Inherited bone marrow failure syndromes: considerations pre- and posttransplant

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Patients with inherited bone marrow failure syndromes are usually identified when they develop hematologic complications such as severe bone marrow failure, myelodysplastic syndrome, or acute myeloid leukemia. They often have specific birth defects or other physical abnormalities that suggest a syndrome, and sequencing of specific genes or next-generation sequencing can determine or confirm the particular syndrome. The 4 most frequent syndromes are Fanconi anemia, dyskeratosis congenita, Diamond Blackfan anemia, and Shwachman Diamond syndrome. This review discusses the major complications that develop as the patients with these syndromes age, as well as additional late effects following hematopoietic stem cell transplantation. The most common complications are iron overload in transfused patients and syndrome-specific malignancies in untransplanted patients, which may occur earlier and with higher risks in those who have received transplants.

Learning Objectives

- Understand the complications that develop with age in patients with the major inherited bone marrow failure syndromes
- Distinguish age-related complications from those that are associated with having a hematopoietic stem cell transplantation

Introduction

Patients with an inherited bone marrow failure syndrome (IBMFS) face a variety of complications involving many systems; hematopoietic stem cell transplantation (SCT) may cure some problems, prevent others, and introduce new ones. The most frequent of these rare genetic syndromes are Fanconi anemia (FA), dyskeratosis congenita (DC), Diamond Blackfan anemia (DBA), and Shwachman Diamond syndrome (SDS). The respective pathologic pathways involve DNA repair (FA), telomere biology (DC), and ribosome biogenesis (DBA and SDS).[1,2] Many patients present with hematologic findings, such as single-cell or pancytopenia, myelodysplastic syndrome (MDS), or leukemia, particularly acute myeloid leukemia (AML). The diagnosis of an IBMFS may be revealed during evaluation for the hematologic manifestations, due to observation of specific clinical phenotypes or use of syndrome-specific screening tests or genomic studies.[3,4] The syndrome-specific tests are as follows: for FA, increased chromosome breakage in lymphocytes cultured with a DNA cross-linker; for DC, short telomeres by lymphocyte flow cytometry and fluorescent in situ hybridization; for DBA, elevated red cell adenosine deaminase; and for SDS, low levels of serum trypsinogen and isoamylase.[5-8]

Patients with an IBMFS are usually diagnosed and followed by pediatric hematologists, although we now realize that some patients are identified as adults. Features that lead to diagnosis in childhood, even without hematologic manifestations, include a multitude of syndrome-specific congenital anomalies, as well as complications that may develop with age (Table 1). The majority of the patients present with or develop cytopenias or hematologic malignancies, and thus the option of SCT is very attractive. Although SCT may cure the bone marrow problem, it may introduce new and, until recently, unanticipated outcomes. It is important to distinguish an SCT-related late effect from a feature of aging in a person with an IBMFS, which might be independent of the SCT, to offer appropriate counseling, surveillance, and treatment.[9,10]

Patients with an IBMFS share many age-related complications, independent of the use of SCT, as well as many adverse events that may be exacerbated by SCT. One major concern is iron overload in transfused patients, which is paramount in those with DBA but also may be relevant in any of the others who received substantial red cell support without adequate iron chelation. Osteopenia or osteoporosis may be increased in patients who were treated with corticosteroids (eg, DBA), although they appear to be unrelated to steroids in FA, DC, and SDS. Cataracts, ophthalmic and renal complications from chelating agents, hypothyroidism, liver disease, dental caries, progressive immunodeficiency, and problems due to delayed intellectual development may occur in some patients with any of the syndromes. Finally, increased rates of malignancies are a major concern in all of the IBMFS patients as they age, although the actual types and risks are syndrome specific.

