Chapter 12: Long-Term Follow-Up After Transplantation

Good to Know

Hematopoietic stem cell transplantation, also called bone marrow transplantation, is performed to treat the blood disorders that often occur in patients with FA.

These disorders may include aplastic anemia (bone marrow failure), myelodysplastic syndrome (improper and insufficient blood cell formation), and a type of cancer known as acute myelogenous leukemia.

Introduction

Patients with Fanconi anemia (FA) who undergo hematopoietic stem cell transplantation (HSCT) face much brighter prospects today than in years past, thanks to major advances in donor matching, supportive care, treatments that prepare the patient's body for transplantation, procedures that prevent the patient's immune system from rejecting the transplanted cells, and procedures that remove or modify immune cells known as T-cells from the donated bone marrow prior to transplantation.

For patients, a successful transplant is a major milestone. However, it must be thought of as a first step. The next step, known as the continuation phase, is of the utmost importance; it is absolutely critical that the patient receives appropriate and systematic long-term follow-up during this phase.

This chapter will describe the importance of long-term follow-up care, potential adverse effects in patients with FA who have undergone HSCT, and the key elements of a long-term follow-up plan.

The Importance of Long-Term Follow-Up Care

Long-term follow-up of patients with FA is *essential*. It must be thought of as an indispensible part of the patient's routine medical care. Failure to complete long-term follow-up may lead to complications that potentially could have been avoided.

Guidelines for the long-term care of survivors of childhood cancer have been developed by the Children's Oncology Group (*available at:* http://www.survivorshipguidelines.org). 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 (*available at:* http://www.nature.com/bmt/journal/v37/n3/pdf/1705243a.pdf) which include suggested screening and preventive practices for adult survivors of HSCT. Many of these recommendations also apply to patients with FA who have undergone HSCT.

The long-term follow-up for patients with FA is considerably more complex than the long-term follow-up for patients with acquired illnesses. Patients with FA require lifelong care for FA and other potential complications caused by FA-associated blood disorders (e.g., aplastic anemia, myelodysplastic syndrome, and leukemia), HSCT, or treatments received prior to HSCT. All of these conditions can cause adverse effects (Table 1) that may negatively impact the patient's physical and mental health, quality of life, growth, development, education, and employment. Therefore, the development of long-term adverse effects must be assessed on an ongoing basis [1-10].

Table 1. Possible long-term adverse effects and their causes in patients with FA.

Organ or system affected	Adverse effects	Causes
General	Short stature	FA
	Primary or secondary malignancies	FA, HSCT, GvHD
Skin	Pigmentation	FA, GvHD
	Dryness	FA, GvHD
	Thickening	FA, GvHD
Central nervous system	Side effects of radiation	HSCT
Eyes	Cataracts	HSCT
	Extremely dry eyes (Sicca, or Sjögren's, syndrome)	GvHD
	Retinitis	HSCT
Ears, nose, and throat	Chronic sinusitis	GvHD
	Hearing loss	FA
	Extremely dry mouth (Sicca, or Sjögren's, syndrome)	GvHD
Heart	Congenital anomalies	FA
	Iron overload	FA treatment
Lungs	Side effects of HSCT	GvHD
Liver	Chronic liver disease (transaminitis or cholestasis)	HSCT, GvHD
	Iron overload	FA treatment
Kidneys and genitourinary system	Congenital anomalies	FA
	Chronic renal insufficiency	HSCT
GI tract	Congenital anomalies	FA
	Failure to thrive	FA, GvHD
Endocrine	Diabetes	FA
	Hypothyroidism	FA, HSCT
Gonadal	Masculinization	FA treatment
	Infertility	FA, HSCT
	Early menopause	FA, HSCT
Musculoskeletal	Hand and arm anomalies	FA
	Hip dysplasia	FA
Psychological	Psychosocial issues	FA, HSCT

Abbreviations: Fanconi anemia, FA; hematopoietic stem cell transplantation, HSCT; graft-versus-host disease, GvHD

Practical Considerations for Long-Term Follow-Up Care

Long-term follow-up care must be led by one specific physician who has experience with both FA and HSCT, such as the **transplant physician** or the **primary hematologist**. The overall long-term follow-up care can be performed with the help of the patient's local physicians and subspecialists if those clinicians have experience with FA and HSCT. The patient's medical team should work in close collaboration to provide comprehensive care. The involvement of multiple types of care providers in the care of patients with FA introduces the risk that medications prescribed by one physician might adversely interact with those prescribed by another. Therefore, it is essential that all subspecialists communicate with the primary physician, usually the hematologist/oncologist, to coordinate care.

