

Recent Advances in Transplantation for Primary Immune Deficiency Diseases: A Comprehensive Review

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Published online: 6 July 2013
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Abstract Hematopoietic cell transplantation (HCT) is a curative therapeutic option for severe combined immunodeficiency (SCID), a group of diseases which otherwise carry life expectancies that are of limited duration and quality. Survival following HCT for SCID has improved from approximately 23 to 91 % over the last 40 years. Success with SCID prompted efforts to apply HCT to the therapeutic challenge of well over 20 molecularly defined primary immune deficiency diseases (PID). Such success is due to both early recognition of PIDs and advances in the field of transplantation. Such advances include high-resolution HLA DNA donor–recipient matching, expansion of donor sources, better tolerated conditioning, new antibiotics, and wider availability. International collaborative efforts have provided patients and caregivers information that permit better treatment decisions now, and direct clinicians and investigators to ensure progress in the future. Pioneers in screening for SCID have taken steps to correct the fundamental challenge to successful treatment, which is the rapid discovery and characterization of cases and offering the transplant option to an affected child early in life; blood spot testing for T and B cell receptor quantification is now available to a growing fraction of newborns. Organizations including the Primary Immune

Deficiency Treatment Consortium in the USA, The European Society for Primary Immunodeficiency, the European Group for Blood and Marrow Transplantation, the Pediatric Blood and Marrow Transplant Consortium, the United States Immunodeficiency Network, the Immune Deficiency Foundation, and the Jeffrey Modell Foundation are contributing mightily to increase awareness and standardize optimal utilization to the benefit of patients. This review will update the allergist–immunologist concerning disease presentations, indications for transplantation, methodologies, conditioning regimens, and clinical outcomes for patients with PID for which timely HCT is critical.

Keywords Primary immune deficiency · Immunodeficiency · Stem cell transplantation · Bone marrow transplantation

Introduction

In 1968, Gatti and Good achieved the first immunological correction for an infant with severe combined immunodeficiency (SCID), by infusing allogeneic hematopoietic cells obtained from the bone marrow of an HLA-matched sibling [1]. Thomas and others demonstrated the utility of hematopoietic cell transplantation (HCT) for the treatment of leukemia, and the procedure is now applied relatively frequently to patients with hematological diseases and cancer worldwide [2]. Innovators improved methods and expanded indications for HCT over the last 45 years, to the extent that scores of otherwise lethal human diseases can be addressed with various degrees of success. An allogeneic (allo)-HCT consists of the intravenous infusion of allogeneic hematopoietic cells, usually after “preparation” of the recipient (host) with a more or less intense “conditioning” immunosuppressive regimen that permits some degree of donor cell engraftment and replacement of lymphohematopoietic function. When all elements (white cells, red cells, and platelets) are donor, the recipient experiences

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“full chimerism.” When some blood cell elements derive from the donor and some remain recipient, the patient is considered a “mixed chimera” [3, 4].

An ideal outcome of allotransplantation for primary immune deficiency diseases (PID) could be characterized as the following: (1) complete immunological reconstitution; (2) minimal transplant-related toxicity; and (3) achievement of full lymphohematopoietic donor chimerism without graft-versus-host disease (GVHD). Most patients with potentially lethal PID are presented with important hurdles that must be overcome for healthy survival. Foremost amongst these include delays in diagnosis, which permit establishment of life-threatening bacteremia, viral infections or infections with other opportunistic organisms, including *Pneumocystis jirovecii* and *Mycobacterium avium intracellulare*. A hematopoietic cell graft which contains HLA-suitable stem cells must be acquired in a timely fashion and referral accomplished to a transplant center expeditiously. The most important allotransplant toxicity, after over 50 years of attempts to minimize, remains GVHD [5–7]. Graft-versus-host alloreactivity is useful and tolerated to a certain degree with transplants for hematological malignancies, given the related graft-versus-tumor effects [8]. Alloreactivity during transplants for immunodeficiencies, although conceivably “useful” in promoting engraftment, is otherwise altogether detrimental. The goal is simply the timely correction of immunological function. Ongoing efforts are directed toward solving the GVHD problem, as well as other complications including conditioning toxicity, engraftment failure, peritransplant infections, delayed or partial immunological reconstitution, and secondary malignancies.

Areas of significant recent progress in the application of transplantation for primary immunodeficiency diseases are depicted in Table 1. This review consists of the following: (1) description of terminology and recent advances regarding conditioning; (2) outline of the general sequence before, during, and after the allotransplant procedure; (3) review of SCID transplantation outcomes; and (4) advances in HCT for other commonly accepted PID, for which HCT offers the only curative therapy.

Conditioning Regimens

Conditioning intensity is one of the most critical considerations in the allotransplant process, and new insights in this area are some of the most important recent advances for patients with PID. For many years, the need for conditioning for profound immune deficiencies was debated: myeloablative conditioning appeared necessary to affect the highest engraftment rates, but was toxic. Using no conditioning naturally eliminated toxicity, but was associated with impaired multilineage engraftment, especially for recipients with intact natural killer cell function [9]. The recognition of alloimmune anticancer effects during transplants for hematological malignancies redirected HCT efforts towards methods that utilized less toxic conditioning [10]. Reduced-intensity conditioning (RIC), followed by allogeneic HCT, provided effective therapy for the treatment of hematological malignant diseases, initially in older or infirm patients who could not tolerate “conventional” (myeloablative) conditioning [11–13]. Patients experienced remarkably high rates of engraftment and relatively low early transplant-related morbidity and mortality rates [14–17]. A summary of different conditioning regimens is depicted in Table 2.