Patients with an IBMFS have some common post-SCT late effects; many of these may be seen in patients receiving transplants for reasons other than an IBMFS, but they may be more frequent or more

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complicated in those with an IBMFS.[10] These may include acute or chronic graft-versus-host disease (GVHD), delayed immune reconstitution, iron overload, pulmonary complications, infertility, renal functional impairment, short stature (from the syndrome, corticosteroids, growth hormone deficiency, or other factors), and psychosocial difficulties of the combination of a syndrome as well as a transplant. In addition, the potential of the preparative regimen, the transplant, or post-SCT medication increasing the already high risk of malignancy, cannot be neglected. Despite the common features, the major rare syndromes are also very different in their manifestations and complications and are discussed separately below. Other syndromes are not discussed here because there is insufficient information about transplant-related late effects. The focus of this review is on the syndrome-specific complications associated with growing older and the distinction between the aging-associated developments and those that may be specific to or made worse by transplant.

Fanconi anemia

Patients with FA may be diagnosed in utero or at birth because of birth defects, in mid-childhood because of aplastic anemia, or as young and older adults because of specific types of cancers.[1,11,12] An additional reason for delayed diagnosis until adulthood, perhaps related to late complications from FA, is the presence of somatic hematopoietic mosaicism, by which a stem cell may have undergone a molecular gene correction, and thus the offspring cells populating the blood and marrow may have a selective advantage over uncorrected FA cells. The patient may not only not have marrow failure (and yet may develop MDS or AML from the residual uncorrected cells) but may be difficult to diagnose if the only test is chromosome breakage in lymphocytes in the peripheral blood rather than in a nonhematopoietic tissue such as fibroblasts.[5] Nonhematologic features include physical findings such as short stature, café au lait spots, radial ray anomalies, microcephaly, microphthalmia, renal structural abnormalities, abnormal gonads and decreased fertility, and brain structural anomalies, as well as others described in Table 1. Many but not all features will continue to create problems as the patients age. Other systems that may be involved, and may worsen with age, include skeletal problems such as osteoporosis, visual problems (cataracts), decreased fertility, endocrine (particularly hypothyroid, diabetes, and growth problems), oral hygiene, abnormal hepatic or renal function, hearing loss, and immunodeficiency.[13]

The life-threatening risks that increase with age are evolution to MDS or AML, as well as with tumors, particularly head and neck squamous cell carcinomas (HNSCC) and gynecologic SCC.[11] Very young patients with biallelic mutations in *FANCD1/BRCA*2 have a more than 90% risk by age 6 years of AML, medulloblastoma, and Wilms tumors.[14] Most of the patients with other FA genotypes have inordinately high risks of other malignancies, which increase with age, but occur at much younger ages than in the general population. These include an overall risk of any cancer of 20- to 50-fold, solid tumors 20- to 40-fold, AML 300- to 800-fold, HNSCC 200- to 800-fold, esophageal cancer 1300- to 6000-fold, vulvar cancer 500- to 4000-fold, and MDS more than 5000-fold. These data came from analyses of several cohorts, comparing the number of patients with these cancers with the expected number in the database from Surveillance, Epidemiology, and End Results, adjusting for age, sex, and birth cohort. Although the ranges are quite wide, the data serve to indicate that patients with FA have very high risks of cancer, at ages younger than are expected in the general population.[11,15-18]

What about the effect of SCT? We recently suggested that the choice for a patient with FA to have an SCT might be evaluated by a shared decision-making model, in which the estimated event-free survival following SCT is conditional on age-based annual cause-specific hazard rates. An early SCT (perhaps "preemptive," before the development of accepted clinical indications) would most likely eliminate the occurrence of aplastic anemia, AML, or MDS, with the tradeoffs of treatment-related mortality or morbidity and the benefit of an elective rather than an emergent procedure.[19-21] Many of the clinical systems might be exacerbated or introduced because of chronic GVHD or made more complicated because of the preparative regimen or the associated immunosuppression (Table 2).

