Biol Blood Marrow Transplant 23 (2017) 1422–1428

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Report

Late Effects Screening Guidelines after Hematopoietic Cell Transplantation for Inherited Bone Marrow Failure Syndromes: Consensus Statement From the Second Pediatric Blood and Marrow Transplant Consortium International Conference on Late Effects After Pediatric HCT

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Article history:
Received 17 May 2017
Accepted 18 May 2017

Key Words:
Late effects
Pediatric allogeneic hematopoietic cell transplant
Inherited bone marrow failure syndromes
Fanconi anemia
Dyskeratosis congenita
Diamond Blackfan anemia

A B S T R A C T

Patients with inherited bone marrow failure syndromes (IBMFS), such as Fanconi anemia (FA), dyskeratosis congenita (DC), or Diamond Blackfan anemia (DBA), can have hematologic manifestations cured through hematopoietic cell transplantation (HCT). Subsequent late effects seen in these patients arise from a combination of the underlying disease, the pre-HCT therapy, and the HCT process. During the international consensus conference sponsored by the Pediatric Blood and Marrow Transplant Consortium on late effects screening and recommendations following allogeneic hematopoietic cell transplantation for immune deficiency and nonmalignant hematologic diseases held in Minneapolis, Minnesota in May 2016, a half-day session was focused specifically on the unmet needs for these patients with IBMFS. This multidisciplinary group of experts in rare diseases and transplantation late effects has already published on the state of the science in this area, along with discussion of an agenda for future research. This companion article outlines consensus disease-specific long-term follow-up screening guidelines for patients with IMBFS.

Financial disclosure: See Acknowledgments on page 1427.

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http://dx.doi.org/10.1016/j.bbmt.2017.05.022
1083-8791/

BACKGROUND

Increasing indications for allogeneic hematopoietic cell transplantation (HCT) in childhood diseases [1-3] and improved survival post-HCT lead to the projection that there will be more than 70,000 childhood HCT survivors under age 18 years at transplantation by 2030 in the United States alone [1]. Children undergoing HCT for nonmalignant diseases, including inherited bone marrow failure syndromes (IBMFS), immune system disorders, and hemoglobinopathies, represent a growing number of patients with special follow-up needs [4].

Much of our understanding of long-term toxicities in survivors of pediatric HCT comes from the study of patients with hematologic malignancies. These patients have a high burden of late effects and mortality compared with the general population [5], as well as compared childhood cancer survivors treated with chemotherapy and/or radiation. Known risk factors include younger age at HCT, conditioning with total body irradiation (TBI), and chronic graft-versus-host disease (GVHD) [6-14]. Recent reports have examined populations with much larger proportions of nonmalignant HCT survivors [15]. Numerous single-center and smaller consortia reports have shown that long-term complications are common in survivors of transplantation for IBMFS, hemoglobinopathies, and immune deficiencies [16-27].

General HCT follow-up guidelines have been published [28-31] and reviewed [32], as summarized in Table 1; however, these guidelines do not consider pretransplantation exposures or disease-specific manifestations that are unique to patients with nonmalignant hematopoietic disorders, and cannot be readily interchanged with exposures for malignant diseases, such as chemotherapy and radiation. Furthermore, the interaction of each specific nonmalignant disorder with the HCT process may alter the natural history

Table 1
General Late Effects Screening Guidelines after Hematopoietic Cell Transplantation