Khouri, Childs, and Storb and their colleagues initially demonstrated that the purine analog, fludarabine, given with the alkylating agent cyclophosphamide or low-dose total body irradiation, permits initially mixed chimeric engraftment, absence of tissue injury to the recipient and progression over weeks or months to full donor lymphohematopoietic chimerism [12, 14, 29]. These particular methods, characterized as “nonmyeloablative” or “minimal intensity” are the least intensive of the myriad of “reduced-intensity” regimens that have been reported over the last decade [12, 30]. Most RIC regimens are more accurately referred to as “reduced toxicity” ablative regimens, in which engraftment is rapidly 100 % donor [29–34]. RIC regimens of several “intensities” have been associated with reductions in the following: (1) rates of high-grade mucositis and liver toxicity; (2) hemorrhagic cystitis; (3) requirement for post-transplant packed cell and

Table 1 Recent advances in allotransplantation for primary immunodeficiency diseases

- (1) Discoveries of the molecular bases of multiple immunodeficiency disorders
- (2) Implementation of high-resolution HLA typing with resultant movement towards parity between outcomes of matched unrelated donor (MUD) vs. matched related donor (MRD)
- (3) Development of reduced toxicity and nonmyeloablative conditioning regimens; early transplant results demonstrating improvement in outcomes
- (4) Long-term outcomes from multicenter series
- (5) Supportive care: improved experience with PID transplants, availability of novel anti-viral and anti-fungal therapies, preemptive diagnosis and therapies
- (6) Clarity of risks/benefits of full vs. partial (mixed chimeric) reconstitution.
- (7) SCID newborn testing and embracement of early transplantation for best outcomes for infants with SCID
- (8) Recognition of leaky phenotypes and early insights as to the role of HCT for patients with “combined” immunodeficiencies

Table 2 Examples of myeloablative, reduced intensity, and non-myeloablative conditioning regimens**Myeloablative**

Cyclophosphamide (120 mg/kg) and total body irradiation [18]

Busulfan (16 mg/kg) and Cy 120 mg/kg [19, 20]

Reduced intensity

Busulfan (<16 mg/kg)+Fludarabine [21]

Busulfan (8 mg/kg)+Fludarabine+Antithymocyte globulin [22]

Melphalan (<140 mg/m²)+Fludarabine [23]

Melphalan+Busulfan+Alemtuzumab [24]

Nonmyeloablative

TBI 200 Gy+Fludarabine [25]

Cyclophosphamide+Fludarabine±Antithymocyte globulin [26]

Fludarabine+Cytarabine+Idarubicin [27]

Total lymphoid irradiation+Antithymocyte globulin [28]

platelet transfusions; (4) peri-transplant infections including cytomegalovirus (CMV); and (5) need of total parenteral nutrition. When used for treatment of hematological malignancies, overall and disease-free survival (DFS) rates have ranged from slightly less, similar to or superior to those of myeloablated recipients [35, 36].

Many investigators over the last decade have incorporated RIC into their institution's protocols or treatment plan transplant methods for the treatment of PID [37]. One example is the work done at the Great Ormond Street Hospital in London, which represents one of the initial moderately sized comparative cohorts of heterogenous group of patients with PID who received matched unrelated donor (MUD) allotransplants. Overall survival of 31 (94 %) of 33 patients was significantly better in the RIC group compared to 10 (53 %) of 19 in the myeloablated group ($P<0.14$), and transplantation-related mortality was reduced [38].

Transplant Methods and Supportive Care

Donor acquisition is followed by the obtainment of parental informed consent for an Institutional Review Board-approved HCT protocol or transplant center treatment plan and the patient proceeds to transplant. Patients are generally admitted to a dedicated Cellular Transplant Unit equipped with laminar airflow or HEPA filtered rooms under conditions of reverse isolation. Acyclovir, fluconazole, and gram-negative antibacterial are administered as preventives for viral, fungal, and gram-negative bacterial infections, respectively. GVHD prophylaxis is begun. Freshly harvested, non-manipulated cells are infused within 24 h of collection on day 0. Irradiated blood products are utilized to prevent transfusion-related GVHD reactions. Important components of the transplant that require documentation include the sex and CMV status of the donor,

the detailed description of the conditioning regimen, and the total number of total cell doses including mononuclear cells per kilogram, CD3+ per kilogram, and CD34+ per kilogram body weight of the recipient. Whether granulocyte colony stimulating factor is used is documented as well as the details of GVHD prophylaxis. Engraftment is described as the first of three consecutive days post-transplant to an absolute neutrophil count over 500 cells/mm³; platelet count of 20,000/mm³ or 50,000/mm³ is evidence of platelet engraftment, and days to red cell transfusion independence is a measure of red cell engraftment. Peripheral white blood cell chimerism analyses are assessed periodically; the chimerism trends of total, myeloid, and T cells are followed [39]. Post-transplant complications include rashes, mucositis, and transient elevation of bilirubin to full-blown liver failure from GVHD or sinusoidal obstructive syndrome. The extent and severity are dependent on a number of known and unknown factors. Fevers are common and managed with administration of empiric broad-spectrum antibiotics while cultures are established. Peri-transplant infections are common and require specific diagnoses that specify appropriate therapy.

Patients are discharged typically between several weeks to months after transplant, depending on the engraftment dynamic and complications. Discharge medications in the uncomplicated cases usually include those for GVHD prophylaxis, anti-microbial prophylaxis, and gammaglobulin infusions (IVIG).