The most striking concern is the apparent increase in cancer in the patients who receive transplants. The most frequent cancer types have been HNSCC and gynecologic SCC, occurring at younger ages and higher rates than in untransplanted patients, as well as nonmelanoma skin cancers. The observation of increased cancer risk post-SCT is derived from our analyses at the National Cancer Institute, and we anxiously await independent validation.[18,22] Others have indicated an increased risk of solid tumors post-SCT but reported data as an interval following SCT rather than patient age, and thus it is difficult to determine the actual magnitude of the risk in those reports, as we have done by using chronologic age.[23,24] Tumors in patients with FA, both untransplanted and transplanted, do not appear to be due to infection with human papillomavirus (HPV) and thus may not be totally prevented by vaccination, although that is recommended as a standard of care and may prevent gynecologic cancers.[25]

When and how to do an SCT? An indication for treatment is pancytopenia, defined as hemoglobin <8 g/dL, absolute neutrophils $<0.5 \times 10^9$ per liter, or platelet count $<20 \times 10^9$ per liter.[13] SCT is the treatment of choice, if there is a well-matched sibling (or even unrelated) donor, rather than androgens. The optimal recipient should have received fewer than 20 units of red blood cells or platelets.[26,27] The prior use of androgens mandates full examination of liver function and morphology for androgen-related complications but is not in itself a contraindication for SCT. It has been suggested that SCT be considered in patients who have developed clonal cytogenetics such as gain of chromosome 1q or 3q26q29, deletion 7q, or abnormal *RUNX1*, or deletions of 5q, 13q, and 20q.[28] However, it is important to consider whether those clonal findings are in the context of morphologic MDS or AML, because some patients may have abnormal clones for extended periods of time without further evolution.[29]

Preparative regimens have been modified over the years, and the current recommendation for patients with bone marrow failure is reduced intensity conditioning, with low-dose cyclophosphamide, fludarbine, and busulfan, or low-dose irradiation, as well as T-depletion to reduce GVHD.[26,30] SCT guidelines vary according to the source of stem cells (marrow better than peripheral blood better than cord), donor type (matched sibling, matched unrelated, haploidentical relative), and indications for SCT (pancytopenia, MDS, or AML). Details for all of these are beyond the scope of this review. Most important for those who do receive an SCT, for whatever reason, is that the patients need to be under life-long surveillance for all of the age- and syndrome-specific complications outlined in Table 2 and for the cancers listed in Table 3. The patient must be reminded that although the bone marrow is "cured" of FA, the nonhematopoietic organs remain at the same or even increased risk of FA complications.