Late Effect/Organ System	Summary of General HCT Late Effects Guidelines
Immune reconstitution/ immunologic	• Patients with GVHD on immune suppression • Encapsulated organism and pneumocystis antibiotic prophylaxis • Broad-spectrum parenteral antibiotics for fevers • Regular screening for CMV and/or other opportunistic infections • Endocarditis prophylaxis according to AHA guidelines • Annual evaluations for recurrent, unusual, or severe infections • Screening for HIV and hepatitis in those exposed to blood products • Immunizations according to published guidelines • Monitoring of T cell and B cell immune reconstitution • Monitoring of T cell proliferative capacity to mitogens • Neoantigen challenge for patients with poor immune reconstitution
Iron overload	• Serum ferritin screening post-HCT, repeat annually or as needed until normal • Consider T2*-weighted MRI if screen is positive or significant transfusion history • Follow LFTs regularly and consider hepatology consult if elevated • Phlebotomy or chelation therapy for management if iron burden clinically significant
Neurocognitive	• Yearly screening for educational and developmental progress • Neuropsychological evaluation at minimum one year post-HCT, repeat as needed • Referral to appropriate school or other resources for those with identified neurocognitive deficits
Subsequent cancer risk	• Lifestyle counseling to avoid high-risk behaviors and encourage good behaviors (eg, smoking, excessive alcohol, sunscreen use, healthy diet, exercise) • Annual history and physical • Encourage self-exam (eg, skin, oral cavity, genitalia) • Follow general population cancer screening guidelines • Regular dental exams for those with chronic GVHD • Mammography in women beginning at age 25 or 8 years after TBI or chest radiation exposure (no later than age 40), with consideration for breast MRI in some patients
Pulmonary	• Annual history and physical • Counsel regarding tobacco avoidance or cessation • PFT every 6 to 12 months initially, then as clinically indicated • Focused radiological exam for those with abnormal findings • Referral to pulmonologist with abnormal findings
Reproductive/gonadal	• At least annual assessment of pubertal development and sexual and reproductive function • LH, FSH, and testosterone in males, consider semen analysis • LH, FSH, and estradiol in females, with some centers using AMH screening • Referral to endocrinologist, gynecologist, or urologist with abnormal pubertal timing or gonadal dysfunction • Treat ovarian failure with hormone replacement therapy • Counsel about birth control in those of reproductive age
Renal	• At least annual hypertension screening • At least annual urinalysis, urine protein or albumin to creatinine ratio, serum creatinine, and BUN • Referral to nephrologist if hypertension or renal dysfunction
Growth	• At least annual height, weight, BMI, and Tanner staging • Annual thyroid function, bone age, and refer to endocrinologist for abnormal growth rate or other abnormalities
Psychosocial	• At least annual assessment for mental health concerns, chronic pain and fatigue, risky behaviors, and access to health care • Encouragement of robust support networks • Additional assessment of family members and caregivers • Referral to mental health professional as needed

HCT indicates hematopoietic cell transplantation; GVHD, graft-versus-host disease; CMV, cytomegalovirus; AHA, American Heart Association; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; LFTs, liver function tests; TBI, total body irradiation; PFT, pulmonary function testing; LH, lutein hormone; FSH, follicle-stimulating hormone; AMH, anti-mullerian hormone; BUN, blood urea nitrogen; BMI, body mass index.

and risk of late effects. This is important for understanding how to screen, diagnose, and treat or prevent these complications. These issues were discussed at the Second International Pediatric Blood and Marrow Transplant Consortium Consensus Conference on Late Effects after Pediatric Hematopoietic Cell Transplantation in Minneapolis in May, 2016. The current state of knowledge, as well as an agenda for future research specific to IBMFS, has been published by this group [33], and is summarized here in support of the surveillance recommendations.

Table 1 presents a starting point for these new long-term follow-up recommendations tailored to each individual IBMFS. The consensus recommendations provided are meant to outline an ideal follow-up approach from which to move forward. It also should be noted that data on long-term follow-up post-HCT for these disorders are limited, making it difficult to create evidence-based guidelines for the management of IBMFS. Thus, this work is based on a combination of available data and expert opinion. Moreover, gene therapy is not addressed in these recommendations; however, because gene therapy is used as a therapeutic modality for these children, different approaches to follow-up may be needed. An important area of consideration for all genetic diseases includes the need for genetic counseling, family planning, and counseling regarding living with chronic conditions.

Of note, within the broad diagnostic categories of Fanconi anemia (FA), dyskeratosis congenita (DC), and Diamond Blackfan anemia (DBA) are a myriad of causative pathogenic germline variants in multiple genes, many conferring very specific phenotypes. This variability may have a bearing on transplantation-related morbidity and mortality as well as late effects in survivors. Although it is beyond the scope of these guidelines, a detailed assessment of each patient keeping this in mind is essential. This has been outlined in detail for patients with FA (http://fanconi.org/index.php/publications/guidelines_for_diagnosis_and_management) and DC (https://www.dcoutreach.org/guidelines) in previously published clinical guidelines.

