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The Second Pediatric Blood and Marrow Transplant Consortium International Consensus Conference on Late Effects after Pediatric Hematopoietic Cell Transplantation: Defining the Unique Late Effects of Children Undergoing Hematopoietic Cell Transplantation for Immune Deficiencies, Inherited Marrow Failure Disorders, and Hemoglobinopathies

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A B S T R A C T

An international consensus conference sponsored by the Pediatric Blood and Marrow Transplant consortium entitled "Late Effects Screening and Recommendations Following Allogeneic Hematopoietic Cell Transplant for Immune Deficiency and Nonmalignant Hematologic Disease" was held in Minneapolis, Minnesota on May 10, 2016 and May 11, 2016. The purpose of the conference was to address the unmet need for greater understanding of and the screening for long-term complications in the growing population of survivors of transplantation for nonmalignant disorders. The conference focused on transplantation for hemoglobinopathy, immune deficiency, and inherited bone marrow syndromes. A multidisciplinary group of experts in the disease areas and transplantation late effects presented the current state of understanding of how the underlying disease, pretransplantation therapies, and transplantation-related factors uniquely interact to influence the development of late toxicities. Recommendations were put forth by the group for the late effects screening of survivors of transplantation for these nonmalignant disorders. The findings and recommendations that came from this conference will be presented in a series of 6 additional manuscripts in the upcoming months. In this manuscript, we explore the need for screening practices specific to the survivors of transplantation for nonmalignant diseases and the methodologic challenges associated with the study of these patients.

BACKGROUND

Improvement in survival and a growing list of indications have led to an expanding population of survivors of allogeneic hematopoietic cell transplantation (HCT) in childhood [1-3]. A report from the Center for International Blood and Marrow Transplant Research (CIBMTR) estimates that

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there will be 242,000 survivors of transplantation by 2020 and 502,000 by 2030, representing a 2.5-fold and 5-fold increase from 2009, respectively [1]. It is predicted that in 2030, 14% of survivors will have been younger than 18 years of age at transplantation.

In more recent years, there has been a steady increase in the number of children who have undergone transplantation for nonmalignant diseases [4]. Between 2009 and 2013, 3151 HCTs were performed in pediatric patients with immune system disorders, histiocytic diseases, inherited abnormalities of erythrocyte differentiation or function, inherited disorders of metabolism, inherited platelet abnormalities, inherited bone marrow failure syndromes (IBMFS), and aplastic anemia [5]. Nonmalignant conditions accounted for 26.5% of the 11,875 transplantations performed in patients younger than 20 years of age, representing a growing population of pediatric transplantation survivors [5].

Transplantation during childhood years can predispose children to late toxicities and, consequently, increased morbidity and mortality compared with age and sex matched counterparts. Survivors of pediatric HCT for hematological malignancies have a much higher burden, both in terms of number and severity, of late effects as compared to childhood cancer survivors treated with chemotherapy only. The cumulative incidence of chronic health conditions after HCT with a median follow-up of 5 to 15 years varies from 30% to 60%, with increasing risk over time [6-8]. Risk factors for late effects in HCT survivors include younger age at HCT, the use of total body irradiation, and chronic graft-versus-host disease (GVHD) [7-15]. Additionally, the Bone Marrow Transplant Survivor Study found an almost 10-fold increased risk of nonrelapse late mortality after HCT compared with the general population, related to chronic GVHD, new malignancies, cardiopulmonary late effects, and other chronic health conditions [16].

Despite the increasing numbers of survivors of HCT for nonmalignant disorders, our knowledge of late effects after childhood transplantation comes primarily from the study of HCT for acute leukemia. With improving survival of childhood cancer patients, focus has shifted from improving survival to improving survival with the best quality of life. This has led to a wealth of studies on chronic health conditions in childhood cancer survivors and on treatment modalities that increase the risk for specific late effects, eg, radiotherapy and secondary malignancy. However, fewer reports detail long-term follow-up after HCT for nonmalignant diseases, in part because of the rarity of these conditions and the relatively recent evolution of HCT as a standard treatment option in disorders such as thalassemia and sickle cell disease, where the risk of dying in childhood from these disorders is very low and effective supportive care practices are in place. One recent single-institution study described late effects in 102 patients surviving for a minimum of 5 years after cord blood HCT. Busulfan was the primary conditioning agent and no total body irradiation was given. HCT was for nonmalignant indications in 82.4% of patients. Significant late effects identified included dental problems, short stature, cognitive deficits, pulmonary dysfunction, and abnormal pubertal development. At least 1 late effect was present in 98% of all patients [17].