Long-term follow-up care of patients with FA who have undergone transplantation should strive to:

- ***Identify existing adverse effects,*** and treat them efficiently to prevent further complications. For example, it is important to diagnose hemochromatosis (iron overload), which can lead to chronic liver disease if left untreated.
- ***Proactively screen for adverse effects*** so that if they develop, they can be diagnosed early and treated accordingly. In particular, screening for primary or secondary cancers is of the utmost importance.
- ***Prevent the development of adverse effects*** that may result in additional complications. For example, patients should be counseled to avoid sun exposure, because it could result in malignancies.

The long-term follow-up plan should include the following elements:

Regular check-ups

- Assess patient's history since the previous visit
- Assess the adverse effects of FA or HSCT on the patient's organs and systems
- Perform a physical examination, with close attention to the adverse effects of FA and HSCT

Evaluation of growth and development [11,12]

- Assess the patient's height and weight; measure growth hormone levels and refer to a growth specialist if needed
- Perform a neuropsychological evaluation; suggest interventions if needed

Evaluation of skin

- Evaluate nevi (birthmarks and moles) and screen for skin cancers yearly
- A HSCT specialist should perform testing to rule out graft-versus-host disease (GvHD) if needed

Neurological and psychological evaluations [13]

- Perform a neuropsychological evaluation
- Perform a psychological evaluation to screen for psychosocial issues related to living with a chronic disease, late effects of androgen therapy, and post-traumatic stress syndrome

Ophthalmologic (eye) evaluation [14,15]

- Screen for cataracts
- Screen for Sicca, or Sjögren's, syndrome (extremely dry eyes, caused by GvHD) and keratoconjunctivitis (inflammation of the eyes)
- Evaluate the patient's vision

Evaluation of ears, nose, and throat [16, 17]

- Screen for hearing loss after HSCT
- Screen for FA-associated neurosensory hearing loss
- Screen for Sicca, or Sjögren's, syndrome (extremely dry mouth, caused by GvHD)
- A head and neck specialist should screen for head and neck malignancies (every 6 months)
- Perform testing to rule out chronic sinusitis

Dental exam [18]

- Screen the oral cavity carefully every 6 months (see *Chapter 10*)

Cardiac (heart) evaluation [19]

- Evaluate FA-associated anomalies
- Screen for late effects of radiation or chemotherapy by electrocardiogram (EKG) and echocardiogram

Pulmonary (lung) evaluation [20, 21]

- Test pulmonary function to rule out obstructive or restrictive disease
- Screen for late effects of radiation or chemotherapy
- Screen for bronchiolitis obliterans with organizing pneumonia (BOOP)

Gastrointestinal and nutrition evaluation

- Monitor nutrition, food intake, and weight gain
- Perform testing to rule out FA-associated failure to thrive
- Perform testing to rule out chronic GvHD

Hepatic (liver) evaluation [22]

- Screen for overall FA-associated anomalies, including chronic transaminitis
- Screen for anomalies associated with treatment of FA (after androgen therapy has ceased), including transaminitis
- Screen for iron overload by measuring ferritin levels; perform T2*MRI (magnetic resonance imaging) if needed
- Screen for chronic cholestasis and chronic GvHD
- Evaluate need for liver biopsy

Renal (kidney) evaluation

- Assess overall kidney function
- Screen for late effects of chemotherapy and radiation therapy