Post-transplant Care

Serial exams, peripheral blood counts, and chemistry profiles are documented usually weekly initially, and then as is clinically indicated. Patients receive IVIG for a period that varies according to center; the presence or absence GVHD and the tempo of immune reconstitution may inform the duration of IVIG continuance which in most cases is at least 1 year or until antibody production is documented. At an appropriate interval, Red Book/Center for Disease Control immunization guidelines are executed. Lymphocyte immunophenotyping and mitogen responses are monitored post-transplant at various intervals. Serial chimerism analyses are performed at different time points after transplantation until 100 % donor is documented or indefinitely if it is not [40]. Immunologic reconstitution is described as appropriate for the particular PID.

Severe Combined Immunodeficiency

Severe combined immunodeficiency (SCID) refers to a spectrum of genetic disorders characterized by a lack of or impaired T lymphocyte-dependent adaptive immunity. Affected individuals carry a genetic defect affecting both the

humoral and cellular immunity; patients exhibit profound decreases in T cell numbers and/or function and usually secondary B deficiencies. This defective immune system predisposes the individual to recurrent infections, chronic diarrhea, and failure to thrive. Left untreated, death usually occurs during the first year of life. SCID affects all ethnic groups and is estimated to occur in 1 in 50,000 to 100,000 live births. There are currently over 20 different forms of SCID [41]. The most frequent type is an X-linked defect, due to mutations in the cytokine receptor component γC (OMIM#300400), a transmembrane protein that forms part of the receptors for interleukin-2, -4, -7, -9, -15, and -21. Examples of other autosomal recessive forms classified as $T^+ B^+$ SCID include mutations of JAK3, IL7R α , CD45, CD3 δ , CD3 ϵ , CD3 ζ , and Coronin-1A. $T^+ B^-$ phenotype is seen with mutations in recombination activating genes 1 and 2, DNA-PKcs, reticular dysgenesis due to mutations in AK2, adenosine deaminase deficiency, and purine nucleoside phosphorylase. Radiosensitive SCIDs include DNA Ligase IV deficiency, Artemis (DCLRE1C), and Cernunnos/NHEJ1.

Newborn screening for SCID has provided a unique opportunity to identify these patients before they come to medical attention due to illness. Because such patients with SCID make few T lymphocytes, detecting low levels of recently made or “naïve” T cells provided the basis for the development of the currently used TREC (T-cell receptor excision circle) assay [42]. Jennifer Puck, M.D., and colleagues initially isolated DNA from dried blood spots and counted TRECs from patients with SCID and from actual blood spots obtained from newborns from the Maryland Newborn Screening Program. In contrast to filters from the newborn screening program, which had a mean of 1,020 TRECs in two 3-mm punches, samples from 23 infants with SCID had <30 TRECs. Therefore, TRECs are a stable analyte that can discriminate between infants with normal and low T cell counts utilizing newborn dried blood spots [43, 44].

In May 2007, experts from newborn screening programs convened, including the pediatric immunology community, pediatric transplant centers, and federal, state, and non-governmental agencies to study screening for SCID. Absence of TRECs was considered as the most developed high-throughput screening method. A consensus was achieved that SCID newborn screening should be pursued with pilot studies. On January 1, 2008, the newborn screening (NBS) program in Wisconsin became the first in the world to routinely test all newborns for SCID [45]. The New England Newborn Screening Program developed and validated a multiplex TREC assay in which both the TREC analyte and an internal control are acquired from a single punch and run in the same reaction. Massachusetts then implemented a statewide pilot SCID NBS program on February 1, 2009, and demonstrated that a SCID NBS is possible on a population basis with reasonable rates of false positives [46].

Diagnostic Evaluation and Management Prior to Transplant: SCID

Classically, the usual clinical presentation for a child with SCID is failure to thrive, between 3 and 12 months of age, with symptoms appreciated retrospectively to have begun several weeks to months prior, including intermittent fevers, diarrhea, cough, and weight loss. There is often a prior hospitalization for pneumonia. Pre-natal and birth history is usually unremarkable, delivery having occurred uncomplicated with normal birth weight. Physical exam may be remarkable for weight less than the 5th percentile, and there is usually no facial dysmorphism. Skin exam is usually normal, but a maculopapular rash may be present. There may be tachypnea, intercostal retractions, or bilateral crackles on chest auscultation. Complete blood count is usually but not always remarkable for decreased numbers or percentages of lymphocytes. Comprehensive chemistry profile may show increase in liver enzymes. Screening immunological evaluation includes the measurement of total and specific antibody titers, and peripheral blood immunophenotype analysis.

The clinical response to initial therapies may be disappointing or atypical; prompt re-evaluation is often necessary to discover persistent or unusual pathogens, which then leads to a second level of investigation. With the first impression that SCID is considered, the initiation of prophylactic antimicrobial therapy should be considered; a typical regimen includes anti-viral, fungal, and pneumocystis prophylaxis (i.e., acyclovir, fluconazole, trimethoprim-sulfamethoxazole). Intravenous immunoglobulin (IVIG) is initiated at a dose of 400 mg/kg that may be repeated monthly, depending on the clinical course. Lymphocyte proliferation to mitogens and antigens (Phytohemagglutinin A, pokeweed, concanavalin A, *Candida albicans*, *Tetanus toxoid*, *Staphylococcus* enterotoxin B and anti-CD3) is performed. Mutational analysis of the genes associated with SCID and other PID is needed as is indicated by the screening evaluation. Findings permit the establishment of an immunophenotypic [i.e., $T\ cell^{+/-}$, $B\ cell^{+/-}$, natural killer (NK) $cell^{+/-}$] and molecular form of SCID. The search for a suitable donor begins with HLA typing of the patient and family members. Currently, class I HLA loci are identified by serological methods and Class II antigens by DNA high-resolution typing. While the diagnosis of SCID is considered, timely consultation with an immunologist and transplant facility and personnel is helpful, and if the diagnosis is established, will facilitate the expedient transfer of care to the transplant team.