Nonmalignant disorders treated by HCT including IBMFS, hemoglobinopathies, and immune deficiencies adversely affect target organ function, cause cognitive impairment, and shorten survival. Single-center and a smaller number of consortia reports have shown that long-term complications are common in survivors of transplantation for IBMFS, hemoglobinopathies, and immune deficiencies, including infertility, endocrine issues, immunologic function, and sequelae of chronic GVHD [18-26]. The pretransplantation therapies and potential comorbidities of children with these disorders are unique and not readily interchangeable with comparisons with malignant diseases, which typically require chemotherapy to induce remission before transplantation. Therefore, knowledge gained from the study of late effects in leukemia does not necessarily apply to patients who undergo transplantation for nonmalignant disorders. Efforts aimed at identifying how features of nonmalignant disorders interact with the HCT process to increase the risk of long-term effects are vital in planning strategies to screen, diagnose, and treat or prevent these complications.

Existing Consensus Guidelines

In 2011 the Pediatric Blood and Marrow Transplant Consortium, National Cancer Institute, and National Heart, Lung and Blood Institute convened the First International Consensus Conference on Late Effects after Pediatric Hematopoietic Cell Transplantation in Bethesda, Maryland. One of the 7 manuscripts resulting from the conference highlighted the need for pediatric-specific post-transplantation late effects screening guidelines [27]. In that manuscript and others from the conference, the authors presented expert panel recommendations to screen for late effects after HCT in children [27-29]. In addition, they provided critical review of the existing recommendations and applicability to survivors of childhood HCT. These recommendations came from multiple consortia including the Children's Oncology Group (COG), CIBMTR/American Society for Blood and Marrow Transplantation/Asia-Pacific Blood and Marrow Transplantation Group/Bone Marrow Transplant Society of Australia and New Zealand/East Mediterranean Blood and Marrow Transplantation Group/Sociedad Brasileira de Transplante de Medula Ossea, UK Children's Cancer and Leukaemia Group Late-Effects Group Therapy-Based Long-Term Follow-Up Practice Statement, and PanCare Childhood and Adolescent Cancer Survivor Care and Follow-up Studies [27]. The guidelines from these groups differ in content, organization, and emphasis placed on survivors of pediatric HCT. Table 1 outlines the recommendations for screening of organ systems that are most applicable in survivors after HCT for nonmalignant diseases. A common weakness of the pediatric-specific recommendations is the lack of focus on organ function and late complications that are specific to nonmalignant disorders, a consequence of the fact that these guidelines have inevitably focused much more on malignant transplantations because of greater numbers and more knowledge.There are few consensus recommendations for late effects screening that take into account the features unique to nonmalignant disorders. An exception is the most recent COG HCT-specific surveillance recommendations [32]. The COG provides evidence-based, pediatric-specific recommendations organized by therapeutic exposure (http://www.survivorshipguidelines.org/pdf/LTFUGuidelines_40.pdf) with a separate section focused on post-HCT follow-up. These recommendations are presented in an organ system–based approach [32]. Of note, the pretransplantation exposures considered in the COG recommendations focus on chemotherapy and radiation. They do not address common pretransplantation exposures in nonmalignant patients, such as hydroxyurea in patients with sickle cell anemia, chronic red blood cell transfusion and chelation agents in IBMFS and hemoglobinopathies, previous infections in immune

Table 1
Select Current Recommendations

Late effect/ Organ/ System	COG	Combined HCT Consortia [30]	PBMTC Consensus Conference [27,31]

Immune reconstitution/ immunologic	• Consideration for antibiotic prophylaxis against encapsulated organisms for the duration of immunosuppressive therapy and broad-spectrum parenteral antibiotics for fevers ≥ 101°F (38.3°C) in patients with active cGVHD
	• Annual evaluation for chronic conjunctivitis, sinopulmonary infection, or recurrent, unusual, or severe infections in patients with cGVHD
	• Screening for HIV and HCV if exposed to blood products before universal screening
	• Vaccinations according to national and professional society guidelines
		• Immunizations after HCT according to published guidelines
		• Administration of antibiotics for endocarditis prophylaxis according to AHA guidelines
		• Patients with cGVHD:
		  • Antimicrobial prophylaxis targeting encapsulated organisms and PCP for the duration of immunosuppressive therapy
		  • Screening for CMV reactivation should be based on risk factors
			• Monitoring T cell reconstitution with lymphocyte subset analysis, high content immunophenotyping, and evaluation of T cell proliferative capacity to mitogens
			• High content B cell immunophenotyping beginning 6 months after HCT
			• Neoantigen challenge for patients with poor or incomplete immune reconstitution based on immunophenotyping

