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Mini Review: Screening and Management of Late Effects in Patients with Severe Combined Immunodeficiency after Allogeneic Hematopoietic Cell Transplantation

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ABSTRACT

Severe combined immunodeficiency (SCID) is a group of the most severe of primary immunodeficiencies and is typically fatal in the first year of life without hematopoietic cell transplantation (HCT). Improved transplantation techniques and supportive care measures have resulted in improved survival following HCT. Furthermore, patients are being diagnosed earlier since the widespread implementation of SCID newborn screening in the United States and moving on to transplantation before 3.5 months of age. As such, most SCID patients are now expected to live well into adulthood following successful HCT. Many centers are using conditioning with alkylating agents, including busulfan and melphalan, pre-transplantation to achieve full T and B cell immune reconstitution; however, significant concerns remain regarding the attendant risks of using chemotherapeutic agents in early infancy. Several long-term follow-up studies have demonstrated high rates of non-immunologic late effects depending on the conditioning regimen employed and SCID genotype. The full risk of conditioning in this patient population remains incompletely characterized, and further research on post-HCT outcomes is needed. It is imperative that all providers caring for SCID survivors both in childhood and adulthood be aware of the risk of late effects. Guidelines for long-term follow-up were recently published, and the recommendations are briefly summarized here.

Introduction

Severe combined immunodeficiency (SCID) is a group of primary immune deficiencies characterized by profound T cell lymphopenia and/or dysfunction with varying degrees of B and NK cell impairment and is generally fatal in the first year of life unless immune reconstitution is achieved. The first successful hematopoietic cell transplantation (HCT) for SCID was performed in 1968, and allogeneic HCT remains the standard of care for SCID today. Outcomes are greatly improved with early transplantation in the first 3.5 months of life and particularly before onset of infection, with reported survival rates of 80% to 95% regardless of donor source or conditioning[1-8]. Newborn screening for SCID was first initiated in Wisconsin in 2008, and today, 93% of all newborns in the US receive SCID screening[9,10]. As such, infants are being diagnosed and treated with curative HCT earlier than historic reports. The use of conditioning before HCT for SCID remains controversial and varies by transplant center, donor type, clinical presentation, and SCID genotype. Preparative conditioning has been associated with

greater likelihood of myeloid engraftment, long-term T cell reconstitution, and freedom from immunoglobulin replacement[7,8,11-14]. However, the long-term consequences of using chemotherapeutic agents in early infancy remain incompletely understood.

The Second International Pediatric Blood and Marrow Transplant Consortium Consensus Conference on Late Effects after Pediatric Hematopoietic Cell Transplantation convened in May 2016 to discuss the issue of late toxicities and lack of clear guidelines for monitoring post-HCT. The current state of knowledge, priorities for future research, and recommendations for screening and management of late effects in patients with SCID after allogeneic HCT have been published[15,16]. We will summarize here the recommendations for screening and management put forth by the expert panel.

Immune Reconstitution

Robust and durable immune reconstitution is crucial for both acute and long-term protection against infection and autoimmunity and is associated with not only improved survival but also improved quality of life. Immune reconstitution following allogeneic HCT can vary significantly depending on SCID genotype, degree of HLA mismatch, graft source and manipulation before HCT, and amount of preparative conditioning employed. Immune monitoring should begin no later than 3 months post-HCT and continue lifelong in conjunction with a clinical immunologist and HCT transplantation specialist even if the patient is well and without signs of infection. Serial evaluation of lineage-specific chimerism and immune reconstitution may allow early detection of gradual declines in lymphocyte counts and/or function before clinical complications develop. Immune deterioration may require intervention with further cellular therapy such as stem cell boosts or second transplant.