Genitourinary evaluation

- Follow-up of congenital renal or genitourinary anomalies with a urologist
- Yearly gynecologic evaluation for females, including Pap smear (the recommendations for Pap smear have changed for individuals in the general, non-FA population, raising questions about the right frequency for either post-HSCT or FA patients)
- HPV (human papillomavirus) vaccination

Evaluation of endocrine system and metabolism [23-27]

- Screen for FA- and/or HSCT-associated anomalies
- Screen for hypothyroidism and thyroid malignancies
- Screen for growth hormone deficiency (if the patient has a short stature)
- Screen for diabetes, including tests for insulin resistance and glucose intolerance
- Screen for dyslipidemia
- Screen for osteoporosis and osteopenia
- Screen for avascular necrosis
- Test for vitamin D deficiency and biochemical rickets (abnormal labs without signs)

Gonadal evaluation [28, 29]

- Monitor pubertal development
- For male patients: measure levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone; evaluate sperm; prescribe hormonal replacement therapy as needed
- For female patients: measure levels of FSH, LH and estradiol; prescribe hormonal replacement therapy as needed
- Counsel about sex and pregnancy

Musculoskeletal evaluation

- Follow-up of FA-associated congenital anomalies
- Evaluation of scoliosis (curvature of the spine)
- Screening for contractures (tightening of muscle, tendon, ligaments, or skin that prevents movement) associated with chronic GvHD

Hematology (blood) evaluation [4]

- Evaluate complete blood count
- Evaluate bone marrow
- Chimerism testing (to evaluate the success of HSCT): This test measures the percent of donor versus host cells in the blood or the bone marrow
- Assess iron and ferritin levels; if needed, perform T2*MRI for more precise iron level; discuss treatment recommendations

Immunology evaluation [4, 30]

- Monitor the restoration of immune function, including assessments of the phenotype (observable characteristics) and function of T- and B-cells (cells involved in innate and acquired immunity)
- Administer immunizations
- Assess titers and response to vaccines
- Revaccinate for high-risk infections, including pneumococcus, *Haemophilus influenzae* type B (HIB), meningococcus, and influenza
- Vaccinate with HPV vaccine in patients older than 9 years; revaccinate patients after HSCT
- Revaccinate for other infectious diseases, such as tetanus and diphtheria

Malignancy surveillance [31]

- Perform strict lifelong surveillance for cancers of the oropharynx, anogenital area, and skin, with close attention to patients with mutations in the *BRCA2* gene (which can increase the risk for multiple secondary cancers) and patients with GvHD

Quality of life evaluation [32, 33]

- Counsel patients about the need to adopt a healthy diet; get regular exercise; avoid alcohol, smoking, and second-hand smoke; limit sun exposure; and use sunscreen
- Perform neuropsychological and psychological evaluations and counseling as needed for patients and their families

A guideline for the long-term follow-up of patients with FA is outlined in Table 2. It outlines the evaluations that patients with FA should receive starting at least 1 year after transplant, and is intended as a general guide for physicians; care must be tailored to each individual patient with FA.

Table 2. Long-term follow-up evaluations for post transplant patients with FA.

	1 year	2 year	3 year	4 year	5 year	Yearly
Regular check-ups, including patient history and physical exam	X	X	X	X	X	X
HEMATOLOGY						
Complete blood counts	X	X	X	X	X	X
Bone marrow aspiration Chimerism testing Cytogenetics studies	X	X	X			
Measure levels of ferritin and iron Perform T2*MRI if ferritin levels are high	X	Repeat if previous test was abnormal	Repeat if previous test was abnormal	Repeat if previous test was abnormal	Repeat if previous test was abnormal	
IMMUNOLOGY						
Assess immune phenotype and function	X	Repeat if previous test was abnormal	Repeat if previous test was abnormal			
Measure levels of immunoglobulins G, A, and M	X	Repeat if previous test was abnormal	Repeat if previous test was abnormal	Repeat if previous test was abnormal	Repeat if previous test was abnormal	
Administer immunizations (including HPV vaccine)	X	As per schedule				Administer boosters as needed
CARDIAC						
Measure fasting lipid profile (levels of total cholesterol, LDL, HDL, and triglycerides)	X	Repeat if previous test was abnormal	X	Repeat if previous test was abnormal	X	Repeat if previous test was abnormal
EKG	X	Repeat if previous test was abnormal	Repeat if previous test was abnormal	Repeat if previous test was abnormal	X	Repeat if previous test was abnormal
Echocardiogram	X	Repeat if previous test was abnormal	Repeat if previous test was abnormal	Repeat if previous test was abnormal	X	Repeat if previous test was abnormal

