vivo* transduced CD34+ cells without any conditioning regimen. Immune reconstitution was impressive in terms of T cell numbers and function. However, restoration of NK cells and B cells was only transient. Only a minority of patients were able to stop immunoglobulin therapy. Unfortunately 5 patients developed acute T cell leukemia, four of whom entered remission after standard chemotherapy. One patient died despite an allogeneic HSCT due to refractory leukemia. New trials with Lentivirus vector are in progress. A total of ten patients with CGD and a similar number of WAS patients have been treated in two separate trials. In these trials only a transient benefit was detected and the trial failed to show any long-term clinical benefit.

Gene Editing

Current and past clinical trials of gene therapy rely on viral delivery and addition of a functional copy of the defective gene. Over the past decades target-specific nuclease enzymes have been investigated to follow a strategy of targeted insertion of a functional copy and correction of the dysfunctional gene [36].

HSCT for PID in India

Primary immune deficiency disorders (PID) are an important cause of mortality in infants and children in India. There is little published data regarding the incidence and outcome of HSCT for PID from India. The main challenge faced so far is the lack of recognition of PID by primary care physicians and the lack of awareness on the success of HSCT for children with PID. This has resulted in very few referrals to tertiary care centres and hence only a handful of transplants for such a large country.

Most children are referred with disseminated BCG infection as BCG vaccination is mandatory on the day of birth. Poor general nutrition, the increasing incidence of hospital and community acquired drug resistant bacteria, lack of access to sophisticated molecular techniques to risk stratify these children and provide early therapy for viral infections have been common challenges faced in the care of these children. During immune reconstitution, BCG infection and cytomegalovirus (CMV) reactivation have been the main causes of morbidity and mortality. Ninety five percent of the population in India is CMV positive and CMV reactivation has been a

major challenge in PID transplants, particularly in the alternate donor setting and in those children who had received granulocyte transfusions to overcome their infections in the peritransplant period.

SCID transplants need to be planned based on the molecular diagnosis. Due to lack of universal access to genetic diagnosis, a flow cytometry based approach to conditioning has been adopted. Babies with T negative, B positive, NK negative SCID can be transplanted early with no conditioning and good success rates. However, babies with T negative, B negative, NK positive SCID could possibly have DNA repair defects and have a better outcome with a treosulphan based reduced intensity conditioning. Late death due to extensive fibroelastosis in a SCID baby with 100 % donor and good immune reconstitution has been seen in one such child in the second authors' centre. Targeted busulphan is essential for transplanting young babies with immunodeficiency and is not available in all centres in India and may account for inferior outcomes with myeloablative regimens using busulphan without therapeutic drug monitoring. All centres had used a myeloablative conditioning protocol which included busulfan and cyclophosphamide until 2011, after which a fludarabine based reduced intensity conditioning (RIC) protocol with either busulphan or treosulphan was adopted.

Long term immunoglobulin replacement is expensive and not feasible in India. Hence, children with X-linked agammaglobulinemia with a matched sibling donor have been offered HSCT. The average cost of HSCT in India is about 15,00,000 rupees for sibling allograft and twice the amount for unrelated transplants. T cell depletion techniques are expensive. Hence, there is an increasing use of post transplant cyclophosphamide, based on the John's Hopkins protocol, following fludarabine and melphalan conditioning using a haplo matched family donor.

Table 1 HSCT for primary immune deficiency disorders - data from India

Type of disorder	Number of children transplanted in India
Severe combined immune deficiency	34
Hemophagocytic lymphohistiocytosis/ Griselli/Chediak-Higashi syndrome	25
Wiskott Aldrich syndrome	19
Chronic granulomatous disease	11
Hyper IGM syndrome	5
Leucocyte adhesion defect/Hyper IGE syndrome	3
Common variable immune deficiency/X-linked agammaglobulinemia	3
Interleukin 12 deficiency/Mendelian susceptibility to mycobacterial disease - MSMD/ GATA2 Monomac syndrome	3
Immune dysregulation, polyendocrinopathy X-linked syndrome - IPEX	1

A total of 104 PID transplants have been done in the country as per data obtained from 10 participating centres that have performed PID transplants (Table 1). Over half of these children are alive and doing well. This data reinforces the fact that PID can be treated successfully in developing countries and outcomes are excellent with reduced intensity conditioning regimens. The outcomes in related transplants are excellent with low morbidity and mortality with good long term outcome. Extended family typing should be done before embarking on an unrelated donor search for children with PID. Outcomes in unrelated transplant will improve with new cord blood and donor registries developing in India.

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Compliance with Ethical Standards

Contributions NK is the senior author and has provided deep insights into BMT for primary immune deficiency disorders. RR has shared the experience and specific challenges in the management of these children in India, and will act as guarantor for the paper.

Conflict of Interest None.

Source of Funding None.

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