Iron overload	• Assessment of serum ferritin 1 year after transplantation with repeat testing or hepatology consult as clinically indicated; consider further evaluation of iron burden and treatment of any iron overload with phlebotomy or chelation therapy	• LFTs every 3-6 months in the first year, then individualized, but at least yearly thereafter • Serum ferritin at 1 year after HCT in patients who received RBC transfusions; consider liver biopsy or imaging study for abnormal results based on magnitude of elevation and clinical context; subsequent monitoring is suggested for patients with elevated LFTs, continued RBC transfusions, or presence of HCV infections	• Annual serum ferritin, consider T2 MRI if elevated • Management: phlebotomy or chelation
Neurocognitive	• Yearly screening for educational/ vocational progress; formal neuropsychological evaluation at 1 year and periodically thereafter among survivors with concerns • Referral to a school liaison or appropriately resourced medical center for survivors with neurocognitive deficits; consideration for psychotropic medication and/evidence-based rehabilitation training	• Clinical evaluation for symptoms and signs of neurological dysfunction at 1 year and yearly thereafter; diagnostic testing for those with symptoms or signs • Annual assessment for cognitive developmental milestones (pediatric-specific recommendation)	
Subsequent cancer risk	• All survivors should be counseled with regard to lifestyle factors that influence future cancer risk; general recommendation for annual history and physical exam and detailed recommendations for specific solid tumors provided	• Counsel patients about risks of secondary malignancies annually and encourage them to perform self-exam (eg, skin, testicles/genitalia) • Counsel patients to avoid high-risk behaviors • Follow general population recommendations for cancer screening • Patients with cGVHD: clinical and dental evaluation with particular attention toward oral and pharyngeal cancer • TBI and chest irradiation recipients: screening mammography in women starting at age 25 or 8 years after radiation exposure, whichever occurs later (no later than 40 years)	No formal recommendations
Pulmonary	• Annual assessment for signs and symptoms of pulmonary dysfunction and PFT (1 year after HCT or when age appropriate, whichever is later) in patients who received bleomycin, busulfan, nitrosourea, and chest radiation or who have a history of cGVHD • Counsel regarding tobacco avoidance/smoking cessation	• Clinical evaluation at 6 months and 1 year after HCT and at least yearly thereafter • Assessment of tobacco use and counseling against smoking • PFT and focused radiological assessment for allogeneic HCT recipients with symptoms or signs of lung compromise	• PFT for allogeneic recipients twice per year for 2 years, with consideration for more frequent screening in recipients of mismatched or URD grafts, or patients with acute or chronic GVHD; after 2 years, consider yearly follow-up PFT based on symptoms and past measurements • With a 15% decrease in PFT values or new pulmonary infiltrate, evaluate for infection/GVHD. Refer to pulmonologist for disease-specific care as needed

(*Continued on next page*)

Table 1 (*continued*)