Table 1. Systems involved in patients with an IBMFS

System	FA	DC	DBA	SDS
Hematology	Aplastic anemia, MDS, AML	Aplastic anemia, MDS, AML, lymphomas	Anemia, MDS, AML	Neutropenia, aplastic anemia, MDS, AML
Oncology	Head and neck SCC (tongue), vulvar SCC, esophagus, brain, skin	Head and neck SCC (tongue), anogenital SCC, stomach, lung, esophagus, skin	Colon, lung, osteosarcoma, gynecologic, stomach	Ovarian cancer
Perinatal	Low birth weight, intrauterine growth retardation	Low birth weight, intrauterine growth retardation	Low birth weight, hydrops	Low birth weight
Skin	Café au lait spots, basal cell, and SCC	Lacy reticulated pigmentation, dystrophic nails (soft, brittle, ridged, disappearing), adermatoglyphia, hyperhidrosis, basal cell, and SCCs	—	Ichthyosis, eczema
Skeletal	Absent or abnormal thumbs, absent or hypoplastic radius; flat thenar eminence; Klippel Feil, congenital hip dislocation	Avascular necrosis hips or shoulders, osteoporosis, scoliosis, spontaneous fractures	Thumbs triphalangeal, bifid, duplicated, subluxed, extra, hypoplastic; web neck, Sprengel, Klippel-Feil, short neck; scoliosis	Metaphyseal dysostosis; small thorax, narrow chest, pectus carinatum; dysplastic hips, bow legs, short legs, Legg Calve Perthes; short neck; scoliosis; flared ribs; osteopenia
Eyes	Microphthalmia, microcornea, ptosis, epicanthal folds, strabismus, cataracts	Epiphora (from lacrimal duct stenosis), blepharitis, exudative retinopathy, retinal neovascularization, retinal hemorrhages, entropion, ectropion, cataracts	Small, epicanthal folds, hypertelorism, hypotelorism, strabismus, cataract, glaucoma	Hypertelorism, retinitis pigmentosum, esotropia
Kidney	Ectopic, horseshoe, absent, small, hydronephrosis, hydroureter	—	Horseshoe, duplicated, ectopic, absent	—
Gonads, male	Small testes, infertility, undescended, micropenis	Urethral stricture, phimosis, small testes, undescended testes, meatal stenosis, hypospadias	Undescended testes, hypospadias, inguinal hernia	Atrophic testes, hypospadias
Gonads, female	Small ovaries, bicornuate uterus, late menarche, early menopause, premature ovarian failure, vulvar cancer, breast cancer	Hymenal and urethral stricture	—	—
Pregnancies	Decreased blood counts, fetal loss, pre-eclampsia, failure of labor to progress, cesarean sections, small babies	No apparent problems	Worsening of anemia, fetal loss, pre-eclampsia, intrauterine growth retardation, preterm deliveries, fetal malformations, placental infarcts	—
Development	Developmental delay, retardation	Developmental delay, retardation	Developmental delay, retardation	Developmental delay, neurocognitive deficits, attention deficit
Otology	Abnormal pinna, narrow canal, conductive or sensory hearing loss	Deaf rare	Low set, small, deaf	Decreased hearing
Cardiology	Congenital heart disease, iron overload	Hyperlipidemia	Congenital heart disease, iron overload	Congenital heart disease
Endocrine	Short, diabetes, metabolic syndrome, growth hormone deficiency, osteoporosis, hypothyroid, delayed bone age	Short, bone problems (see skeletal), hypogonadism, elevated cholesterol (on androgens)	Short	Short
Gastroenterology	Imperforate anus, TE fistula, esophageal/duodenal atresia, annular pancreas, gastric emptying delay, poor weight gain, poor feeding, esophageal SCC	Esophageal stenosis, telangiectasias, varices, ulcers, enteropathy (small bowel), enterocolitis (colon), rectal adenocarcinoma	Stomach and colon cancer	Malabsorption due to exocrine pancreatic insufficiency; diarrhea; inguinal hernia

Information is from many sources plus personal experience.[1,11,13,33,41,42,46]

DEB, diepoxybutane; ENT, ear, nose, throat; FISH, fluorescence in situ hybridization; GI, gastrointestinal; MMC, mitomycin C; TE, tracheoesophageal.

Table 1. (continued)

System	FA	DC	DBA	SDS
Liver	Cirrhosis, fibrosis, elevated enzymes, iron overload, androgen toxicity, adenoma, hepatocellular carcinoma, peliosis hepatis	Cirrhosis, fibrosis, hepatocellular carcinoma, hepatopulmonary syndrome, portal hypertension, iron overload	Iron overload, hepatocellular carcinoma	Rare hepatomegaly
Head	Microcephaly	Microcephaly	Microcephaly, hydrocephalus; cleft palate, cleft lip	Microcephaly, macrocephaly, hydrocephaly; cleft palate, cleft lip
Brain	Pituitary stalk interruption, small pituitary, hypopituitarism, absent corpus callosum, cerebellar hypoplasia	Cerebellar hypoplasia, intracranial calcifications	Hypopituitary, Chiari, myelomeningocele	Chiari, cerebellar tonsillar ectopia, hypopituitarism
Dental	Poor hygiene, abnormal tooth development, oral ulcers, gum infections, oral SCC	Caries, tooth loss, periodontitis, taurodontism (enlarged pulp chamber), decreased root/crown ratio, leukoplakia, tongue cancer, lichen planus	—	Caries, oral ulcers
ENT	Head and neck SCC (oral, pharyngeal, hypopharyngeal, laryngeal)	Head and neck SCC	—	—
Immunology	Decreased immunoglobulins, some lymphocyte deficiencies with age	Immunodeficiency of immunoglobulins or lymphopenia in younger children	Essentially normal	Some B- and T-cell deficiencies
Lung	—	Pulmonary fibrosis, pulmonary arteriovenous malformations	—	—
Hair	—	Early gray, early hair loss, sparse eyebrows and eyelashes	—	—
Vascular complications	—	Telangiectases and arteriovenous malformations (retinal, GI, pulmonary)	—	—
Psychiatry		Some psychiatric problems		
Diagnostic screening test	Increased chromosome breakage with DEB or MMC	Decreased telomere length by flow FISH	Increased red cell adenosine deaminase	Decreased pancreatic enzymes (trypsinogen, isoamylase)

