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Current Results and Future Research Priorities in Late Effects after Hematopoietic Stem Cell Transplantation for Children with Sickle Cell Disease and Thalassemia: A Consensus Statement from the Second Pediatric Blood and Marrow Transplant Consortium International Conference on Late Effects after Pediatric Hematopoietic Stem Cell Transplantation

Shalini Shenoy [1,*], Emanuele Angelucci [2,3], Staci D. Arnold [4], K. Scott Baker [5], Monica Bhatia [6], Dorine Bresters [7], Andrew C. Dietz [8], Josu De La Fuente [9], Christine Duncan [10], Javid Gaziev [11], Allison A. King [1,12], Michael A. Pulsipher [8], Angela R. Smith [13], Mark C. Walters [14]

[1] *Department of Pediatrics, Washington University School of Medicine and St. Louis Children's Hospital, St. Louis, Missouri*
[2] *Department of Hematology, Ospedale Oncologico di Riferimento Regionale "Armando Businco", Cagliari, Italy*
[3] *Department of Hematology, IRCCS Azienda Ospedaliera Universitaria San Martino—IST Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy*
[4] *Department of Pediatrics, Emory University School of Medicine, Atlanta, Georgia*
[5] *Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington*
[6] *Department of Pediatrics, Columbia University Medical Center, New York, New York*
[7] *Willem-Alexander Children's Hospital, LUMC, Leiden, The Netherlands*
[8] *Division of Hematology, Oncology, and BMT, Children's Hospital Los Angeles, Los Angeles, California*
[9] *Department of Pediatrics, Imperial College Healthcare, London, United Kingdom*
[10] *Department of Pediatrics, Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, Massachusetts*
[11] *International Center for Transplantation in Thalassemia and Sickle Cell Anemia, Mediterranean Institute of Hematology, Policlinico Tor Vergata, Rome, Italy*
[12] *Program in Occupational Therapy, Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, St. Louis, Missouri*
[13] *Department of Pediatrics, University of Minnesota Children's Hospital, Minneapolis, Minnesota*
[14] *Department of Pediatrics, UCSF Benioff Children's Hospital, Oakland, California*

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A B S T R A C T

Sustained donor engraftment after allogeneic hematopoietic cell transplantation (HCT) converts to healthy donor hemoglobin synthesis and halts disease symptoms in patients with sickle cell disease and thalassemia major. A disease-free survival probability that exceeds 90% has been reported when HCT using an HLA-matched sibling donor is performed in young patients with low-risk disease or treatment-related risk factors. Alternate donor HCT and HCT in adults is performed infrequently because of a higher risk profile. Transplant-specific risks include conditioning regimen-related toxicity, graft-versus-host disease, graft rejection with marrow aplasia or disease recurrence, and infections associated with immunosuppression and delayed immune reconstitution. The magnitude of risk depends on patient age, clinical status of the underlying disease (eg, organ injury from vasculopathy and iron overload), donor source, and intensity of the conditioning regimen. These risks are commonly monitored and reported in the short term. Documenting very late outcomes is important, but these data are rarely reported because of challenges imposed by patient drop-out and insufficient resources. This report summarizes long-term follow-up results after HCT for hemoglobin disorders, identifies gaps in knowledge, and discusses opportunities for future investigations. This consensus summary will be followed by a second article detailing comprehensive long-term follow-up recommendations to aid in maintaining health in these individuals and identifying late complication risks that could facilitate interventions to improve outcomes.

INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) for genetic hemoglobin disorders such as sickle cell disease (SCD) and thalassemia has curative potential. This is evidenced by

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* Correspondence and reprint requests: Shalini Shenoy, MD, Department of Pediatrics, Washington University School of Medicine, Box 8116, 660 S Euclid Avenue, St. Louis, MO 63110.
E-mail address: shenoy@wustl.edu (S. Shenoy).

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a cessation of the acute signs and symptoms of the underlying disorder after stable engraftment of donor cells. The assumption that a successful transplant will extend lifespan and stop disease-related complications is central to decision-making about HCT. The goal of this summary article is to define and address current gaps in knowledge to create a roadmap of clinical investigation in this field. In a subsequent article we will suggest comprehensive monitoring guidelines to inform clinical decision-making that might facilitate health maintenance after HCT for these disorders. These efforts follow an international working group that convened at the Second Pediatric Blood and Marrow Transplant International Consensus Conference on Late Effects after HCT in Minneapolis, Minnesota, USA in May 2016.