Late effect/ Organ/ System	COG	Combined HCT Consortia [30]	PBMTC Consensus Conference [27,31]
Reproductive/ gonadal	• Annual assessment of pubertal development, sexual and reproductive function in patients exposed to TBI, cranial radiation, alkylating or similar crosslinking agents • Morning testosterone assessment beginning no later than 14 years and as clinically indicated in at risk males • LH, FSH, and estradiol levels beginning no later than 13 years of age in at risk females • Evaluation for vaginal fibrosis and stenosis in females who received radiation to the reproductive syndrome or cGVHD • Referral to endocrinology, gynecology, or urology for patients with abnormal pubertal timing or gonadal dysfunction	• Clinical and endocrinologic gonadal assessment for prepubertal boys and girls within 1 year of transplantation, with further follow-up as determined in consultation with a pediatric endocrinologist (pediatric-specific recommendation) • Clinical and endocrinologic gonadal assessment for post-pubertal women at 1-year, subsequent follow-up based on menopausal status • Gonadal function in men, including FSH, LH, and testosterone, should be assessed as warranted by symptoms • Consider referral to appropriate specialists for patients who are contemplating a pregnancy or who are having difficulty conceiving • Counsel sexually active patients in the reproductive age group about birth control	• Women: • Monitor for ovarian failure (FSH, assess cycling) • Anti-Müllerian hormone may assess ovarian reserve •Treat ovarian failure with hormone replacement therapy • Men: • Semen analysis • If oligospermia noted, may offer intracytoplasmic sperm injection
Renal	• Annual hypertension screening • Annual urinalyses with measurement of BUN, creatinine, and electrolytes at 1 year after transplantation, and then as clinically indicated	• Blood pressure assessment at every clinic visit, with aggressive hypertension management • Assess renal function with BUN, creatinine, and urine protein at 6 months, 1 year, and at least yearly thereafter • Consider further workup (kidney biopsy or renal ultrasound) of renal dysfunction as clinically indicated	• Urine albumin: creatinine ratio at day 80, then annually; if ratio >/30 and <300 mg/g, then confirm with 2 or more tests in 3-6 months and monitor every 3-6 months; if ratio is >300 mg/g monitor every 3-6 months • Treat with angiotensin-converting enzyme inhibitor or angiotensin blocker if albumin :creatinine ratio is >300 mg/g on 1 occasion or persistent ratio > 30g/kg on 3 occasions in a 6 month period and hypertensive
Growth	• Height, weight, BMI, and Tanner staging every 6 months until skeletal maturity reached • Thyroid function, bone age evaluation and referral to endocrinology if the growth rate is abnormal • Referral to endocrinology if received ≥ 30 Gy of cranial radiation	• Monitor growth velocity in children annually; assessment of thyroid, and growth hormone function if clinically indicated	• Accurate measurement of growth yearly through full growth • Bone age as needed • Bone age and referral to an endocrine specialist for a patient not growing appropriately
Psychosocial	• Annual psychosocial assessment with attention to social withdrawal, educational/ vocational progress, chronic fatigue, pain, risk behaviors, and mental health concerns • All survivors should be asked about their access to insurance and health care	• Clinical assessment throughout recovery period, at 6 months, 1 year, and annually thereafter, with mental health professional counseling recommended for those with recognized deficits • Encouragement of robust support networks • Regularly assess level of spousal/caregiver psychological adjustment and family functioning	No formal recommendations

PBMTC indicates Pediatric Blood and Marrow Transplant Consortium; cGVHD, chronic graft-versus-host disease; HIV indicates human immunodeficiency virus; HCV, hepatitis C virus; AHA, American Heart Association; PCP, pneumocystis pneumonia; CMV, cytomegalovirus; LFT, liver function tests; MRI, magnetic resonance imaging; TBI, total body irradiation; PFT, pulmonary function testing; URD, unrelated donor; LH, lutein hormone; FSH, follicle-stimulating hormone; BUN, blood urea nitrogen; BMI, body mass index.

deficiency patients, and androgen therapy in patients with IBMFS syndromes. We know of no consensus long-term screening guidelines that address the pathophysiology of the nonmalignant conditions or the pretransplantation therapies given to these patients. Also important is the need to account for individual disease-related manifestations in the development of these screening guidelines.

To address the unique and critical needs of children undergoing HCT for nonmalignant disorders, we convened a Second International Pediatric Blood and Marrow Transplant Consortium Consensus Conference on Late Effects after Pediatric Hematopoietic Cell Transplantation in Minneapolis in May, 2016. In a series of 6 manuscripts from this conference, we will provide recommendations for long-term follow-up and late effects screening of survivors of HCT for severe immune deficiencies, specific marrow failure syndromes (Fanconi anemia [FA], Diamond-Blackfan anemia, and dyskeratosis congenita) and common hemoglobinopathies (sickle cell disease and thalassemia). In addition, we will outline current knowledge of late effects in each disease and then specify scientific priorities for future late effects research. The greatest challenges in performing HCT in these

patients are problems inherent in the underlying disease process, with a natural history of progression that may or may not be cured and in some cases can be potentially exacerbated by HCT. The recommendations will be unique to each of the 3 groups discussed at the conference: IBMFS, hemoglobinopathies, and immune deficiencies. Our recommendations will outline an ideal for follow-up along with guidelines for critical minimal follow-up in order to be useful for populations with variable resources.