FA

Five-year survival after a matched sibling HCT for FA is now approximately 90%, with similar improvements after alternative donor HCT [24,34-37]. Many patients with FA are now surviving to adulthood after undergoing HCT, and long-term side effects of HCT are becoming more apparent. FA is the most widely studied IBMFS to date with respect to late effects after HCT. The follow-up of patients with FA who underwent HCT may differ from the follow-up of patients who underwent HCT for other indications and from the management of patients with FA who did not undergo HCT with regard to nonhematologic systems, such as endocrine manifestations and cancer risk. Table 2 summarizes the recommended screening guidelines for FA-specific late effects.

The wide variety of FA-related complications, including those related to congenital anomalies, indicates the need for close attention to these problems before, during, and long after HCT. This can include neurodevelopmental issues as well as genitourinary, renal, cardiac, gastrointestinal, and musculoskeletal anomalies [38,39]. Patients with FA who progressed to severe marrow failure may have been treated previously with transfusion support. Multiple red blood cell transfusions without adequate iron chelation may lead to iron

Table 2
Late Effects Screening Guidelines after Hematopoietic Cell Transplantation for Fanconi Anemia

Late Effect/Organ System	Fanconi Anemia Specific Guidelines
Immune reconstitution/immunologic	• Ensure HPV vaccination
Iron overload	• Earlier and more aggressive evaluation and management starting at 6 months post-HCT
Neurocognitive	• Attention to FA-associated neurodevelopmental issues
Subsequent cancer risk	• Dermatology: skin cancer screening every 6-12 months • Monthly oral self exam, dental exam every 6 months, and ENT evaluation every 6-12 months by head and neck physician, including nasolaryngoscopy (more frequent if unable to do self exam) • Increased screening for SCC in those with chronic GVHD and in those with *BRCA2* gene mutations, specifically to look for medulloblastoma and Wilms tumor
Pulmonary	• Follow-up as needed
Reproductive/gonadal	• Follow-up of congenital genitourinary anomalies with a urologist • Yearly gynecologic evaluation for females with Pap smear and HPV screening, starting in the early teenage years • Measure serum AMH as a potential early marker of gonadal insufficiency, with consideration for fertility preservation measures
Renal	• Follow-up congenital renal anomalies and renal function with a nephrologist
Growth	• Full endocrine evaluation including GH levels (potentially with stimulation testing), IGF1, IGFBP3, Tanner staging and bone age • Monitor weight and assess for FA-associated failure to thrive
Psychosocial	• Inclusion of genetic counseling for patient and family • Assistance with family planning • Counseling about living with chronic conditions
Cardiac	• Follow up with cardiology for congenital cardiac anomalies and screen with ECG and Echocardiogram
Endocrine	• Screening for diabetes, dyslipidemia, and Vitamin D deficiency • Screening for osteoporosis with DEXA pre-HCT and every 2 years post-HCT • Screening for avascular necrosis if bone or joint pain develop
Other	• Screening for vision and cataracts • Screening for hearing loss if clinically indicated • Follow LFT regularly and consider hepatology consult if elevated • Follow-up of congenital musculoskeletal anomalies and evaluation for scoliosis • Lifestyle counseling to promote good health habits: encourage healthy diet and regular exercise, avoid alcohol, smoking, and second-hand smoke, limit sun exposure and use sunscreen

HPV indicates human papilloma virus; HCT, hematopoietic cell transplantation; ENT, ears, nose, and throat physician; SCC, squamous cell carcinoma; GVHD, graft-versus-host disease; AMH, anti-mullerian hormone; GH, growth hormone; IGF1, insulin-like growth factor 1; IGFBP3, insulin-like growth factor binding protein 3; ECG, electrocardiogram; DEXA, dual-energy x-ray absorptiometry; LFT, liver function tests.

overload in the liver, heart, and endocrine organs. Timely and aggressive screening and management for iron overload are recommended.

Endocrinopathies, including thyroid dysfunction, growth hormone deficiency, glucose intolerance, and gonadal dysfunction, are common in patients with FA independent of HCT, and can be exacerbated in the post-HCT period [40-43]. Routine and comprehensive follow-up with an endocrinology team is strongly recommended and remains a key area of post-HCT follow-up care.