CURRENT RESULTS OF HCT FOR HEMOGLOBIN DISORDERS

Thalassemia

More than 4000 individuals with thalassemia major have received HCT, with most reports focused on results in children and young adults. Risk category assignments have been developed in several transplant series, determined by recipient age, liver size, liver histology, and whether or not there is compliance with iron chelation therapy [1-4]. Outcomes are best in young patients who lack risk factors and receive HLA-identical sibling HCT. Among 1493 consecutive transplant registry cases reported to the European Group for Blood and Marrow Transplantation hemoglobinopathy database, the 2-year overall survival (OS) and event-free survival (EFS) rates were 88% and 81%, respectively. However, among children < 2 years of age who received an HLA-identical sibling allograft, the OS and EFS rates at 2 years were 95% and 93%, respectively. Conversely, recipients > 18 years of age had OS and EFS rates of of 80% and 76%, respectively [5]. Results after HLA-identical sibling umbilical cord blood transplantation are very similar, with lower rates of acute and chronic graft-versus-host disease (GVHD) after umbilical cord blood compared with bone marrow transplantation [6]. Thus, most clinicians agree that HCT for thalassemia should be considered in young patients with favorable risk profiles who have an HLA-identical sibling donor [7].

Sickle Cell Disease

Like thalassemia, HCT for SCD is curative in most individuals who receive this treatment, but, unlike thalassemia, HCT is a treatment option that very few families and patients pursue in the United States [8-11]. The principal reason for the lower number of SCD transplants is the lack of a suitable donor. However, concerns about the toxicity of HCT also limit its broader application. Among those who have an HLA-identical sibling donor, results are excellent, and a compilation of several series showed OS and EFS rates of 95% and 92%, respectively [12-14]. In addition, reduced-intensity and nonmyeloablative regimens have been explored as a method to reduce long-term side effects and mitigate the impact of vaso-occlusion–induced organ damage on transplant-related toxicity, particularly in adolescent and adult recipients [15,16]. Results observed after a melphalan/alemtuzumab-based reduced-intensity conditioning (RIC) regimen applied in children and a nonmyeloblative alemtuzumab-based regimen in adults were similar to results after myeloablative conditioning, and EFS rates of 90.7% and 87%, respectively, were observed. The largest registry series reported to date included 1000 recipients with a median age of 9 years treated between 1986 and 2013 [17]. EFS was lower with increasing age at transplant (hazard ratio, 1.08; $P = .002$) and higher if treated after 2006 (hazard ratio, .94, $P = .02$). Of interest, 7 of 70 deaths occurred 5 years or longer after HCT, which highlights the need for long-term follow-up.

Alternate Donor Transplantation for Hemoglobin Disorders

Early reports of unrelated donor HCT for thalassemia were characterized by high rates of graft rejection and transplant-related mortality, in part related to the older age of recipients, advanced disease, and unrefined donor selection methods [5]. T cell–depleted haploidentical transplants for thalassemia had a disease-free survival (DFS) rate of 70% [18]. Registry results after unrelated umbilical cord blood transplantation for thalassemia and SCD were poor, with a DFS rate of 21% in thalassemia and 50% in SCD recipients [19]. Recent modifications in donor selection and transplant conditioning have improved thalassemia-free survival rates during early follow-up. The addition of hydroxyurea/azathioprine before conditioning in mismatched and matched related HCT (94% and 82%, respectively); dexamethasone/fludarabine in advance of conditioning in haploidentical donor HCT (94%); fludarabine, thiotepa, and treosulfan in unrelated donor HCT (82%); and a RIC combination of hydroxyurea, alemtuzumab, fludarabine, melphalan, and thiotepa (79% and 80% after unrelated donor cord and bone marrow, respectively) together have improved outcomes [20-24]. Long-term follow-up after these varied HCT modalities is essential to judge the merits of alternate donor HCT.

Alternate donor HCT in SCD is less well developed compared with thalassemia. The largest pediatric study in severe SCD showed 1- and 2-year EFS rates of 76% and 69%, respectively [25]. Complications related to chronic GVHD that occurred in 38% of recipients, all in the adolescent age group, resulted in late toxicity after this alemtuzumab/melphalan-based RIC regimen. In addition, the application of a reduced-intensity HLA-haploidentical bone marrow transplant in children with severe SCD demonstrated safety with 97% OS but 57% DFS due to graft rejection [26]. Clinical trials are underway that aim to reduce HCT-related complications and increase DFS in both disorders. Again, it is imperative to pair these short-term aims with long-term healthcare goals as listed below.

Research Priorities

1. Develop improved alternative donor HCT approaches for patients who fail standard supportive care (hydroxyurea, RBC transfusions, iron chelation therapy).
2. Optimize conditioning regimens for alternate donor HCT that minimize GVHD risk and reduce long-term consequences of alternate donor HCT.
3. Define the optimal timing and indications for HCT, particularly with respect to survival outcomes and late effects; develop HCT pathways for adult patients who are eligible after optimum supportive care.

ENGRAFTMENT AND CHIMERISM

Thalassemia

Conventional myeloablative conditioning HCT with busulfan and cyclophosphamide in thalassemia showed a 30% incidence of mixed hematopoietic chimerism early after HCT, and those with >25% recipient cells within 2 months were prone to graft rejection [27]. When reduced-toxicity or RIC regimens were used, there was an increased incidence of

mixed chimerism, particularly in those with high-risk thalassemia [15,28]. Although the presence of persistent mixed chimerism can predispose to graft rejection, whole blood mixed chimerism does not always result in graft loss [29]. In addition, most individuals with mixed chimerism achieve RBC transfusion independence after HCT and have a clinical phenotype indistinguishable from full donor engraftment. This follows the assumption that donor–host chimerism in the lymphomyeloid lineages does not predict donor erythroid lineage expansion, which can predominate on the basis of having a survival advantage compared with recipient thalassemic erythrocytes [30,31]. Overall, registry data suggest that approximately 10% of patients with thalassemia experience stable mixed chimerism beyond 2 years after HCT with donor chimerism varying between 15% and 90%. Even when there are some donor cells in the marrow, stable mixed chimerism generally extends transfusion independence in the long-term and only very rarely progresses to late graft rejection [32-34].

