

Chapter 11

Late Effects in Fanconi Anemia Patients Post-Transplant

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Introduction

A greater proportion of FA patients are now surviving into adulthood, largely due to major advances in the field of hematopoietic stem cell transplantation (HSCT), particularly donor selection, preparative therapy, graft-versus-host-disease (GvHD) prophylaxis, and supportive care measures. The medical community is now faced with the challenge of optimizing long-term care for these patients through early intervention to prevent late effects. Early intervention must include systematically evaluating FA patients to understand the issues they may face in the future.

Overview

No published studies exist that specifically address late effects in FA patients. However, studies conducted in other populations of patients are instructive, particularly those for patients who have undergone treatment for cancer or have had a HSCT. Guidelines for following childhood cancer survivors have been developed by the Children's Oncology Group (available on-line at <http://www.survivorshipguidelines.org>) and can serve as a foundation for developing a long-term follow-up plan for transplanted FA patients, based on the specific chemotherapy agents and radiation to which they were exposed. In addition, the European Group for Blood

and Marrow Transplantation (EBMT), the Center for International Blood and Marrow Transplant Research (CIBMTR) and the American Society of Blood and Marrow Transplantation (ASBMT) recently developed joint recommendations, which include suggested screening and preventive practices for adult HSCT survivors. Many of these recommendations also apply to FA children after HSCT.¹

Long-term follow-up in FA patients is considerably more complex than for those patients with acquired illnesses later in life. FA patients need lifelong follow-up, including ongoing assessment of adverse effects on physical and mental health, quality of life, growth, development, education, and employment.

As shown in Table 1, the etiology of late effects can be attributed to the underlying diagnosis of FA as well as to the treatment the individual patient has received.

The goal of long-term follow-up is to develop and implement strategies to prevent harmful late effects. Thus, treatment protocols are being modified, where possible, to reduce radiation exposure and to eliminate GvHD, as both play important roles in the development of late effects after HSCT. To assess a patient's exposure to possible late effects, the physician should consider mediating and moderating factors, including the patient's current age, family history, genotype, comorbidities (especially chronic GvHD), past treatments, and environmental issues, and must provide vigilant screening for early detection of late effects. Patients should be encouraged to lead a healthy lifestyle, which should include a healthy diet, regular exercise, avoidance of alcohol, smoking and second-hand smoke, limited sun exposure and use of sunscreen. The physician

Table 1: Etiology of Late Effects**Related to Fanconi Anemia**

- Congenital anomalies: GI tract, heart, kidney, urinary, dental
- Endocrine abnormalities: diabetes, GH deficiency, hypothyroidism
- Reproductive issues: infertility, high-risk pregnancy, early menopause
- Nutritional issues: GI tract anomalies, poor oral intake
- Neurological issues: vision, hearing
- Musculoskeletal issues: hand and arm anomalies, hip dysplasia
- High risk of malignancy
- Genotype/phenotype correlation (*BRCA2*)
- Psychosocial impact of chronic illness

Related to Treatment

- Multiple transfusions: iron overload
- Androgens: liver toxicity, masculinization
- Bone marrow transplant (BMT): toxicity of chemotherapy and radiation, acute and chronic GvHD

should educate the primary caregivers and the families about the risks for late effects and preventative strategies.

Long-Term Follow-up Evaluations

A guideline for long-term follow-up of FA patients is outlined in Table 2 at the conclusion of the chapter. It is written primarily for patients who are at least one year post-transplant and is intended only to guide the physician; it must be tailored to the individual FA patient. The FA patient's primary physician must

discuss planned follow-up with the other physicians involved in the individual's care, including hematologists, bone marrow transplant physicians, and all other subspecialists.

In addition, this guideline can serve as a framework for FA patients who have not yet had a transplant, as these patients have a myriad of potential health issues.

History and physical examination

One of the most important aspects of long-term care of FA patients is a thorough history and physical examination, performed at least annually. Each patient needs a primary care provider to orchestrate the comprehensive care of the patient, obtain consultation when necessary, and ensure appropriate implementation and follow-up.

Hematology

After transplantation, the patient's transplant physician will decide how often bone marrow (BM) tests are needed. In general, BM aspirates and biopsies are performed several times during the first year after transplant and then again at two years after transplant. Subsequent BM examinations are warranted if the patient has mixed chimerism, remains transfusion dependent or if there are concerns about low peripheral blood counts.

Iron overload

An assessment of total body iron should be performed one year after transplant, as most patients have received a significant number of red blood cell transfusions.

Repeated serum ferritin levels may be helpful to monitor a trend, but ferritin is an inaccurate measure of iron burden. Liver biopsy or newer non-invasive magnetic resonance imaging measurements are much more sensitive and specific. Depending on the result, monthly phlebotomy or iron chelation may be necessary. For an

extensive discussion of the management of iron overload, refer to Chapter 3.