	1 year	2 year	3 year	4 year	5 year	Yearly
PULMONARY						
Perform pulmonary function testing to rule out obstructive or restrictive disease	X	Repeat if previous test was abnormal	Repeat if previous test was abnormal	Repeat if previous test was abnormal	X	
HEPATIC						
Measure liver function panel	X	X	X	X	X	X
If liver function panel values are high: Perform MRI Evaluate the need for liver biopsy	Only if previous test was abnormal					
Measure levels of ferritin and iron Perform T2*MRI if ferritin levels are high	X	Repeat if previous test was abnormal	Repeat if previous test was abnormal	Repeat if previous test was abnormal	Repeat if previous test was abnormal	
RENAL						
Measure levels of electrolytes, BUN, and creatinine in the urine	X	X	X	X	X	X
Perform urinalysis	X		X		X	
ENDOCRINE and METABOLISM						
Perform an oral glucose tolerance test (OGTT)	X	X	X	X	X	X
Measure levels of TSH and FT4	X	X	X	X	X	X
Measure levels of FSH and LH in patients younger than 10 years Measure estradiol levels in female patients older than 10 years Measure testosterone levels in male patients older than 11 years	X	X	X	X	X	As needed
Measure levels of IGF-1 and IGFBP3 in patients younger than 18 years	X	X	X	X	X	

Table 2 continued on next page.

	1 year	2 year	3 year	4 year	5 year	Yearly
Measure levels of 25-OH vitamin D and calcium	X	X	X	X	X	X
Assess bone age in patients between the ages of 5 and 18 years	X	X	X	X	X	
DXA scan (with adjustment for height; see *Chapter 7*)	X	As needed	As needed	As needed	As needed	As needed
GROWTH and DEVELOPMENT						
Plot patient's height and weight on a growth chart	X	X	X	X	X	X
Neuropsychological evaluation	X	As needed	As needed	As needed	As needed	
HEAD and NECK						
Ophthalmology evaluation	X	As needed	As needed	X	X	As needed
Screen for head and neck cancers (performed by a head and neck specialist)	Every 6 months	Every 6 months	Every 6 months	Every 6 months	Every 6 months	Every 6 months
Hearing evaluation	X		As needed		As needed	
Biannual dental evaluations	Every 6 months	Every 6 months	Every 6 months	Every 6 months	Every 6 months	Every 6 months
GYNECOLOGIC						
General gynecologic evaluation and cancer screening in female patients older than 13 years	X	X	X	X	X	X
DERMATOLOGY						
Evaluate nevi (birthmarks and moles) and check for skin cancers	X	X	X	X	X	X

Abbreviations: Magnetic resonance imaging, MRI; human papillomavirus, HPV; low-density lipoprotein, LDL; high-density lipoprotein, HDL; electrocardiogram, EKG; blood urea nitrogen, BUN; thyroid-stimulating hormone, TSH; free thyroxine, FT4; follicle-stimulating hormone, FSH; luteinizing hormone, LH; insulin-like growth factor, IGF-1; IGF-binding protein, IGFBP3; 25-hydroxy-vitamin D, 25-OH vitamin D; dual X-ray absorptiometry, DXA

Conclusions

Long-term follow-up care is essential in patients with FA who have undergone HSCT. Failure to complete long-term follow-up may lead to avoidable complications. One specific physician who has experience with both FA and HSCT must lead the long-term follow-up. Follow-up care can be performed with the help of the patient's local physicians and subspecialists if those individuals have experience with FA and HSCT.

Chapter Committee

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