Sickle Cell Disease

Persistent mixed chimerism has been observed in 18% to 28% of patients at 24 months after HCT for SCD, where circulating hemoglobin fractions mirror levels in the healthy donor (sickle trait or HbAA) [10,35]. In 1 case, 11% donor chimerism was sufficient for a strong clinical effect. Mixed chimerism occurred more often after RIC or nonmyeloablative conditioning (23% and 100%, respectively) and was judged unstable (with donor T cell chimerism < 50%) in roughly half the recipients after nonmyeloablative HCT from HLA-identical siblings [15,16]. In the RIC report of HCT for SCD (immunoablation with alemtuzumab, fludarabine, and melphalan), donor chimerism stabilized and immunosuppression withdrawal was accomplished in 13 of 15 HCT recipients. However, the maintenance of mixed chimerism after minimal-intensity nonmyeloablative conditioning required extended duration immunosuppression [15,16,36]. The clinical effect of long-term immunosuppression in this patient population is not known. As in thalassemia, graft rejection typically occurs in the first 2 years after HCT, especially if a progressive decline in donor chimerism is noted early. Monitoring the durability and variability of stable mixed chimerism takes on added importance after gene-inserted or gene-modified autologous HCT in which the stability of an underrepresented or even rare hematopoietic clone over the long term is less certain.

Research Priorities

1. Mixed chimerism occurs after myeloablative and reduced-intensity HCT. Is it stable in the long-term? What are the effects of extending mixed chimerism by prolonged immunosuppression?
2. Development of measures that distinguish stable mixed chimerism versus impending graft rejection (frequency and sensitivity of testing, lineage tracking, when and if to intervene)?
3. Define pre- and post-HCT interventions to maximize or stabilize donor erythropoiesis?

PAIN AFTER HCT

Sickle Cell Disease

Clinical vaso-occlusive painful episodes after HCT for SCD are eliminated if recipients have sufficient donor erythroid chimerism to inhibit intracellular sickle polymer formation. Specifically, acute vaso-occlusive painful episodes, acute chest syndrome, and similar clinical events are abrogated after HCT. In addition, reducing the HbS fraction to <30% before transplant as a method to repress an inflammatory milieu that would otherwise promote cytokine secretion and lymphocyte activation has been widely adopted as a supportive care measure [37]. However, the chronic pain syndrome of SCD is not immediately halted after successful HCT and can persist for up to 3 to 6 months or even longer [16]. This observation supports the notion that not all pain in SCD is vaso-occlusive in origin. In a series of adults with SCD treated by nonmyeloablative transplantation that established mixed donor–host chimerism, a protracted period of pain treatment by opioids was reported. Over time, however, a gradual taper in the opioid dosing was accomplished, and by 6 months post-transplant most patients were no longer receiving treatment for chronic pain. This observation suggests that as the painful stimuli were eliminated after transplant, it was possible to reset pain threshold levels needed to reduce opioid therapy. We also speculate that remodeling of previously activated/dysfunctional vascular/endothelial channels might occur after HCT to promote cessation of painful stimuli.

Research Priorities

1. How long do pain symptoms persist after successful HCT? What is the influence of age and pre-existing joint and bone disease on pain persistence after HCT?
2. Are there biomarkers of pain and vascular dysfunction that might be tracked after HCT to correlate with pain and other patient-oriented outcomes?

LUNGS AND HEART

Sickle Cell Disease

The natural history of sickle lung disease is progressive restrictive disease that follows recurrent vaso-occlusive events and loss of functional lung parenchyma. In childhood, there is also a propensity for asthma and obstructive lung changes. In most cases serial assessments of lung function after HCT showed stabilization and, in some cases, improvement in contrast to the steady tempo of progression and mortality predicted by the natural history of this disease [8,9,38]. Because the duration of follow-up study has been short, it is difficult to predict a long-term trajectory after HCT. Pulmonary hypertension (defined as a mean pulmonary artery pressure > 25 mm Hg) is strongly associated with a risk of sudden death in SCD [39]. Thus, defining the effect of HCT on this process and on the risk of sudden death in adult recipients is a key research priority. Noninvasive methods of estimating pulmonary hypertension are controversial; however, a tricuspid regurgitation jet velocity ≥ 2.5 m/s and an N-terminal-pro-B-type natriuretic peptide level > 164 pg/mL or a 6-minute walk distance < 333 m are associated with a 10-fold increased risk of sudden death. The impact of HCT on cardiovascular health has not been systematically reported.