T cell reconstitution is the primary objective of transplantation for all forms of SCID, and normal T cell function is generally achieved between 4 to 9 months after HCT[17-20]. B- SCID genotypes, active infection at time of HCT, and graft-versus-host disease (GVHD) are all associated with poor T cell recovery[3,7,8,17]. Evaluation of T cell reconstitution should include enumeration of T cell populations (i.e., CD3, CD4 and CD8 T cell counts), naïve (CD4+CD45RA+) T cells and/or recent thymic emigrants (CD4+/CD45RA+/CD31+), and T cell function via proliferation to mitogens and/or anti-CD3. T cell receptor excision circle (TREC) counts are an indicator of thymic output, and robust TREC counts have been associated with higher CD3 and naïve T cell counts, T cell proliferation to mitogen, and T cell receptor diversity in some studies[12,20]. The TREC count early after HCT has also been proposed as a biomarker for long-term T cell reconstitution[21]. T cell spectratyping is recommended to evaluate diversity of the T cell repertoire[20], where a skewed repertoire may be associated with a high risk of infection and autoimmunity. A restricted Vβ T-cell receptor repertoire was also recently shown to be associated with need for second transplant and death[8]. Measurement of lineage-specific engraftment is also imperative, as autologous T cell re-emergence in the setting of graft failure may be missed by standard T cell flow cytometry, particularly in those with hypomorphic SCID. Prophylaxis against Pneumocystis jirovecii should continue for at least 6 months or until CD4 cell count >200 cells/μL, normal T cell function is achieved (PHA >50% of the lower limit of normal for the laboratory), and chronic immunosuppression is discontinued[22]. Of note, many patients with chronic GVHD require long-term antimicrobial prophylaxis until they are off immune suppression for an extended period of time. Sufficient T cell reconstitution should also be demonstrated before administration of live vaccines (see below). Recent studies have demonstrated that T cell reconstitution and thymic output remain stable for the majority of patients[11,12,20,21]. Satisfactory T cell numbers, evidence of thymopoiesis via the presence of naïve T cells and/or detectable TRECs, and normal T cell proliferation to phytohemagglutinin within the first 1 to 2 years after HCT are all linked to durable T cell reconstitution[13,21].

B cell reconstitution occurs at a median of 1 to 2 years or more and is impacted by SCID genotype and use of conditioning. Overall, poor B cell reconstitution defined by continued need for IVIG replacement is common (15% to 58%) on long-term follow-up[11,13,23]. Patients with IL7Rα, CD3, and ADA SCID are more likely to recover B cell immunity, as host B cells may function normally with competent donor T-cell help[23]. Conversely, IL2RG and JAK3 SCID patients have intrinsically dysfunctional B cells and require donor B cell engraftment for normal B cell function post-HCT[23]. The use of either myeloablative or reduced-intensity conditioning, particularly busulfan-containing regimens, is associated with improved ability to achieve B cell engraftment and immunoglobulin independence in all forms of SCID. B cell lineage chimerism and CD20 and/or CD19 cell counts should be monitored serially as part of routine immune evaluation. Immunoglobulin levels (IgA, IgG, and IgM) and isohemagglutinin titers should also be followed as indices of normal B cell function. The presence of switched memory B cells (CD19+/CD27+/IgD-) to demonstrate normal B cell maturation may also be useful[23].

Normal or near-normal serum IgA and IgM levels and/or presence of IgM isohemagglutinins may be used as indicators for discontinuation of immunoglobulin replacement. Trials off immunoglobulin replacement should ideally be timed for spring and/or early summer to decrease the risk of contracting viral illnesses during the fall-winter viral season. After 3 months, immunizations with

inactivated vaccines may be initiated per the most up-to-date guidelines, with post-vaccination titers measured 4 to 6 weeks after immunization to ensure vaccines are inducing a protective response. After a positive vaccine response and adequate T cell immunity have been documented, live viral vaccines may be considered. Immunogloublin levels should continue to be monitored lifelong following discontinuation of immunoglobulin replacement, and vaccine titers should be monitored periodically, as titers may wane with time in post-transplant patients as compared to normal individuals[24]. In patients who remain on immunoglobulin replacement, IgG levels should be monitored periodically to ensure minimum IgG trough levels of 800 mg/dL for patients on intravenous therapy and 1000 mg/dL for patients on subcutaneous therapy[25].

Finally, NK cells have cytotoxic activity against viruses, malignant cells, and HLA-mismatched donor cells. There are few reports on long-term NK cell reconstitution, and the consequences of inadequate NK cell reconstitution remain incompletely described[26,27]. The current recommendation is to monitor NK cell counts (CD3-/CD56+ &/or CD16+) plus/minus NK cell function after HCT.

Nonimmune Organ System Late Effects

Long-term complications are common in SCID survivors, with increased risk of autoimmune disease, neurocognitive dysfunction, poor growth requiring nutritional supplementation, physical disability, and a myriad of other late effects involving essentially every organ system after HCT[27]. Myeloablative conditioning is expected to result in greater long-lasting toxicity compared to reduced-intensity conditioning, and busulfan in particular has been implicated in a number of late adverse effects, including dental anomalies, thyroid dysfunction, growth failure, and delayed puberty[28-31]. Conversely, many of these long-term complications are rare in SCID patients who do not receive preparative conditioning or post-transplant GVHD prophylaxis[32]. Effects of pre-transplantation conditioning on organ function, particularly the lungs, liver, central nervous system, and endocrine system should be monitored regularly (see Table 1).

The risk of long-term complications is also dependent

Table 1. Long-Term Monitoring and Treatment Recommendations by Organ System.