Endocrine

Endocrine issues are common in FA patients and require lifelong endocrine evaluation and follow-up.² After HSCT, additional endocrinopathies may develop, including hypothyroidism, growth hormone deficiency, gonadal dysfunction, osteoporosis, and infertility.³ Post-transplant, all patients should receive the endocrine evaluation as outlined in Table 2 as a minimum and undergo annual lifelong endocrine evaluations. Particular attention to age, stage of pubertal development and growth is important to determine timing and extent of the endocrine assessment for the individual.

HSCT can induce osteopenia, osteoporosis, and avascular necrosis of the bone, each of which can be accelerated by cumulative doses of glucocorticoids. A Dual Energy X-ray Absorptiometry (DXA) scan should be performed at one year after transplant. For children <5 years of age, normal comparative values are not available, but the DXA scan can still be used to look for changes over time in these individuals. If the initial DXA scan is abnormal, the decision regarding treatment (vitamin D, calcium, bisphosphonates or other agents) and when to perform follow-up DXA scans should be decided in consultation with the patient's endocrinologist.

Growth and development

Growth and development need to be assessed at least annually. A formal neuropsychology evaluation should be performed for patients at risk, particularly those transplanted before the age of three years.^{1,4} Early intervention to assist in identified problems is mandatory to optimize the patient's development. Although most FA

patients are petite and relatively picky eaters, if growth is suboptimal, both endocrine and nutritional evaluations should be performed to identify potential etiologies. Therapy with growth hormone may be indicated in some patients.

Organ function

Patients with FA may have organ dysfunction stemming from congenital anomalies or from treatments, including the conditioning regimen used in transplantation. Additional late complications after HSCT may arise from chronic GvHD, infections, immune deficiency, and from medications to treat these complications.^{4,6} Therefore, although all patients require an evaluation at one year after transplantation, as outlined in Table 2, the severity and duration of the organ dysfunction will dictate the follow-up, which needs to be determined in consultation with the patients' subspecialists. Further details of specific potential organ dysfunction can be found in the medical literature.^{1,4,5}

Metabolic syndrome

Metabolic syndrome is a constellation of central obesity, insulin resistance, glucose intolerance, dyslipidemia, and hypertension, and is associated with an increased risk for Type 2 diabetes mellitus and atherosclerotic cardiovascular disease. BMT survivors have a higher age and body mass index-adjusted risk of diabetes and hypertension, potentially leading to a higher than expected risk of cardiovascular events with age.^{7,8} Although there are no data to determine the exact risk of metabolic syndrome in FA patients, the risk may be significant as FA patients are inherently more prone to diabetes. Therefore, all FA patients must be monitored for early indications of metabolic syndrome and be encouraged to follow a healthy diet and exercise regimen.

Immunology

Infections remain a major cause of morbidity and mortality in FA patients after HSCT. Immune reconstitution is a gradual process after HSCT; most patients achieve immune recovery 1-2 years after HSCT. However, immune recovery is markedly delayed in patients with GvHD or those receiving immunosuppressive therapy.

At one year after transplant, screening for immune reconstitution should include measuring T-cell subsets and immunoglobulin levels. The primary care physician should discuss the exact timing of starting the immunizations with the patient's transplant physician. If the patient has no active GvHD and is off all immunosuppressive medications, inactive immunizations should be administered starting one year after HSCT, with live virus vaccines delayed until two years after transplant. In addition, all patients and their family household members should receive the influenza vaccine on an annual basis. Only the intramuscular formulation should be administered as intranasal influenza vaccine contains live virus and puts the patient at risk of becoming ill. HPV vaccination should be given to all FA patients beginning at age nine.

Malignancy surveillance

FA patients are at an extraordinary risk for malignancy at an early age and require lifelong surveillance regardless of whether they have undergone a transplant.⁹⁻¹¹ A subset of FA patients are at even higher risk of malignancy, including those with *BRC A2* mutations¹² and those who develop GvHD^{13,14} after transplantation.

Oropharyngeal screening should occur every six months (Chapter 13) after transplant, regardless of the age of the patient. Because of the risk of bacteremia, patients should not have dental cleaning, extraction or

other invasive procedures performed until at least one year after transplantation.

Gynecological examinations and screening for malignancy should occur at least annually once females are 13 years of age (Chapter 6). Breast cancer screening should be initiated by 25 years of age.

Earlier and/or more frequent malignancy screening may be warranted for any issues raised by the patients or primary care physician. As mentioned above, all patients should receive the HPV vaccine beginning at age nine to reduce the risk of HPV-associated malignancies. All FA patients should wear sunscreen to reduce the risk of skin cancer and cutaneous chronic GvHD. Patients with suspicious nevi or other abnormal skin lesions should be examined by a dermatologist.