Research Priority

1. The cardiopulmonary system is vulnerable to damage in SCD and thalassemia. What is the long-term outcome of these systems after transplant, and what role does the age at transplant play on the reversal of complications such as cardiac iron overload and pulmonary hypertension?

GROWTH

Sickle Cell Disease

Growth velocity has been measured after HCT for SCD, and in general linear growth does not appear to be adversely affected by myeloablative doses of busulfan in the preparative regimen. Linear growth velocity after HCT was compared with supportive care alone in the Cooperative Study of Sickle Cell Disease [40] or by hydroxyurea [41], and transplanted males had more rapid growth compared to males in the CSSCD (Table 1). In addition, growth velocities in males and females treated with hydroxyurea after reaching the maximally tolerated dose was not different after HCT. However, recipient age and stage of pubertal development do influence the effect of busulfan on growth. Prepubertal children who were near the onset of the adolescent growth spurt experienced a decrease in linear growth velocity after busulfan administration. In contrast, younger children did not experience decreased growth during the 2 years after transplantation [42,43].

Thalassemia

Growth delay is common in children with thalassemia due to iron toxicity and classical iron chelation drugs, particularly in those >7 years of age [44-46]. As many as 55% have short stature; 27% are severely affected. Growth parameters can gradually improve after HCT, but this catch-up can be compromised by toxicities encountered from preparative regimens or post-HCT complications such as GVHD.

Research Priority

1. Because most transplants are performed in children, monitoring growth and development is a very high priority. Which HCT regimens adversely affect growth? What effect does the underlying disease exert on growth and bone and joint health?

GONADAL FUNCTION, PUBERTY, AND INFERTILITY

Sickle Cell Disease

Gonadal dysfunction related to the hemoglobinopathy can predate HCT and is associated with chronic medical therapies, iron deposition, and iron-induced oxidative stress leading to hypothalamic-pituitary-gonadal dysfunction (most commonly hypogonadotropic hypogonadism) in those who are chronically transfused [47-49]. Other potential contributing factors for gonadal dysfunction in SCD include priapism, testicular ischemia/infarction, and the use of hydroxyurea [50]. Although gonadal dysfunction is not universal after HCT for SCD, it is a significant risk, and most patients who receive a busulfan-based regimen will be infertile [51-53]. Females are particularly sensitive to gonadotoxic therapy because of having a finite reserve of ovarian follicles. Ovarian failure occurs soon after HCT or manifests longer after HCT as premature menopause. Recipients who are postpubertal who have received myeloablative conditioning (high-dose busulfan) have a higher risk of ovarian dysfunction after HCT [43,51,54]. Male recipients with SCD have low to normal levels of testosterone accompanied by elevated gonadotropin blood levels after transplantation, most consistent with hypogonadotropic hypogonadism in pubertal males. Gonadal dysfunction is also dependent on the intensity and content of the conditioning regimen. The risk of infertility was 50% and 10% in postpubertal males treated with busulfan/cyclophosphamide and cyclophosphamide alone, respectively [55]. RIC regimens appear to have a milder impact on gonadal function [56,57].

Table 1
Comparison of Height and Weight Velocities in Males and Females after HCT to CSSCD and Pediatric Hydroxyurea Groups

Comparison Group	Linear Height Velocity		Linear Weight Velocity	
	Male *P*	Female *P*	Male *P*	Female *P*
CSSCD [40]	.01	.12	.0004	.08
Hydroxyurea [41]	.68	.25	.30	.92

CSSCD indicates Cooperative Study of Sickle Cell Disease.

Thalassemia

In thalassemia major there is dual toxicity on gonadal function after HCT caused by iron overload and myeloablative chemotherapy. The risk of ovarian failure was very high in girls of pubertal age, approaching 80% to 100% [44,58,59]. Ovarian toxicity was less frequent if HCT was performed before puberty. Males had a higher tolerance, and those who were pubertal at the time of HCT had normal testosterone levels. HCT in the prepubertal period affected puberty and testosterone levels in 30% to 40% of recipients [59].

Research Priority

1. Gonadal function and fertility pre- and post-HCT are poorly characterized in large registries. Novel transplant regimens that modify the chemotherapy intensity and reduce the toxicity profile are under development. However, the effect of these regimens on gonadal function is not yet known. It will be very important to collect these data prospectively to better inform families about fertility.