Donor Selection for SCID

The current treatment of choice for patients with SCID is HCT using a matched-related donor (MRD), from which the graft is extracted from the marrow (BM; Table 3). CD34+ mobilized

Table 3 Overall survival outcomes from studies of HCT for SCID

Year of publication	Reviews	No. of pts/ transplants	Center/s	Year	Age at transplant	Donor source	Overall survival (time post-txp)
1977	AB Kenny and WH Hitzig (Eur J Pediatr 1979)	80/123	Review of cases reported in medical literature	1968–1977	1–24 months	Group I HLA+MLC compatible=31 Group II only MLC compatible=11 Group III only HLA compatible=3 Group IV HLA=MLC incompatible=31 Group V histocompatibility not stated=4	15/31=48 % 3/11=27 % 0/3=0 % 0/31=0 % 0/4=0 % OS=23 % (10 months–9 years)
1990	Fischer et al. (Lancet 1990)	183	Europe	1968–1990		HLA-identical=70 HLA-non-identical+T-depleted=100	OS=79 % OS=52 %
2010	Gennery et al.	699	Multicenter EBMT/ESID	1968–2005		Related genotypically identical=135 Related phenotypically identical=68 Unrelated donor=81	84 % ^a 64 % ^a 66 % ^a
2011	Buckley et al.	166	Single Center Duke University, United States	1983–2009	Newborn to 21 months	Related HLA-mismatch=415 Haplo-identical+T depleted=149 HLA-Identical = 17	54 % ^a 73 % 100 %
2012	Fernandes et al.	249	Multicenter EBMT	1995–2005	6.45 months (1–45)	Mismatched related+T-depleted=175 Unrelated cord blood=74	62 %±4 ^b 57 %±6 ^b
2012	Eapen et al.	201	Multicenter, CIBMTR	1980–2003	<24 months	HLA-matched sibling=51 Mismatched related=93 Unrelated=57	N/A N/A N/A OS=93 % ^c

Pls patients, OS overall survival, CIBMTR International Bone Marrow Transplant Registry, EBMT/ESID European Group for Blood and Marrow Transplantation; European Society for Immunodeficiency Database

^a Ten-year OS

^b Five-year probability of survival

^c Seven-year probability of survival

peripheral blood cells (PBST) may also be used, but given the higher rate of GVHD with PBST, BM is at present the preferred product. Patients with SCID and a human leukocyte antigen (HLA)-matched related donor may or may not receive conditioning, with several series reporting DFS rates of greater than 90 % [47, 48]. However, the majority of patients (75–80 %) lack a suitable matched sibling donor.

Alternative hematopoietic stem cell sources include partially matched related donors or T-depleted haploidentical parental marrow cells [49–52]. Over the past 20 years, registries that collect, store, and distribute hematopoietic cells obtained from unrelated volunteer participants or umbilical cord blood have permitted alternatives to haploidentical donor transplants for patients without closely matched related donors. At many institutions, if an HLA-matched related donor is not identified, a search through National Marrow Donor Program (NMDP), other international or cord blood registries is initiated to identify a suitable unrelated donor. Each has advantages and disadvantages with respect to the number of various mononuclear cell types, requirement for conditioning, rates of engraftment, achievement of complete multi-lineage donor engraftment, incidence and severity of GVHD, and rates and degrees of immunological reconstitution. It is important to recognize that an optimal and standardized conditioning regimen and alternative donor source is yet to be determined for the majority of patients with SCID and other PID.

For those without a matched sibling donor, a haploidentical transplant can be performed relatively quickly if the procedure is accessible to the patient. T-depleted, haploidentical parental cells are immediately available, there is no chemotherapeutic toxicity, and the GVHD rate is very low after T cell depletion. However, the time to full immunological reconstitution may be comparatively long, and recipients remain IVIG-dependent approximately 50 % of the time [53, 54]. Such an approach may not be ideal in a patient with significant pre-transplant infections. Recipients with functional NK cells may be capable of rejecting the graft; however, NK cells are usually absent in γ C-deficient SCID, though T^+B^+/NK^+ is occasionally observed, particularly in infants who have experienced infections over a period of several months prior to diagnosis.

A MUD provides another alternative as a stem cell source. The frequency of a 10/10 HLA match in the population is roughly estimated to be 1 in 10,000; given this frequency and the fact that there are over 11 million willing potential donors in the community, there is an approximate 75 % chance of finding a suitable unrelated donor for patients in need. This estimate may be less for certain ethnic or biracial backgrounds. Umbilical cord blood (UCB) is increasingly employed for the allotransplantation of children and adults with a variety of hematological malignancies and PID. In certain cases, the risk–benefit estimate may favor UCB transplantation, given the relatively low risk of GVHD observed and the relatively rapid availability of these pre-collected cells. The time required

to find a MUD donor is usually 2–4 months. What is not known with UCB transplants is evidence for very long-term life expectancy; nonetheless, since the mid-1990s UCB transplants have demonstrated near-term results similar to those of MUD transplants. A summary of outcomes involving the larger cohorts of transplanted patients with SCID is depicted in Table 3.