The risk of acute myelogenous leukemia (AML) and myelodysplasia (MDS) is markedly decreased by HCT, whereas solid tumors, most notably squamous cell carcinoma (SCC) of head and neck and genital region, remain the most common malignancies [44]. Oral cavity SCC in patients with FA is not associated with human papillomavirus (HPV) in the same way as oropharyngeal SCC is in the general population [45]; however, HPV vaccination is still recommended for prevention of HPV-associated genital SCC regardless of sex. Although chronic GVHD involving the mouth and/or genitourinary tract has a strong association with the risk of SCC, the impact of radiation is less clear but remains a possible risk factor [23,24,46-50]. Whether busulfan or lowering the total dose and dose rates of radiation or shielding has affected the risk of cancer remains to be determined. Importantly, patients whose FA is due to mutations in *FANCD1/BRCA2* or *FANCN/PALB2* need genotype-specific cancer screening because of increased risks of medulloblastoma, Wilms tumor, and other cancers [51-54].

The long-term follow-up issue that merits the greatest degree of attention in patients with FA post-HCT is the apparent increased risk of cancer[55]. The importance of screening for these cancers is increasingly recognized by the development of specifically designed surveillance schedules.

DC

Survival for patients with DC after HCT has not reached the level of that for patients with FA, but there have been significant improvements over time [56], such that more patients with DC are living much longer after HCT. In contrast to FA, DC-associated bone marrow failure develops more gradually, with a cumulative incidence of 40% by approximately age 40 [48], and thus patients with DC may be older than those with FA when they undergo HCT. Although long-term events, whether disease-related and/or late effects after HCT, are becoming more apparent, data on long-term follow-up after HCT in this population are limited. There are important differences in HCT follow-up practices compared with otherwise standard HCT follow-up with respect to nonhematologic manifestations of DC and cancer risk. Table 3 summarizes the recommended DC-specific late effects screening guidelines.

Given the wide variety of DC-related complications, including progression of the clinical manifestations, careful attention to these problems is needed before, during, and long after HCT. These include neurodevelopmental issues as well as genitourinary anomalies and visual problems [39,57,58]. Life-threatening issues include pulmonary fibrosis, liver cirrhosis, enteropathy, gastrointestinal bleeding, and pulmonary arteriovenous malformations [39,57,58]. Patients with DC who progressed to severe marrow failure may have been treated previously with transfusion support, and multiple transfusions may lead to iron overload in the liver, heart, and endocrine organs. Thus, early and aggressive screening and management

Table 3
Late Effects Screening Guidelines after Hematopoietic Cell Transplantation for Dyskeratosis Congenita

Late Effect/Organ System	Dyskeratosis Congenita Specific Guidelines
Immune reconstitution/immunologic	• Ensure HPV vaccination
Iron overload	• Earlier and more aggressive evaluation and management starting at 6 months post-HCT
Neurocognitive	• Attention to DC-associated neurodevelopmental issues, particularly in those with HH or Revesz syndromes
Subsequent cancer risk	• Dermatology for skin cancer screening every 6-12 months • Monthly self oral exam, dental exam every 6 months, and ENT evaluation yearly by head and neck physician, including nasolaryngoscopy (more frequent if unable to do self exam)
Pulmonary	• Lifelong pulmonary symptom screening for DC-associated pulmonary fibrosis and other post-HCT issues • PFT screening yearly with low threshold for referral to pulmonologist for decline in lung function • Surveillance for pulmonary AVM with low threshold for bubble echo prior to HCT as well as in long-term follow-up depending on pre-HCT results and symptoms
Gastrointestinal	• Screening for esophageal stenosis with treatment as needed • Surveillance for bleeding, ulceration, telangiectasias, and varices as clinically indicated • Follow LFTs regularly and consider hepatology consult if elevated for DC-associated liver cirrhosis and fibrosis
Reproductive/gonadal	• Follow-up of congenital genitourinary anomalies with a urologist • Examination for urethral stenosis, which may need dilation • Yearly gynecologic evaluation for females with Pap smear and HPV screening
Renal	• Follow-up as needed for congenital genitourinary anomalies and related renal dysfunction if present
Growth	• Full endocrine evaluation including GH levels (potentially with stimulation testing), IGF1, IGFBP3, Tanner staging, and bone age • Measure weight and assess for DC-associated failure to thrive
Psychosocial	• Inclusion of genetic counseling for patient and family • Assistance with family planning • Counseling about living with chronic conditions
Other	• Screening for vision, lacrimal duct stenosis, retinal pathology, and cataracts • Screening for hearing loss • Lifestyle counseling to promote good health habits: encourage healthy diet and regular exercise, avoid alcohol, smoking, and second-hand smoke, limit sun exposure and use sunscreen • Screening for osteoporosis with DEXA pre-HCT and every 2 years post-HCT • Evaluate for avascular necrosis if bone or joint pain develop