Patients with biallelic *BRCA2* mutations require at least annual brain MRIs to assess for the development of medulloblastoma. Renal ultrasounds should be performed at least annually in these high-risk individuals to assess for Wilms tumors.¹²

Other medical considerations

The three major ocular complications after transplantation are cataracts, keratoconjunctivitis sicca syndrome (usually associated with GvHD), and ischemic microvascular retinopathy.¹ All patients should be considered for an ophthalmology evaluation one year after HSCT, depending on symptomatology. In addition, patients with signs or symptoms of chronic GvHD should have a Schirmers' test to screen for decreased tear production. Any change in visual acuity should be assessed immediately.

A significant proportion of FA patients have congenital neurosensory auditory deficiencies. All patients should

be considered for audiograms after HSCT as hearing may significantly worsen after exposure to ototoxic medications.

Quality of life

Late effects include the medical needs and the care of the entire person, including neurocognitive deficits, anxiety, depression, social withdrawal, the effects of re-entry into society or school, and insurance problems. These quality of life issues are a vital component in the assessment of long-term health in all FA patients, regardless of age or type of therapy received. In a survey conducted by the University of Minnesota group, parents reported an improved quality of life after transplant as restoration of normal hematopoiesis resulted in fewer physician visits and less worry about risks for bleeding and infections.

Conclusions

Fortunately, advances in the care of FA patients have led to larger numbers of patients who survive for many years post-transplant. The goals are to understand and monitor the late effects that they face as they age, to identify the mediating factors, and to develop strategies to prevent these late effects.

Return Visit Post-Transplant	1 year	2 year	3 year	4 year	5 year	Every year	Every 5 years
History, exam, vital signs	X	X	X	X	X	X	X
Hematology							
CBC with differential	X	X	X	X	X		X
Bone marrow aspirate/biopsy with chimerism, cytogenetics ^a	X	X					
Ferritin plus total body iron assessment ^b	X	R	R	R	R		X
Endocrine							
Oral glucose tolerance test (OGTT)	X	X	X	X	X	X	X
Free T4, TSH	X	X	X	X	X	X	X
LH/FSH (females ≥ 10 yr, males ≥ 11 yr) ^c	X	X	X	X	X		C
Ultrasensitive Estradiol (females ≥ 10 yr) ^c	X	X	X	X	X		C
Testosterone [†] (males ≥ 11 yr) ^c	X	X	X	X	X		C
IGF-1, IGFBP-3 (<18 yr)	X	X	X	X	X		C
25-OH vitamin D, calcium	X	X	X	X	X	X	X
Bone age (5-18 yr)	X	X	X	X	X	X	
DXA Scan (≥ 5 yr) ^c	X	R	R	R	R	R	X ^d
Growth and Development							
Height and weight	X	X	X	X	X	X	X
Growth chart (<18 yr)	X	X	X	X	X	X	X
Neuropsychology evaluation ^c	X	C	C	C	C		C
Cardiology							
Lipid profile (fasting)	X				X		X
ECHO	X	R	R	R	X		X
EKG	X	R	R	R	X		

Return Visit Post-Transplant	1 year	2 year	3 year	4 year	5 year	Every year	Every 5 years
Pulmonary							
Pulmonary function tests with DLCO (carbon monoxide diffusing capacity)	X	R	R	R	X		C
Hepatic Function							
ALT, AST, bilirubin, Alkaline Phosphatase, Albumin	X	X	X	X	X		
Hep B sAg, Hep B sAb, Hep C Ab	X				C		
Renal							
BUN, Cr, Urinalysis	X	X	X	X	X		X
Immunology							
T-cell subset	X						
Ig G, A, M, E	X	R	R	R	R		R
Immunizations including HPV ^f	X	X					
ENT	X	X	X	X	X	X	
Dental every 6 months	X	X	X	X	X	X	
Gynecology (females ≥13 yr)	X	X	X	X	X	X	
Dermatology	C	C				C	
Audiology	C	C			C		C
Ophthalmology	C	C			C		C
If <i>BRC42</i>, head MRI, renal ultrasound	X	X	X	X	X	X	
Quality of life assessment	X	X			X		X

X = to be done.

C = consider; check with MD.

R = repeat if previously abnormal.

†Repeat annually until full pubertal development achieved.

^aIf mixed chimerism, follow BM ± PB chimerism beyond two years.

^bSee text for details; if high, consider phlebotomy or chelation.

^cAssess at puberty if not already being performed.

^dWhen >18 years of age.

^eIf considered high risk, e.g., <36 mo. at time of HSCT.

^fAs per individual's transplant center.

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