Organ System	Treatment Recommendations
Immune system	Immune monitoring starting no later than 3 mo after HCT and continuing lifelong in conjunction with an immunologist/transplantation specialist* PJP prophylaxis until 6 mo post-HCT or until evidence of T cell reconstitution (CD4 >200 and PHA >50% control) and off immunosuppressive therapy Immunization with inactivated vaccines starting 3 mo after discontinuation of immunoglobulin replacement with pre- and post-vaccination titers; post-vaccination titers should be obtained 4-6 weeks after immunization and followed periodically thereafter Live vaccines only after response to inactivated vaccines demonstrated No live vaccines for patients with cGVHD, on immunosuppression, poor T cell reconstitution, or continued need for immunoglobulin replacement Influenza vaccine for all HCT patients >6 mo of age Patients with poor B cell reconstitution should remain on immunoglobulin replacement without interruption and with close monitoring of IgG levels
Growth	At least annual monitoring of height and weight** Bone age and referral to Endocrinology for abnormal growth rate
Development	Developmental screening per age-appropriate pediatric guidelines with low threshold for referral for supportive interventions (PT, OT, Speech) Neurocognitive testing once able to participate and then every other year
Neurologic	Annual clinical evaluation of neurologic symptoms Hearing assessment for reticular dysgenesis and ADA patients and in any patient with a history of prolonged aminoglycoside exposure
Psychosocial	HR-QOL periodically in the first year after HCT and annually thereafter Regularly assess level of caregiver psychosocial adjustment/family function Encourage robust social support networks Referral to mental health professional as needed
Endocrine	Thyroid function tests annually; if TSH abnormal with normal T4 then reassess in 2 mo and refer to Endocrinology if indicated Adrenal axis testing at time of steroid cessation Evaluation for growth hormone deficiency in patients with Artemis or other RS-SCID and abnormal growth rate
Pulmonary	Counsel regarding tobacco avoidance Annual spirometry/PFT starting at 5 yr of age, more frequent for those with symptoms/signs of lung compromise Chest CT and/or MRI as clinically indicated; prefer MRI for RS-SCID Pulmonary consultation for >15% change on PFTs

Cardiovascular	Routine clinical assessment of cardiovascular risk factors Discuss heart healthy lifestyle (e.g., exercise, healthy weight, no smoking) Hypertension management per routine health guidelines
Liver	LFTs every 3-6 mo in the first year after HCT then annually at minimum Annual hepatocellular cancer screening if hepatitis B/C +, obese, and/or with low platelet count
Renal	BUN, serum CR, and urine protein at 6 and 12 mo after HCT then annually More frequent assessments for those on chronic calcineurin inhibitors Ultrasound/biopsy as clinically indicated Referral to Nephrology if hypertension or renal dysfunction
Reproductive	Endocrine gonadal assessment and Tanner staging at 12 mo after HCT Endocrine re-assessment if girls do no experience puberty by 12-13 yr, boys as needed LH, FSH, testosterone/estradiol, and inhibin B at 10 yr of age then annually Ask age-appropriate questions about sexual function Counsel about birth control in those of reproductive age
Musculoskeletal	Assessment of ROM and ability to stand from sitting at each clinic visit for patients on chronic steroids or with cGVHD DEXA 1 year after HCT and then yearly if Z score <1 Calcium/vitamin D supplementation Referral to Orthopedics if osteonecrosis on MRI
Dental	Annual dental exam starting at one yr of age or at 6 mo after HCT, whichever is later Every effort should be made to preserve primary teeth in Artemis SCID Counsel patients to avoid tobacco exposure, decrease sugary beverage intake, and avoid oral piercings
Dermatologic	Routine self-examination of the skin Counsel patients to limit sun exposure/use sunscreen Dermatology referral for treatment of warts, particularly in IL2RG, JAK3, or IL7Rα SCID genotypes
Ocular	Clinical exam starting at 24 mo post-HCT and annually thereafter
Secondary malignancy	Counsel regarding risks of secondary malignancy Lifestyle counseling (e.g., tobacco exposure, sunscreen use) Encourage self-examination General population recommendations for cancer screening
Genetic	Molecular diagnosis should be sought for all patients Genetic counseling for family members and SCID patients who have undergone HCT and are approaching childbearing age

PJP, Pneumocystis jirovecii; PHA, phytohemagluttinin; cGVHD, chronic GVHD; PT, physical therapy; OT, occupational therapy; HR-QOL, health-related quality of life; TSH, thyroid-stimulating hormone; PFT, pulmonary function test; CT, computed tomography scan; MRI, magnetic resonance imaging; LFT, liver function test; BUN, blood urea nitrogen; Cr, creatinine LH, luteinizing hormone; FSH, follicle stimulating hormone; ROM, range of motion; DEXA, dual-energy X-ray absorptiometry

* See Heimall et al.[16] for most recent guidelines with specific immunologic studies and intervals of testing.