Transplantation for Non-SCID PID

Wiskott-Aldrich Syndrome

Wiskott-Aldrich syndrome (WAS1; OMIM 301000) is a rare primary immunodeficiency caused by mutations in the WAS gene [55]. The disease is inherited as an X-linked recessive disorder, and female carriers demonstrate nonrandom X-inactivation [56]. Population genetics describe an incidence of 4/1 million live births [56]. WAS-protein (WASP), the gene product of WAS, is exclusively expressed in hematopoietic cells, and belongs to a family of proteins that regulate the actin cytoskeleton. Normal WASP expression is critical for chemokinesis, hematopoietic cell development, cell signaling, immunologic synapse formation, and lymphocyte apoptosis [57, 58]. Mutations along the WAS gene give rise to different clinical phenotypes: X-linked thrombocytopenia (XLT), intermittent thrombocytopenia, classic WAS, and X-linked neutropenia [59, 60]. Genotype/phenotype correlations have been reported and depend on the degree of WASP expression. XLT is associated with missense mutations, primarily located in exons 1 through 4, in-frame deletions or insertions and results in the presence of WASP but usually of reduced quantity. Deletions, insertions, and nonsense mutations, distributed throughout the WAS gene and splice-site mutations predominantly in introns 6, 8, 9, and 10, result in absent or truncated WASP and the classic severe WAS [59]. When missense mutations occur in the Cdc42-binding site of WASP, the disease results in X-linked neutropenia which lacks any of the features of WAS [61–63]. In order to help distinguish the different phenotypes, a clinical scoring system was developed [59]. Scores of 1–2 identify patients with XLT with mild eczema and micro-thrombocytopenia, while scores 3–5 distinguished the classic WAS associated with combined immunodeficiency, malignancy, and autoimmunity [59].

Despite advances in diagnosis and medical management, the long-term outcomes remain poor, and most patients with classic WAS will die of infections, malignancy, autoimmunity, and bleeding consequences [64]. The life expectancy is less than 20 years [65]. HCT remains the only curative therapy since first performed in 1968. This first successful transplant was performed in a 22-month-old male with his matched sister as a donor [66]. Two transplants were required for engraftment. Azathioprine (5 mg/kg) and prednisone (2 mg/kg) given for 2 days before the transplant followed by a marrow infusion

(6.5×10^9) proved unsuccessful. The second transplant was conditioned differently: 2×10^9 peripheral blood cells from the donor were given intravenously followed 36 h later by cyclophosphamide (60 mg/kg/day) for 3 days. On the fourth day, a smaller dose of cyclophosphamide was given (20 mg/kg), and 36 h later, a fresh bone marrow aliquote (2.7×10^9 nucleated cells) was infused intravenously. Fifteen years later, a follow-up report demonstrated normal T cell engraftment but incomplete B cell function and persistent thrombocytopenia [67].

Before 1990, most stem cell transplants for WAS utilized matched sibling donors, and most series reported were single-center experiences. In the last 15 years, an effort to report multicenter collaborative studies has been successfully conducted, and analysis of transplant outcomes for patients transplanted between 1968 to 2013 is available (Table 4). In the Filipovich analysis, an important result demonstrated that boys transplanted before age 5 years, despite receiving an unrelated donor transplant, had comparable survival rates to those receiving HLA identical sibling transplants [68]. More recently, these data continue to hold true, but with improvement in stem cell transplantation experience, the overall 5-year survival for children transplanted over the age of 5 reaches 73 % and suggests that transplantation for these children should not be restricted if their clinical status is good [69]. A unique set of infants with early-onset life-threatening complications of WAS (<2 years of age and clinical scores of 5) represent a high risk group with pre-transplant mortality of 18 %. HCT should be performed as soon as possible, as successful outcomes are reported in 77 % of cases, even in the setting of unrelated donors [70].

The overall 5-year probability of survival for patients with WAS receiving HCT since 2001 has increased from 70 to 89 % if transplanted after the year 2000 [69]. In addition, the 5-year survival is 92.4 % for patients with clinical scores of <3 versus 79.3 % for patients with clinical scores >5 [69]. Donor selection does influence outcomes, and patients receiving matched sibling transplants constitute the group of patients with best overall 5-year probability of survival (>80 %) which, interestingly, has not significantly changed since the 1960s. What has improved, with better transplantation experience, is the overall survival for recipients of mismatched related donor from 52 to 91.7 % [69].

Myeloablative conditioning regimens that include busulfan/cyclophosphamide with or without antithymocyte globulin therapy are associated with best myeloid engraftment [71–73]. RIC regimens have been used successfully since 2000, and in multivariate analysis, these regimens have not been identified as risk factors for post-transplant complications (RR 1.80 95 % CI 0.97–3.31). However, how such regimens may influence long-term survival is not reported [69].

Ozsaahin, following up on previous report from 1996, that first identified autoimmunity as a potential complication,

reported on 96 WAS patients undergoing HCT and surviving at least 2 years after HCT, from 19 European centers. Autoimmunity, which tended to occur 1.5 years after HCT, was recognized in 20 % of patients independent of cGVHD and pre-transplant autoimmunity [74, 75]. In this analysis, autoimmune cytopenias were more commonly seen in the setting of unrelated donors and correlated with the pattern of donor chimerism. Unusually high incidence of autoimmunity was noted in patients with mixed/split chimerism (72 %) in contrast to patients with full donor chimerism (8 %) [75]. A subsequent review by Moratto in 2011 confirmed these findings but at a lower rate 13.9 % of patients, 66 % of whom had no pre-transplant episodes of autoimmunity [69] and similarly associated with mixed donor chimerism with incomplete lymphocyte reconstitution. Persistent post-transplant thrombocytopenia was associated with poor donor myeloid chimerism [69]. Primary graft failure (7 %), chronic GVHD (14.8 %), fatal sepsis (2.2 %), and neurologic sequelae (7.4 %) comprise complications reported in 135 patients who had survived at least 2 years after transplantation [69]. Overall complications were also influenced by donor type (unrelated>matched sibling), and severity of disease as assessed by clinical score at time of HCT: 32.4 % for patients with clinical scores <3 vs 53.6–56.1 % for patients with clinical scores of 3–4 or >5 [69]. Post-transplant malignancy was reported in <4 % of patients [69, 75]. Pre- or post-transplant splenectomy carries a post-transplant mortality of 10–21 % due to sepsis and should be carefully weighed against the potential benefit to improve thrombocytopenia [75, 69].