IRON OVERLOAD

Iron accumulation is inevitable as a consequence of chronic transfusion dependence and contributes to long-term morbidity post-HCT (Figure 1) [60]. Cardiomyopathy from iron overload in young adulthood remains the leading cause of mortality in medically treated thalassemia major [61]. After a successful transplant, iron overload is “frozen” (there is no additional iron loading and presumably fewer reactive iron species are generated). However, the acquired iron overload can interfere with the delicate intracellular labile iron balance, thus generating damaging reactive oxygen species. The persistence of tissue iron overload can exert long-term risks. The risk of persistent iron overload after HCT has been demonstrated in prospective studies in which progression of liver disease to cirrhosis and cardiac abnormalities has been documented in some patients long after HCT [62,63]. This implies that any tissue insult should be considered in the long term (in decades) as a potential cause of morbidity and mortality potentiated by additional comorbidities [63]. Moreover, other comorbidities or acquired toxic insults that commonly present during “normal” life result in some degree of iron overload as demonstrated by the presence of mild iron overload with hepatitis C virus infection. Large epidemiologic population-based studies and follow-up in patients with hemoglobinopathies have shown that elevated transferrin saturation was associated with increased morbidity and mortality, providing further evidence for the need to tackle iron-related problems after HCT [64]. Endocrine organs affected by iron overload include hypothyroidism in 10%, parathyroid insufficiency, and diabetes mellitus. Toxicity caused by preparative regimens also can exacerbate endocrine function.

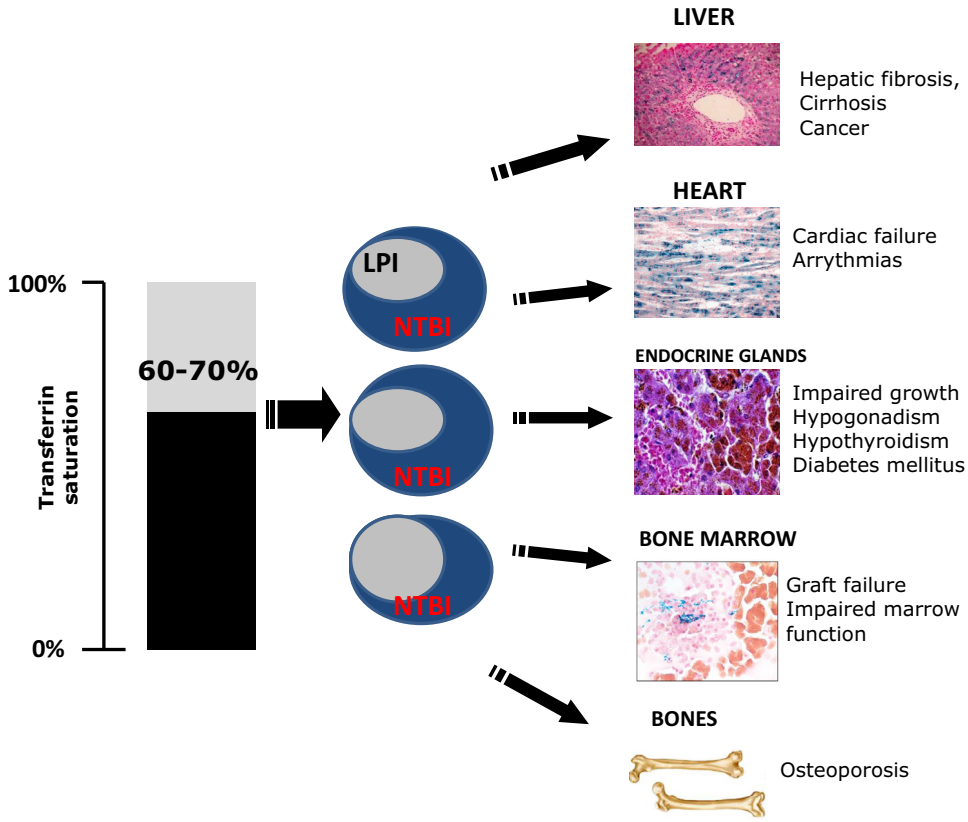

Figure 1. Mechanism of iron-related tissue injury in thalassemia patients. At transferrin saturation levels > 60% to 70%, levels of nontransferrin-bound serum iron (NTBI) and labile plasma iron (LPI) increase, resulting in iron-related damage to the liver, heart, bone marrow, and bones in situations of chronic iron overload after chronic transfusion therapy for thalassemia. (Modified from Angelucci and Pilo [60]).

For example, alemtuzumab increases the risk of autoimmune thyroid disease [57,65].

Sickle Cell Disease

In SCD the interaction of disease pathophysiology and iron overload appears to modulate iron deposition and tissue injury to a lesser extent than thalassemia [66]. However, post-transplant monitoring of iron overload and therapeutic management still remain applicable in this disorder as in thalassemia major.

Research Priorities

1. Study the function of primary organs (brain, heart, lungs, kidneys) impacted by iron overload before and after HCT.
2. Endocrine organs at risk also require systematic long-term follow-up to determine the incidence of late effects on function. Assess interventions (phlebotomy and iron chelation therapy) to reduce iron burden.