Methodological Challenges

When considering how best to further study the ways in which HCT may interact with underlying disease, there are a number of methodological challenges.

The first challenge is to define the appropriate cohorts of patients with these rare conditions to address specific study questions and to ensure long-term access to them for follow-up studies. This applies to each of the retrospective, cross-sectional, and prospective studies needed to build a more comprehensive understanding of late effects after HCT in children with these disorders. With increasing success of HCT in nonmalignant conditions, there are new cohorts surviving and teaching us more each day, while at the same time, there is often a long latency for many of the long-term conditions of interest. Advances will be strengthened if investigators develop consortia and combine databases that link multiple pediatric and adult institutions in global collaborations. Within these structures, there will need to be development of standardized data collection tools that can be complete and current but that will also account for time trends with long length of follow-up. Current infrastructure to address some of these questions resides within the CIBMTR and the Pediatric Diseases Working Party of the European Society for Blood and Marrow Transplantation, but because of the rare nature and the complexity of the disorders, disease-specific infrastructures are attempting to address these questions as well (ie, the Primary Immune Deficiency Treatment Consortium, disease-specific registries [Diamond-Blackfan anemia and Shwachman-Diamond registries], etc.).

Another major challenge in the study of late effects in nonmalignant conditions lies in establishing an appropriate comparison group(s). Should patients with nonmalignant disorders who undergo HCT be compared with patients with the same condition who do not undergo HCT, patients with other nonmalignant disease conditions who also undergo HCT, or to patients who undergo HCT for malignant conditions? Comparisons with the general population are potentially problematic as the underlying disease may have other characteristics that lead to chronic health conditions unrelated to the HCT process. Examples of different comparisons include work done with FA patients where those with and without HCT have been compared [33] and FA patients who have been compared with other IBMFS patients, as well as with population norms through the Surveillance, Epidemiology, and End Results Program [34]. However, those patients transplanted are inherently different given that HCT is typically only offered to IBMFS patients who have had malignant transformation or who have severe bone marrow failure. Similar issues exist for patients with sickle cell anemia, who are eligible for HCT if they have a more severe phenotype with sickle-related complications. There is a challenge to clarify if chronic health conditions and late effects are caused by the underlying disease, the HCT procedure and related complications, and/or the interaction of these. Choosing the right comparison groups can help disentangle these elements and better define risk factors for HCT-specific late effects in these patients.

If appropriate cohort and comparators can be established, there are still challenging statistical questions that can arise. For example, time is an important factor, but time can be expressed as an interval after diagnosis, interval after intervention such as HCT, or attained age. Each study design will need to determine the most appropriate time scale for analyses. Additionally, it is important to define the analysis methods that will minimize bias. Competing risks, where patients may experience an event that changes risk of another event, will be best in some settings. In other settings, actuarial analysis will be best, where a patient is censored at an event and those censored are representative of those who remain on study and would experience the event if followed long enough.

Ultimately, a critical aspect of these studies is to provide data allowing for shared decision-making, where clinicians can advise families on potential risks and benefits of transplantation. An example of this kind of thought process is earlier or pre-emptive HCT in FA [35,36]. The authors of these studies suggest the methods applied could be used to model survival for other disorders with limited empirical data and a pressing need for clinical guidelines.

State of the Science and Future Directions

The International Consensus Conference in Minneapolis brought together international experts in hematology, immunology, blood and marrow transplantation, and survivorship from North America, South America, and Europe. The first half-day session focused on IBMFS; specifically FA, dyskeratosis congenita, and Diamond-Blackfan anemia. The second half-day session focused on hemoglobinopathies; specifically thalassemia and sickle cell anemia. The third half-day session focused on primary immune deficiency, with an emphasis on severe combined immunodeficiency. The current manuscript provides basic general recommendations for long-term follow-up from which more individualized recommendations can be created. Based on an exhaustive literature review, a series of premeeting conference calls, and summary discussions at the conference, each of the 3 working committees has prepared 2 manuscripts—the first discussing knowledge to date and identified gaps and the second outlining disease-specific long-term follow-up recommendations. These publications will appear sequentially in *Biology of Blood and Marrow Transplantation* for the next several months. It is our hope that this work will inspire and promote research in this area and funding agencies to consider the importance of the priority studies outlined. We also hope to establish the key importance of specialized long-term follow-up and enjoin insurers to provide coverage for appropriate screening visits in these high-risk children as they progress through their lives.

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