There has been considerable progress since 1968 in treating patients with classic WAS. Analysis of the molecular defect coupled with clinical scoring systems improved transplant experience, introduction of effective and less toxic immunosuppressive drugs provides hope for patients with newly diagnosed WAS. However, 13–30 % late complications warrants continued multicenter collaborative efforts.

Hyper-IgM Syndromes or Defects in Class Switch Recombination

The hyper-IgM syndromes comprise a group of heterogeneous disorders currently named defects in class switch recombination [76]. X-linked and both autosomal recessive and dominant forms of inheritance exist: (1) X-linked hyper-IgM (XHIGM; HIGM type 1; OMIM # 308230; gene: CD40Ligand); (2) autosomal recessive hyper-IgM type 2 (HIGM type 2; OMIM # 605258; gene AICDA/AID); (3) autosomal recessive hyper-IgM type 3 (HIGM type 3; OMIM # 606843; gene CD40/TNFSFR5), and (4) hyper-IgM type 4 (HIGM type 4; OMIM #608184; C-terminal domain of AID). The common characteristic is an inability of B cells to undergo isotype switching from IgM to IgG, IgA

Table 4 Overall survival outcomes from studies of HCT for Wiskott-Aldrich syndrome

Year of publication	Reviews	No. of pts/transplants	Center/s	Year	Age at transplant median (range)	Donor source	Survival (time post-tpx) or 5-year OS ^a , 7-year OS ^b
1996	Ozsahin et al.	26/28	Single Center Hospital Necker-Enfants Malades, Paris, France	1979–1994	8 months–15 years	11 HLA identical (1MUD) 17 HLA-incompatible (parents/sibs)	81 % (1.5–16.5 years) 29 % (3.8–10.2 years) OS=55 %
2001	Filipovich et al.	170/190	Multicenter IBMTR/NMDP	1968–1996	3 years (<1–16 years)	55 HLA identical 48 Other related 67 Unrelated	87 % ^a 52 % ^a 71 % ^a OS=70 % ^a
2006	Kobayashi et al.	57/64	Multicenter Japan	1985–2004	1.6 years (3 months–19 years)	11 Match related (BM or PBST) 10 Mismatched related (BM or PBST) 21 Unrelated BM 15 Unrelated cord	81 % ^a 37 % ^a 80 % ^a 80 % ^a OS=73 % ^a
2006	Pai et al.	23/+IBM Boost	Single Center University Brescia, Italy	1990–2005	22 months (6 months–5.6 years)	4 Related Identical 1 Cord related identical 2 Mismatched related 16 MUD	100 % 100 % 0 % 81 % OS=78 % (3 months–11 years) 88 % ^b
2008	Ozsahin et al.	96 (surviving >2 years)	Multicenter EBMT/ESID	1979–2001	2.2 years (0.5–17.7 years)	45 Matched (sibling/parent) (42 sibs; 3 cords) 32 Matched unrelated (BM=24; PBSC=8) 19 Mismatched related (BM=15; PBSC=5; BM+PBCT=2)	71 % ^b 55 % ^b OS ^b =75 % Ten-year OS=71 %
2010	Gemery et al.	168	Multicenter EBMT/ESID	1968–2005	N/A	48 Matched sibling 10 Matched related non-sib 51 Mismatched related 59 Matched unrelated 39 Matched sibling 35 Mismatched related 91 Unrelated 24 Unrelated cord	>90 % N/A >80 % >80 % OS=82 % (12–346 months) OS for tpx after year 2000=89 % ^a , 83 % ^c OS=82 % ^a OS=81 % ^a
2011	Moratto et al.	194	Multicenter European & US Centers	1980–2009	34.6 months (2–240 months)		
2011	Mario et al.	23	Multicenter Japan	1998–2008	14 months (4–84 months)	23 UCB	
2013	Mitchell et al.	27	Multicenter Australia & New Zealand	1992–2008			

Ptspatients, OS overall survival, IBMTR International Bone Marrow Transplant Registry, NMDP National Marrow Donor Program, EBMT/ESID European Group for Blood and Marrow Transplantation; European Society for Immunodeficiency Database

^a Five-year probability of survival

^b Seven-year probability of survival

^c Eight-year probability of survival

or IgE, and patients demonstrate low serum IgG and IgA levels with normal or elevated IgM.

XHIGM is the most common and the first of the hyper-IgM syndromes described with an estimated prevalence of 1:1,000,000 [77]. Between 1987 and 1993, the gene responsible for XHIGM was mapped to the long arm of the X chromosome (Xq26) [78, 79], and by 1993, five different groups identified mutations in the CD40Ligand (CD40L) gene [80–84].