Information is from many sources plus personal experience.[1,11,13,33,41,42,46]

DEB, diepoxybutane; ENT, ear, nose, throat; FISH, fluorescence in situ hybridization; GI, gastrointestinal; MMC, mitomycin C; TE, tracheoesophageal.

Table 2. Systems involved in patients with an IBMFS following SCT

System	FA	DC	DBA	SDS
General	Chronic GVHD	Chronic GVHD	Chronic GVHD	Chronic GVHD
Oncology	Head and neck SCC (tongue), vulvar SCC, PTLD, skin	Head and neck SCC (tongue), anogenital SCC, PTLD, skin	Colon, lung, stomach, osteosarcoma	
Skin	Basal cell carcinoma and SCC	Basal cell carcinoma and SCC		
Skeletal	Osteopenia and osteoporosis	Osteopenia and osteoporosis		
Eyes	Cataracts, dry eyes, retinitis, blepharitis	Cataracts, lacrimal duct stenosis	Cataracts	
Gonads, male	Infertility	Infertility	Infertility	Infertility
Gonads, female	Infertility, early menopause	Infertility, early menopause	Infertility, early menopause	Infertility, early menopause
Otology	Sensory hearing loss			
Cardiology	Iron overload	Iron overload, hyperlipidemia	Iron overload	
Endocrine	Diabetes, growth hormone deficiency, hypothyroid, dyslipidemia	Hypogonadism, dyslipidemia		
Gastroenterology	Poor eating	Rectal adenocarcinoma	Stomach and colon cancer	
Liver	Cirrhosis, fibrosis, elevated enzymes, iron overload, adenoma, hepatocellular carcinoma	Cirrhosis, fibrosis, hepatopulmonary syndrome, portal hypertension, iron overload, hepatocellular carcinoma	Iron overload	
Dental	Oral SCC	Oral SCC		
ENT	Head and neck SCC	Head and neck SCC		
Immunology	Slow immune reconstitution	Slow immune reconstitution	Slow immune reconstitution	Slow immune reconstitution
Lung	Bronchiolitis obliterans	Pulmonary fibrosis, pulmonary arteriovenous malformations		
Vascular complications		Telangiectases and arteriovenous malformations		
Psychiatry	Psychosocial issues	Psychosocial issues	Psychosocial issues	Psychosocial issues
Diagnostic test after SCT	Increased chromosome breakage with DEB or MMC, need to use skin fibroblasts	Genotype with nonhematopoietic tissue	Genotype with nonhematopoietic tissue	Decreased pancreatic enzymes (trypsinogen, isoamylase), genotype with nonhematopoietic tissue

Systems listed are those that have been reported in the literature or that are plausible.[11,21,42] Many of these may be associated with aging per se, but have been reported to be worse following SCT.
PTLD, posttransplant lymphoproliferative disease.