IMPACT OF HCT ON THE CENTRAL NERVOUS SYSTEM IN SCD

Two of the largest patient series of HLA-identical sibling HCT in children with SCD in the United States and France showed that most patients treated by HCT experience stabilization of pre-existing cerebral vascular disease [8,9]. Twenty-nine individuals had a stroke as indication for HCT in the US multicenter trial (Table 2). In this group 3 participants had a new stroke after the HCT procedure (1 stroke occurred after graft rejection) corresponding to a stroke event rate of 2.8 events per 100 patient years. There were 10 participants who had a silent cerebral infarction observed as an incidental finding before HCT. With a mean of 1.7 years after HCT, brain magnetic resonance imaging exams showed no

Table 2
Neurologic Outcomes in Surviving Patients Enrolled in the Collaborative Trial (N = 55) [54]

CNS Status Pre-HCT (Median, Range)	Stroke after HCT	Cerebral Hemorrhage after HCT	MRI Appearance after HCT (Median Duration, Range in Years after BMT)
"Clinical" stroke, n = 29 (7.0; 3.4-12.4 yr)	n = 1	n = 1 (SAH)	27/28 studied had stable or improved MRI; 1 not studied (3.2 yr; .6-7.3)
"Silent" stroke*, n = 10 (6.7; 3.4-10.6 yr)	n = 0	n = 0	All 8 studied had stable (n = 4) or improved (n = 4) MRI; 2 not studied (1.7 yr; .6-4.9)
Normal, n = 16† (6.6; 3.1-11.1 yr)	n = 0	n = 0	All 10 studied had normal MRI; 6 not studied (3.1 yr; .5-5.2)

CNS indicates central nervous system; BMT, bone marrow transplantation; SAH, subarachnoid hemorrhage; MRI, magnetic resonance imaging.
* "Silent stroke" refers to individuals with silent cerebral infarction.
† Including 4 with no baseline exam.

new or progressive infarct in these 10 patients. A similar experience was reported by the French consortium in 87 recipients with SCD. Among 36 children who had a stroke before HLA-identical sibling HCT, 2 had recurrent strokes. With a median follow-up of 6 years, the risk of recurrent stroke in those with stroke as the indication for HCT was ~.93 per 100 patient years. Together, these observations suggest that HCT is an effective therapy for secondary prevention of strokes in children with either overt strokes or silent cerebral infarcts, but it is not universally protective. However, systematic long-term follow-up in a larger group of patients is needed to establish the natural history of cerebrovascular disease after HCT.

There appears to be a limited period of time after HCT when ensuring adequate hemostasis by maintaining the platelet count > 50,000/mm^3 until stable engraftment protects from intracranial hemorrhage. In addition, there appears to be a risk during the peritransplant period when the evolution of brain injury by magnetic resonance imaging can progress before subsequent stabilization [67]. Finally, strict control of hypertension, seizure prophylaxis, and avoidance of hypomagnesemia are important in preventing posterior reversible encephalopathy syndrome after HCT for SCD. Even when these measures are used, posterior reversible encephalopathy syndrome and seizures can occur in up to 25% of recipients [25,68].

Research Priorities

1. Assess the therapeutic effect of HCT for cerebral vasculopathy stabilization and protection from progressive brain injury.
2. Assess the reversibility of vascular damage after successful HCT by systematic brain imaging, especially in older recipients with established vascular disease pretransplant.

NEUROCOGNITION AND RELATED FOLLOW-UP

Cognitive deficits that impact educational attainment are common among children with SCD. Central nervous system injury is 1 of the greatest risk factors for cognitive deficits among people with SCD where approximately 40% of children will have a silent cerebral infarct [69]. Without treatment, infarcts are progressive in the form of transient ischemic attacks, recurrent silent cerebral infarct, or overt stroke. Recently, results from the Silent Infarct Transfusion Trial supported chronic transfusion as a method to decrease this risk of recurrence [70]. However, no treatment has been found to reverse the cognitive deficits, and the cognitive impairments appear to progress over time, with a decrease of one IQ point each year [71]. Biologic risk factors for cognitive impairments include anemia, decreased oxygen saturation, and elevated TCD [72]. Children with SCD have lower scores on measures of intelligence compared with unaffected peers or siblings. Children with SCD commonly have deficits in cognitive domains, including impairments in processing speed [73,74], executive function [75], visuomotor functioning [76], and attention [76]. These cognitive functions carry particular importance for educational attainment. Over 60% of children with SCD and silent infarcts had either failed a grade or received special education services [77]. Educational interventions are typically implemented to address specific challenges (rather than global impairment) that impact a student's ability to learn.

HCT may ameliorate cognitive decline among children with SCD. In the only published data of longitudinal cognitive outcomes of children with SCD and HCT from the French in a cohort spanning 1992 to 2006, 15 children (mean age, 8.9 years) were evaluated before and 36 and 60 months after transplantation [78]. Thirteen had an ischemic stroke before HCT. The median full-scale IQ was 87, 94, and 94 before HCT and 36 months and 60 months after HCT, respectively. Unfortunately, uniform data on a large scale have not been available or published in the United States. Although some clinical evaluations are completed before and after HCT, the same tests were not uniformly used at both time points. Without the inclusion of cognitive outcomes in HCT research protocols, uniform evaluations will not be used across centers or may not be completed at all. Given the importance of cognitive function in adherence to medical treatment and educational outcomes, cognition needs to be measured and shared with medical providers, families, and educators to provide supportive interventions.