** Unless otherwise indicated, all monitoring should be formed at the indicated frequency lifelong.

on SCID genotype, with high rates of late effects reported in ADA and radiosensitive SCID (RS-SCID). Patients with RS-SCID frequently have abnormalities outside the immune system such as microcephaly and neurocognitive impairment. Furthermore, patients with DNA repair defects have increased sensitivity to ionizing radiation and alkylator-based conditioning[33]. Artemis SCID in particular is associated with poor transplant outcomes. Late effects are seen in 70% of Artemis patients with high rates of growth failure (particularly in those who receive alkylator-based conditioning), severe or recurrent infections, cGVHD/autoimmunity, need for nutritional support, and death occurring greater than 2 years post-HSCT[30]. Effects uniquely observed in Artemis patients include dental anomalies, growth hormone deficiency, central hypothyroidism, type 1 diabetes mellitus, renal tubulopathy, exocrine pancreatic insufficiency, and pulmonary fibrosis[34].

ADA deficiency is also a multisystem disease with high rates of neurocognitive impairment, attention-deficit/hyperactivity disorder, and other learning challenges both before and after HCT[35,36]. Hearing impairment is also common in ADA SCID[35,36].

Genetic Counseling

A definitive molecular diagnosis should be sought for every SCID patient. Identification of the gene defect may influence the decision whether or not to use preparative conditioning and the regimen ultimately employed. This is particularly important for RS-SCID before initiation of alkylator conditioning. Rapid identification of ADA deficiency allows prompt initiation of enzyme replacement therapy and consideration for gene therapy[34-36]. Gene therapy may also be offered as a treatment option for X-linked SCID[37-38]. Finally, having a molecular diagnosis allows for risk stratification with regard to late effects following transplantation. In patients who have already

undergone transplantation, the use of a skin biopsy or other nonblood tissue (e.g., hair follicle) may be used for genetic testing. Genetic counseling should also be offered to family members, especially as it relates to prenatal planning.

Research Priorities And Future Directions

There are few large studies reporting on late effects following transplantation for SCID[7,11,13,33]. Prospective studies are needed to investigate long-term survival and quality of life, immune reconstitution, need for stem cell boost or second transplantation, and rates of GVHD by SCID genotype and phenotype, donor source, graft manipulation, and conditioning regimen. Early and late immunologic biomarkers to predict immediate and long-term immune reconstitution need to be identified. The effects of acute and chronic GVHD and immunosuppressive medications on immune reconstitution are also incompletely understood. Additionally, there is no consensus on the use of conditioning for SCID, and the optimal conditioning regimen by SCID genotype needs to be established. Further efforts must also be undertaken to decrease the toxicity associated with the current conditioning regimens. The lowest dose of busulfan and other marrow niche-opening agents necessary to achieve durable engraftment while minimizing side effects has yet to be defined for SCID patients. The development and use of alternative agents should be encouraged and will hopefully lead to decreased long-term morbidity and mortality. Treosulfan is a structural analogue to busulfan approved for use in Europe and is associated with improved short-term survival when compared to busulfan[42-43]. However, how treosulfan compares to busulfan in the long term remains to be seen. Non-chemotherapeutic conditioning agents such as the conjugate antibody targeting C-kit (CD117), which has shown promise in mice and is currently in clinical trials[44-46], may allow for effective conditioning without the cytotoxic and genotoxic effects of chemotherapy. Finally, gene therapy trials are open for X-linked and ADA SCID, and gene therapy for ADA SCID has been approved for commercial use in Europe. Gene therapy minimizes the need for alkylating agents and may result in fewer late effects, although long-term follow-up is lacking.

Conclusions

Long-term survival is expected for most patients with SCID following successful HCT. All providers who care for SCID patients after HCT should be aware of the risk for delayed immune deterioration and late effects in other organ systems, particularly in those patients who receive pre-transplantation conditioning. The recently published guidelines for long-term follow-up were formulated to facilitate optimal care for SCID patients treated with allogeneic HCT both through time and across specialties. However, further investigation into late effects associated with functional status prior to transplant, genotype, and pre-transplant conditioning is needed. The collaborative efforts of the North American centers participating in the Primary Immune Deficiency Treatment Consortium's research studies focused on SCID outcomes represent a valuable opportunity to collect and report these data.

Conflict-of-interest disclosure

Danielle E. Arnold and Jennifer Heimall declare no competing financial interests.

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