CD40L is a critical molecule in T–B cell interaction and is upregulated on activated T cells. CD40L binds CD40 on the surface of B cells permitting immunoglobulin isotype switching and antigen-specific antibody production [85, 86]. In addition to controlling immunoglobulin class switching, CD40L enables antigen priming of T lymphocytes, activates macrophages, and allows for maturation of dendritic cells [87, 88].

Clinical presentation includes recurrent sinopulmonary and gastrointestinal infections caused by intracellular and extracellular pathogens [77, 89]. Susceptibility to rare fungal pathogens [90], opportunistic infections such as *Pneumocystis jirovecii* can frequently be the initial presenting illness in up to 32 % of patients [91]. *Cryptosporidium* is common and has been associated with sclerosing cholangitis contributing to significant morbidity and mortality [77, 89, 92]. Parvovirus-induced aplastic anemia has been reported, and neutropenia can occur in up to 50 % of patients [77]. In addition, susceptibility to autoimmune diseases and malignancies is recognized [89, 93, 94].

The long-term morbidity and mortality for XHIGM became evident after a series of retrospective collaborative studies. The first included a series of 16 children who had been referred for evaluation of immunodeficiency over a 14-year period (1977 to 1991) [95]. In 1997, Levy et al. [89] reported on the first European collaborative study. Fifty-six patients were analyzed: 48 with specific CD40L mutations and 8 with clear evidence of X-linked inheritance and associated with defective CD40L expression. The most prominent clinical feature was the occurrence of opportunistic infections, four patients required a liver transplant for sclerosing cholangitis, and two patients had fatal hepatocellular carcinoma. The overall survival was poor: 20 % by age 25 years. In addition, the authors reported 23 pedigrees with familial presentation where 35 boys had died before adolescence. The last report, by Winkelstein et al. [77], included data on 79 patients collected through a national registry within the USA. Over 75 % of patients developed symptoms of immunodeficiency before their first birthday, and elevated IgM levels were only found in 30 % of cases. While the overall mortality in this cohort of patients was reported at 10 %, the authors concluded that their morbidity warranted a guarded prognosis.

Medical therapies include replacement IgG therapies and prevention of opportunistic infections such as *Pneumocystis*

with trimethoprim-sulfamethoxazole. Because of the morbidity and mortality related to this condition, HCT has been proposed as a curative therapy for XHIGM. Since the first report in 1995 [96], success of such therapy has been forthcoming, with larger number of patients undergoing this procedure [47, 77, 96–105]. The most comprehensive of these comes from the Newcastle group and includes an analysis of 38 patients with an overall survival of 68 % (follow-up of 1.2 to 9.3 years; median 3.4 years). In 58 % of patients, CD40L was normally expressed and represented a cure from the disease. Thirty-two percent of patients died, all associated with infection, of which in 50 % could be attributed to pre-transplant cryptococcal infection [106]. More recently, recombinant CD40L (rCD40L) was administered to three patients with XHIGM. Evidence for delayed type hypersensitivity, adequate IFN- γ and TNF- α production by mitogen-activated T cells, and changes in lymph node architecture was demonstrated [107].

However, what variables contribute to best outcomes for the management of these patients is not well established. Comparative analysis of HCT vs medical management has not been performed, and long-term clinical outcomes data are necessary to establish best therapeutic options.

Chronic Granulomatous Disease

Chronic granulomatous disease (CGD), an inherited disorder of neutrophil function, is caused by mutations in one of five subunits of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. This multicomplex enzyme is critical for phagocytic killing of intracellular pathogens by producing superoxide within the phagolysosomes. Both X-linked (gp91phox OMIM#306400) and autosomal recessive forms exist (p22^{phox} OMIM#233690; p47^{phox} OMIM#233700; p67^{phox} OMIM#233710; and p40^{phox} OMIM#601488). The X-linked form is the most frequent, generally presents early in life, presents a severe clinical phenotype, and patients have limited life expectancy. Severe and prolonged infections of the lungs, lymph nodes, and skin caused by pathogens such as *Aspergillus* spp., *Staphylococcus aureus*, *Burkholderia cepacia* complex, *Serratia* spp., and *Nocardia* spp. are frequently encountered at diagnosis. In the year 2000, a report by Winkelstein showed that the overall mortality for CGD was 21 %, and only 22 % of patients survived past their second decade of life [108]. Prophylactic antibiotics, use of interferon- γ , regular itraconazole use, improved antifungal therapies, and center experience have undoubtedly improved outcomes [109–111]. Mortality has decreased to 13 % [109], and survival has increased to 87 % by 20 years of age [110]. Despite these encouraging reports, morbidity and mortality remain high, and patients experience poor growth, chronic pulmonary, gastrointestinal, and urogenital infections that require prolonged and repeated courses of

antibiotic therapies leading to 55 % survival by age 30 [112, 113]. Inflammatory complications and autoimmunity also contribute to morbidity and mortality in these patients. Inflammatory bowel disease (IBD) is reported in 40 % of patients, and an estimated 10 % of patients may have some autoimmune manifestation other than IBD. In addition, quality of life measures are lower in patients treated with medical therapies as compared to those who had undergone HCT, and these were no different than healthy controls [114].