Research Priorities

1. Assess in greater detail whether successful HCT stabilizes cognitive function and/or helps improve it.
2. What are the effects of complications such as seizures, posterior reversible encephalopathy syndrome, or GVHD on neurocognitive functions during follow-up?

IMMUNE RECONSTITUTION

Immune reconstitution typically occurs over the first year after HCT as immunosuppression is withdrawn after HLA-identical sibling HCT for hemoglobin disorders [15,79]. Factors that delay immune reconstitution include cord blood or T cell–depleted grafts, delayed engraftment, or the use of extended periods of systemic immunosuppression to treat chronic GVHD [57,80,81]. Newer approaches such as selective depletion of alloreactive T cells and infusion of T cell lines/clones specific for life-threatening pathogens may offset GVHD, prevent infection-related mortality, and allow immune reconstitution early [82,83]. Response to reimmunization and the development of protective antibody titers depend on immune reconstitution. This is of particular importance in SCD patients who are susceptible to sepsis from encapsulated bacteria in the absence of immune recovery. Protein conjugates of the pneumococcal vaccine are more potent antigens evoking antibody responses earlier in a recovering immune system compared with the pneumococcal polysaccharide vaccine that should be administered subsequently after the former. Although several transplant studies have described immune reconstitution in small numbers of patients, uniform measurements of immunologic recovery would assess the tempo of recovery by regimen used, facilitate supportive care until full recovery, and guide re-immunization in HCT recipients.

SPLEEN

Sickle Cell Disease

The spleen is subject to autoinfarction in SCD, and asplenism occurs in 90% of children with sickle cell anemia by 5 years of age. Because of the regenerative capacity of the spleen, recovery of spleen function has been observed after successful HCT. In a recent, large, multicenter retrospective analysis, splenic recovery was observed in >90% of recipients. Splenic recovery beyond 15 years of age is less certain, and most individuals > 15 year of age treated by regular RBC transfusions do not recover spleen function [84].

Table 3
Overview of Studies Evaluating HRQoL in Patients with Thalassemia after HCT

Source	Module	Number	Timing	Conclusions
Cheuk et al., 2008 [85]	WHOQOL-BREF(HK) PedsQL™ 4.0	74 Thalassemia patients on supportive care 24 Thalassemia patients after HCT	Cross-sectional analysis	*Adults >18 years:* Overall health better after HCT—less medical aids, higher activity, better relationships, and physical health. *Children <18 years:* Better physical function after HCT. Lower scores on school attendance restriction and hospital visits.
Caocci et al., 2011 [86]	PedsQL™ 4.0	28 Thalassemia HCT patients	Before HCT, 3, 6, and 18 months after HCT	High agreement between child–self and patient–proxy ratings. Physical function decline noted until 3 months after HCT and subsequently increased. No significant difference in emotional, social, or psychosocial domains.
LaNasa et al., 2013 [87]	SF-36 FACT-BMT	109 Ex-thalassemics who underwent HCT between 1980 and 2000 124 Thalassemia patients on supportive care	Cross-sectional analysis	Higher HRQoL after HCT. Older age and chronic GVHD affected HRQoL negatively.

WHOQOL-BREF(HK) indicates World Health Organization Quality of Life Measure Abbreviated; PedsQL™4.0, Pediatric Quality of Life Version 4.0; SF-36, Short Form 36 version 1; FACT-BMT, Functional Assessment of Cancer Therapy—Bone Marrow Transplant.

Thalassemia

The massive splenomegaly associated with hypersplenism in selected thalassemia syndromes traditionally was treated by splenectomy to reduce the transfusion burden, although this practice has been modified more recently. After HCT, the asplenic patient should be managed per published guidelines.

Research Priorities

1. Develop uniformity in assessing immune reconstitution to be able to compare transplant conditioning regimens.
2. Determine splenic function after HCT, especially the impact of age at HCT in SCD.
3. Systematically evaluate response to immunization after transplant as a measure of protection against encapsulated bacteria.

HEALTH-RELATED QUALITY OF LIFE

Thalassemia

Health-related quality of life (HRQoL) measurements in thalassemia are shown in Table 3. Overall, HCT was associated with improved health, activity, and emotional well-being compared with chronic transfusion therapy. These improvements were not as robust when transplants were performed in older patients with advanced disease or in the presence of chronic GVHD. The immediate post-HCT period (the first 3 months) was also associated with impaired physical function especially in children with no simultaneous impact noted on emotional and psychosocial domains [85-87].