HPV indicates human papilloma virus; HCT, hematopoietic cell transplantation; HH, Hoyeraal-Hreidarsson; ENT, ears, nose, and throat physician; GVHD, graft-versus-host disease; PFT, pulmonary function testing; AVM, arteriovenous malformation; LFTs, liver function tests; GH, growth hormone; IGF1, insulin-like growth factor 1; IGFBP3, insulin-like growth factor binding protein 3; DEXA, dual-energy x-ray absorptiometry.

for iron overload are imortant. A comprehensive review of case reports and case series has identified the major late adverse events as pulmonary disease, liver disease, and vascular complications. These complications differ from infection, graft failure, and hemorrhage, the most common early causes of mortality after HCT in other contexts [56]. Surveillance and timely intervention for these late deadly complications are important, given the reports of successful lung and liver transplantation in patients with DC [59,60]. Osteoporosis and osteopenia are commonly associated with DC [57] and can worsen after HCT from the use of steroids. Surveillance for and optimization of bone health after HCT also may help reduce avascular necrosis of the hips and shoulders, which in severe cases may necessitate joint replacement surgery at a young age.

The risks of AML and MDS are markedly decreased by HCT, and thus solid tumors, most notably SCC of the head and neck and genital region, remain the most common malignancies [48,57,61]. There are very little data on the association between HPV and oral cavity SCC in DC, although notably, one study of head and neck SCC in 4 patients with DC did not detect HPV in the tumors [45]. However, HPV vaccination is recommended for prevention of HPV-associated genital SCC regardless of sex. Similarly, close follow-up with dermatology is an integral part of post-HCT care owing to the increased risk of skin SCC.

The long-term follow-up issues that may occur with aging but merit the greatest degree of attention in patients with DC post-HCT are pulmonary fibrosis, liver fibrosis, pulmonary arteriovenous malformation, gastrointestinal bleeding, and increased risk of SCC.

DBA

Increasing numbers of patients are undergoing HCT for the anemia of DBA with improved survival [62-64], and thus long-term events, whether disease-related and/or late effects after HCT, are becoming more apparent. There are little data on long-term follow-up after HCT in this population. There are some important differences in HCT follow-up in these patients compared with otherwise standard HCT follow-up with respect to nonhematologic manifestations of DBA and cancer risk. Table 4 summarizes the recommended screening guidelines for DBA-specific late effects.

The wide variety of DBA-related complications, including craniofacial, cardiac, genitourinary, renal, and musculoskeletal anomalies [65,66], calls for multiple subspecialty care teams throughout the entire pre-HCT and post-HCT period. The other major issues faced by patients with DBA throughout the transplantation process and into longer-term follow-up are related to a previous history of regular transfusions and long-term corticosteroid use. Significant endocrinopathies, including problems with bone health are of particular concern [66,67]. The impact of iron burden specifically presents one of the major challenges for patients with DBA and the importance of addressing this challenge before HCT cannot be overemphasized [68]. Iron abatement via chelation must be addressed before HCT with additional post-HCT phlebotomy or chelation to prevent cardiac or hepatic complications.

The risks of AML and MDS are markedly decreased by HCT, but solid tumors, most notably luminal gastrointestinal cancers and osteosarcoma, remain the most common malignancies in patients with DBA [69,70]. Individualized cancer screening practices need to evolve with recognition of these risks and better understanding of the additional effects of HCT on the risk of developing these and other cancers. In addition, it should be noted that reduced-intensity HCT with partial chimerism may not fully mitigate the risk of AML and MDS.