HCT is the only curative therapy for CGD today and has been performed since the mid-1980s [115, 116]. Sources of stem cells have included bone marrow, PBSC, and cords, the choice of which is center dependent. In addition, both non-ablative conditioning and ablative regimens have reported successful outcomes [112, 117]. In 2002, the European Bone Marrow Transplant Registry (EBMTR) group reported results of 27 transplants from 1985 to 2000 [118]. Twenty-three of 27 patients survived despite utilizing myeloablative conditioning regimens, and full donor chimerism was reported [118]. The selection of which patients would benefit from HCT is still debated. Yet those patients with very low NADPH superoxide production, increased alkaline phosphatase level, history of liver abscess, and features of portal hypertension along with inflammatory or autoimmune complications carry guarded prognosis and should be considered sooner rather than later, particularly if a matched sibling donor is available [118–120]. In 2009, the Newcastle group reported 90 % survival with a median follow-up of 61 months [121]. There is no doubt that the last decade has offered patients with CGD an improved quality of life and survival outcome; however, continued collaborative efforts are necessary to define best clinical long-term outcomes.

Other PID Syndromes Treated by HCT

X-linked lymphoproliferative disease (OMIM#308240), also called Duncan syndrome, is a rare PID affecting 1–2 boys: 1 million [122]. The defect lies in mutations in SH2D1A, the gene that encodes SLAM-associated protein [123]. These patients have a unique susceptibility to EBV after which they can develop fulminant fatal disease, with features of hemophagocytic lymphohistiocytosis (HLH), dysgammaglobulinemia, and lymphoma. Mortality is high, and the only curative treatment is HCT [124]. Both ablative and reduced intensity regimens have been proposed [38, 125–127]. A multicenter study of 91 patients from 32 centers worldwide compared outcomes of 43 patients who had been treated with HCT to 47 patients who had not been transplanted [37]. The overall survival for the transplantation group was 81 % (35/43) with a mean follow-up of 52 months. Twenty-eight percent of patients in this group were off IVIG (80 %), while 7 patients continued to receive IVIG therapy (20 %). Chimerism was reported as full in 92 % of cases, 8 % demonstrated mixed chimeric states. Importantly, all patients

who died in the transplant group had been diagnosed with HLH before or during the transplant, making it the most important factor influencing mortality. In contrast, those patients who had not been transplanted had an overall survival of 62 % (30/48). Of these, 21 patients were receiving IVIG (70 %) and 7 patients were off IVIG (23.3 %). While taken together, these data are encouraging; the treatment of a newly diagnosed child who is clinically asymptomatic is still debatable as therapies such as IVIG can be instituted promptly. If a matched sibling donor is identified, there is a general consensus amongst experts that, in both cases of either HLH presentation or a newly diagnosed asymptomatic child, should transplantation be offered. The decision to transplant older children or patients with HLH manifestation but without matched sibling donors should be carefully considered and performed in centers with experience in the transplantation of such patients.

Hemophagocytic lymphohistiocytosis (HLH) comprise a group of familial (FHLH type 1: OMIM#267700; FHLH type 2: OMIM#603553; FHLH Type 3: OMIM#608898; FHLH type 4: OMIM#603552; FHLH type 5: OMIM#613101) and non-inherited disorders characterized by tissue infiltration of lymphocytes and histiocytes associated with systemic uncontrolled inflammation. The well-characterized familial forms of the disease are due to defective genes involved in cytotoxic function of both natural killer (NK) cells and cytotoxic T lymphocytes (for review see [128]). The use of diagnostic criteria has provided guidance for differential diagnosis and a tool for treatment and outcome analysis [129]. If untreated, the familial forms are fatal, and secondary forms have an overall mortality of 50 % [130, 131]. A comprehensive review of results from the HLH-94 treatment protocol was published in 2011 [132]. This treatment protocol includes a combination of immunosuppressive and cytotoxic chemotherapy followed by HCT for patients with familial, recurrent, or persistent disease. A total of 227 patients were followed for $\geq$ than 5 years. One hundred twenty-four patients underwent HCT, the 5-year probability of survival was 66.8 %, while those with familial forms had a 5-year survival of 50 ± 13 %; none survived without HCT. There is no doubt that the institution of HLH-treatment protocols has indisputably improved outcomes, yet these remain guarded deserving quicker and better diagnostic indicators, and the rapid identification of familial forms may improve survivals.

Immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (OMIM#304790) is a severe systemic autoimmune disorder caused by mutations in Forkhead Box P3 [133]. These patients have a limited life expectancy and will present before the age of 1 year with severe enteropathy, type I diabetes, severe eczema, thyroiditis, infections, and autoimmune cytopenias [134, 135, 136]. Without HCT, these children do not survive past the first–second decade of life. Outcome data on large cohort studies are limited, but successful outcomes have been reported in small groups and

individual case reports of patients with both ablative and non-myeloablative conditioning [137, 136, 138, 139].

Summary

The past 45 years has seen the emergence of HCT as a therapeutic modality for patients born with inherited defects of immune function. Early recognition, availability of molecular diagnosis in clinical settings, gammaglobulin infusions, prophylactic antibiotics, and novel therapies has seen an improvement in the life expectancy for many patients with these disorders. However, definitive cures can only be achieved today by either HCT or gene therapy. Rapidly evolving recombinant technologies are forthcoming for some PID and may provide alternative therapeutic options in the future. The morbidity associated with HCT makes clinicians shy away from this therapy if pediatric patients are fairly well controlled. That said, as patients enter adulthood, a set of added morbidities, including lack of access to healthcare, come into play that certainly affect their quality of life, limit their life expectancy and the hope for a normal existence. Despite the rarity of many PIDs, these disorders have led the way toward innovative therapies and provide insights into mechanism of immune reconstitution that can be applicable to all HCT transplants. When studying rare diseases, multinational collaborative studies are imperative, and the last 15 years has seen the emergence of such collaborations for PID. Critical analysis of outcomes and prospective multicenter clinical trials are critical to further our understanding for best therapeutic approaches for patients with PID.

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