Sickle Cell Disease

Table 4 summarizes HRQoL reported after HCT for SCD. Over different assessments there is consensus that HRQoL generally worsens immediately after HCT but returns to baseline

Table 4
Overview of Studies Evaluating HRQoL in Patients with SCD after HCT

Source	Module	Number of Patients	Assessments	Conclusions
Kelly et al., 2012 [88]	CHRIs	7 SCD HCT patients 6 Thalassemia HCT patients Comparison group: children undergoing HCT for acquired disorders	Before HCT, day +45, 3, 6 and 12 months after HCT	Lower physical and emotional function domain scores for 3 months after HCT and subsequently returned to pre-HCT baseline.
Bhatia et al., 2014 [13]	PedsQL™4.0	17 SCD HCT patients 23 Caregivers for SCD patients	Before HCT, days +180 and +365 after HCT	At 1 year after HCT, patient and parent proxies showed improvement in overall, physical, social, and emotional HRQoL domains.
Shenoy et al., 2016 [25]	CHQ-Parent Form 50 CHQ-Child Form 87	13 SCD HCT children 21 Caregivers	Before HCT, days +100, 180, and +365 after HCT	At 100 days parents reported significantly worse self-esteem HRQoL scores but better general health perception. At 6 and 12 months after HCT, children and parents reported significantly improved change in health scores.
Saraf et al., 2016 [89]	SF36 version 1	13 Adult SCD patients	Before HCT, Days +30, +90, and +365 after HCT	One year after HCT, significant improvement in body pain, general health, and vitality domains reported. Lower degree of improvement reported in social and mental health function domains.

CHRIs indicates Child Health Rating Inventories General Heath and HCT module; CHQ-Parent Form 50, Child Health Questionnaire Form 50; CHQ-Child Form 87, Child Health Questionnaire Form 87.

thereafter and continues to improve with time, with correlation between patient and parent perceptions. Improvements were reported in multiple domains including general health, physical, emotional, and social functions [13,25,88,89].

Research Priorities

1. Does longitudinal tracking of HRQoL after HCT reflect improvement over supportive treatment for hemoglobinopathies? These comparisons will require nontransplanted control subjects.
2. Define assessment tools that are age appropriate for monitoring HRQoL in SCD and thalassemia to capture the QoL domains.
3. How does HRQoL differ in older patients with advanced disease after HCT or who develop GVHD? The reversibility of disease-related sequelae and the variable severity of GVHD will influence HRQoL.

HEALTHCARE UTILIZATION

The cost of care with regard to the physical, psychosocial, and financial burden of hemoglobin disorders has not been rigorously studied after HCT.

Sickle Cell Disease

Recent cost estimates range from $150,000 to $250,000 in the first year post-transplant [90] after HCT for SCD. In contrast, single-center publications have reported actual total median costs as high as $451,000 for both inpatient and outpatient care [91]. Despite this broad range of costs, there is general agreement that HCT for SCD generates higher medical and hospitalization costs in the first year after HCT [91-93] that subsequently decrease over time [88,91,92]. Current estimates suggest that HCT for SCD is cost-efficient compared with standard supportive care with current standard care hydroxyurea and/or chronic transfusions representing a substantial burden to the healthcare system with an estimated $1.6 billion per year [90,91,94,95]. Further analysis of costs of care for standard treatment *including* curative therapies will help assess the utility of treatment options.

Thalassemia

Treating thalassemia major, like SCD, is a major healthcare challenge and a burden on the national healthcare system in many countries. The Italian Thalassemia Cost & Outcomes Assessment study reported mean direct societal costs (limited to transfusions and chelation with deferoxamine and/or deferiprone) of €1242 per patient per month in 2006 [96]. In the Italian society with approximately 7000 patients with thalassemia major, the annual direct society cost corresponds to €107 million per year, 56% (€60 million/year) attributed to iron chelation therapy and 33% (€35 million per year) to transfusions. Deferasirox (Exjade, Novartis Pharmaceuticals Inc., Basel, Switzerland) is the preferred oral chelator in terms of compliance. However, deferasirox costs 3 times as much as deferoxamine, thus increasing the cost further. Studies from Thailand comparing cost-effectiveness of HLA-identical sibling HCT measured in terms of quality-adjusted life-years gained in children and young adults with thalassemia compared with conventional therapy suggest that it is a cost-effective strategy, although the actual financial burden is high [97,98]. With improvement in transplant methods and supportive care, alternate donor transplants aim to match survival after HLA-identical sibling HCT. Continued assessment of the cost-effectiveness of HCT especially after alternate donor transplants will be informative.

Research Priority

1. How does post-transplant healthcare utilization long-term (>2 years after HCT) compare with disease- and age-matched nontransplanted control subjects with SCD and thalassemia?

SUMMARY

Early follow-up after HCT for hemoglobinopathies suggests that the procedure protects and in some cases reverses disease-related organ damage, which together enhance HRQoL. As transplant outcomes improve and the toxicity of the procedure is reduced, the future application of HCT for hemoglobin disorders will focus on prevention of disease-related complications and improved quality of life. The benefits of cure must be balanced with HCT complications such as GVHD, graft rejection, and transplant-related morbidities in the short and long term. Post-HCT follow-up studies in hemoglobinopathies and other malignant and nonmalignant disorders have informed us about kidney, cardiovascular, endocrine, and gonadal sequelae in the long term. Each of these aspects requires systematic follow-up and intervention to understand and mitigate these events. This report summarizes current knowledge and highlights gaps in understanding about late effect of HCT for thalassemia and SCD. We will use this summary to help guide and develop a comprehensive roadmap for future long-term studies after HCT and other curative therapies.

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