The long-term follow-up issues that merit the greatest attention in patients with DBA post-HCT are iron

Table 4
Late Effects Screening Guidelines after Hematopoietic Cell Transplantation for Diamond Blackfan Anemia

Late Effect/Organ System	Diamond Blackfan Anemia Specific Guidelines
Immune reconstitution/ immunologic	• Ensure HPV vaccination
Iron overload	• Likely to be one of the major issues both pre- and post-HCT, with need for the earliest and most aggressive evaluation and management pre- and post-HCT • T2*-weighted MRI (for both hepatic and cardiac iron load) in addition to ferritin yearly until iron overload is resolved • Follow LFTs regularly and consider hepatology consult if elevated • Phlebotomy or chelation therapy as appropriate for management
Endocrine	• Complete endocrine evaluation is necessary as any/all endocrine organs can have organ dysfunction (thyroid, parathyroid, pancreatic, adrenal, gonadal, hypothalamic and pituitary) from iron overload
Neurocognitive	• Attention to neurodevelopmental issues, particularly in those patients with craniofacial abnormalities and large ribosomal protein gene deletions
Subsequent cancer risk	• Surveillance strategies for luminal GI cancers, osteosarcoma, and others are being developed for these patients and will apply post-HCT as well
Pulmonary	• Follow-up as needed
Reproductive/gonadal	• Follow-up of congenital genitourinary anomalies with a urologist and full endocrine evaluation mentioned above
Renal	• Follow-up congenital renal anomalies with a nephrologist
Growth	• Full endocrine evaluation including GH levels (potentially with stimulation testing), IGF1, IGFBP3, Tanner staging, and bone age
Psychosocial	• Inclusion of genetic counseling for patient and family • Assistance with family planning • Counseling about living with chronic conditions
Other	• Screening for vision and cataracts (especially with pre-HCT steroid use) • Follow congenital cardiac anomalies and screen with ECG and Echocardiogram in addition to T2*-weighted MRI mentioned above • Follow-up of all congenital anomalies • Lifestyle counseling to promote good health habits: encourage healthy diet and regular exercise, avoid alcohol, smoking, and second-hand smoke, limit sun exposure and use sunscreen

HPV indicates human papilloma virus; HCT, hematopoietic cell transplantation; MRI, magnetic resonance imaging; LFTs, liver function tests; GI, gastrointestinal; GH, growth hormone; IGF1, insulin-like growth factor 1; IGFBP3, insulin-like growth factor binding protein 3; ECG, electrocardiogram.

overload, much of which is carried over from pre-HCT treatment, and the increasing risk of solid tumors with aging.

CONCLUSION

This report presents late effects screening guideline recommendations for patients with IBMFS post-HCT that have been developed through an international collaboration and consensus process. These recommendations are meant to outline an ideal follow-up as a starting point for management of these patients moving forward. With consistency in follow-up and continued observation of these patients post-HCT, we hope to learn additional information that will lead to modification of these guidelines over time. These recommendations focus on FA, DC, and DBA, but it is important to understand and develop syndrome-specific guidelines for all patients who undergo HCT for nonmalignant disease.

ACKNOWLEDGMENTS

Financial disclosure: This work was supported in part by grants from the National Institutes of Health (1R13CA159788-01, to M.A.P. and K.S.B.; U01HL069254, to M.A.P.; R01 CA078938, to K.S.B.; and 5R01HL079571, to J.M.L. and A.V.), the Pediatric Blood and Marrow Transplant Consortium, and St. Baldrick's Foundation (U01HL069254, to M.A.P.). B.P.A. and S.A.S. are supported by the Intramural Research Program of the National Cancer Institute. The views expressed in this paper do not reflect the official policies of the Department of Health and Human Services, nor does mention of trade names, commercial practices, or organizations imply endorsement by the US Government. The content is solely the responsibility of the authors and does not necessarily represent the official views of those that provided funding.

Conflict of interest statement: There are no conflicts of interest to report.

Authorship statement: J.E.W. and B.P.A. contributed equally to this work.

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