Table 3. Types of malignancies reported in untransplanted and transplanted patients

	FA	DC	DBA	SDS
No transplant	HNSCC (tongue)	HNSCC (tongue)	Lung	Leukemia
	Leukemia (AML)	Leukemia (AML)	Colon	MDS
	Gynecologic	Lymphoma (NHL)	Gynecologic	
	Esophagus	Anorectal	Osteogenic sarcoma	
	Brain	Stomach	Leukemia (AML)	
	Breast	Lung	MDS	
	MDS	MDS	Skin BCC	
	Skin SCC	Skin SCC	Skin SCC	
	Skin BCC	Skin BCC		
Transplant	HNSCC (tongue)	HNSCC	PTLD	
	Gynecologic	PTLD	Colorectal	
	PTLD		Osteogenic sarcoma	

Data are from various sources.[11,12,18,22,35,42,43,47]
BCC, basal cell carcinoma; NHL, non-Hodgkin lymphoma.

Nontransplant alternatives to SCT may include medical management such as androgens or future gene therapy.[31,32]

Dyskeratosis congenita

Patients with DC have a variety of presentations, and diagnostic ages range from infancy to older adults. The youngest patients often have cerebellar aplasia, microcephaly, delayed development, and early onset aplastic anemia (the Hoyeraal Hreidarsson variant). Many patients are diagnosed during childhood because of thrombocytopenia or aplastic anemia, whereas older patients may be diagnosed after the development of pulmonary fibrosis or hepatopulmonary syndrome. Patients may also present at atypically early ages with MDS or even AML, or with marrow failure as young adults, and DC needs to be in the differential diagnosis. The phenotypes outlined in Table 1 are thus age dependent and vary according to age and genotype. The pathognomonic findings include the diagnostic triad of dysplastic nails, lacy reticular pigmentation, and oral leukoplakia, which are sufficient but not necessary. Other nonhematologic features are strictures of lacrimal ducts, esophagus, or urethra, gastrointestinal enteropathies, abnormal teeth, early gray hair, and early hair loss.[33]

Clinically important complications that develop with age include avascular necrosis of hips and shoulders, retinal hemorrhages, hyperlipidemia (especially in patients treated with androgens), and hepatic and pulmonary fibrosis. The most serious problems are associated with the pulmonary or liver fibrosis, as well as arteriovenous malformations in the lungs, liver, and gastrointestinal tract,[34] for which there are no easy treatments. In addition, patients with DC share the high risks of malignancies reported in FA.[11,35] We initially found the overall risk of cancer to be 11-fold; recent analysis of our larger cohort resulted in a smaller but still significant risk of about 4-fold.[18] The types of cancers are head and neck (~70-fold) and anogenital SCC (~50-fold) and MDS (~500-fold) and AML (~70-fold), similar sites but not as high relative risks as in FA.[35] The head and neck SCC may not be prevented by HPV vaccination, although the vaccine may have a role in prevention of the anogenital SCCs.[25]

The indications for SCT in patients with DC are similar to those outlined above for FA.[33] Patients with DC may present with or develop MDS or AML and thus may be candidates for SCT. The most frequent indication is marrow failure; some patients respond to androgens, albeit at lower doses than in FA, with risk of abnormal lipids,[36] and with the caveat that they should not also receive granulocyte colony-stimulating factor because of possible splenic peliosis and rupture, which have not been reported in patients with FA.[37] Patients with DC may present with marrow failure prior to the recognition of DC (identified by physical findings, telomere length assay, or genotype). In those cases, SCT from a matched sibling who also turns out to have DC will not succeed.[38] SCT for patients with DC should be done with reduced intensity conditioning (RIC), owing to potential pulmonary toxicity from irradiation or chemotherapy.[39,40]

The major post-SCT late effects in patients with DC involve pulmonary and liver disease (fibrosis) and arteriovenous malformations. These have been reported in untransplanted patients but appear to occur more frequently in transplanted cases. We reported 1 case in which the patient received a lung transplant because of fibrosis, several years after an SCT for aplastic anemia[39]; this patient subsequently died of tongue cancer (Alter and Giri, unpublished observation). Preliminary data suggest that the risk of solid tumors (including skin cancers) is also increased following SCT in DC, as in FA (Tables 2 and 3).[18] In addition, posttransplant osteoporosis may develop, perhaps associated with the use of corticosteroids.

Diamond Blackfan anemia

Patients with DBA are usually diagnosed because of symptoms of anemia in utero, at birth, or within the first year. They may have physical anomalies, such as abnormal thumbs, short stature, and other features described in Table 2. However, unlike FA, in which birth defects may lead to the diagnosis of the syndrome prior to bone marrow failure, the red cell hypoplasia precedes the diagnosis of the syndrome based on the phenotype. Despite the long list of possible congenital anomalies, most patients have few or only subtle physical findings. About 20% of patients with DBA may have an apparently spontaneous remission and become independent of the usual treatment, which is corticosteroids or transfusions.[41]

Age-associated side effects are related to the treatment (chronic steroids) or to liver and cardiac iron overload from the transfusions, despite the use of iron chelators. In some cases, an asymptomatic parent is identified as having a mutation in the same ribosomal gene as his or her affected child. At the other end of the spectrum there are children who remain anemic and for whom SCT is considered. Patients with DBA also have an increased risk of cancer, about 5-fold. The relative risks for individual cancers were 45 for colon cancer, 42 for osteogenic sarcoma, and 29 for AML.[42,43]

Indications for SCT for patients with DBA include failure to respond to corticosteroids and parental or patient preference to avoid potential toxicities from steroids or to avoid chronic transfusions and iron chelation, elimination of which will improve the quality of life. Recommended circumstances include a young patient (below age 10) and a matched sibling donor who does not have clinically or genetically proven DBA.[44] The current recommendation is to use standard myeloablative preparative regimens with fludarbine and busulfan or treosulfan; there are no published data on the use of RIC.[26]

The major problem after SCT is due to the iron overload. There may be long-standing residual damage to the liver and heart from iron accumulated prior to the SCT, as well as from additional transfusions. The usual methods of iron homeostasis include not only chelation but also routine phlebotomy for an extended period, with monitoring by magnetic resonance imaging of heart and liver iron burdens. The other problem in DBA after SCT is the development of malignancies, but the number of these has so far been too low to determine whether the risk is increased by SCT or is the expected risk for age.[43]

Shwachman Diamond syndrome

Patients with SDS are often diagnosed with the combination of exocrine pancreatic insufficiency with malabsorption (often manifest as diarrhea) and neutropenia in infancy, although they may have aplastic anemia, MDS, or AML at older ages.[1,45] They may have low birth weight, short stature, metaphyseal dysostosis, neurocognitive deficits, some immunodeficiency, and other less common findings, as are described in Table 1.[46,47] Pancreatic function may improve with age, whereas marrow failure may progress to aplastic anemia, MDS, or AML. Some patients are diagnosed only by molecular studies of germline DNA after the diagnosis of MDS or AML.[45]

SCT may be recommended for patients with progressive pancytopenia. Frequent clonal cytogenetic results demonstrate i(7)(q10) or del(20)(q). However, neither clone alone progresses to MDS or AML, which may develop if additional unrelated clones appear. Thus SCT should be recommended only for severe cytopenias, MDS, or AML and not just for the benign clones.[48] There are insufficient data to determine whether any new features develop or are worse following SCT.

Summary

The effect of transplantation on adverse events in the major IBMFS is often difficult to quantify and separate from the complications of aging in patients with those syndromes. It appears that solid tumors are increased in FA and DC, but data so far do not permit clearly assigning causality to the preparative regimens (eg, irradiation) or to the inflammatory pathways due to chronic GVHD. Use of collaborative transplant preparative regimens and management of patients during and beyond transplantation will result in evidence-based recommendations for surveillance and treatment of complications, which may be syndrome specific.[10] Vigilance must be directed against the organ sites and systems noted in Table 2, with the focus on cancer in FA; cancer as well as pulmonary, liver, and lipid abnormalities in DC; and iron overload in DBA. The SCT experience in SDS is too small to lead to specific recommendations at this time. Overall, the decision for or against SCT depends on a dialogue between physicians and families, with consideration of the clinical indications, the risks of death, and the post-SCT complications that might affect quality of life different from continuation of current or alternative non-SCT management.

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