Chapter 3. Clinical Care of Fanconi Anemia Hematologic Issues

Introduction

Patients with Fanconi anemia (FA) develop hematologic complications primarily related to bone marrow failure (BMF), but they are also at increased risk of developing myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). Bone marrow failure and hematologic dysplasia in patients with FA have been attributed to a faulty DNA repair pathway that damages hematopoietic stem and progenitor cells (see Chapter 1). This chapter provides an overview of the hematologic care of patients with FA, including general guidelines for clinical monitoring and the decision process for determining the need for hematopoietic cell transplantation (HCT), the only proven curative treatment for FA hematologic disease [1]. Alternative therapeutic options beyond HCT, such as gene therapy, also are discussed. Medical decisions regarding the hematologic care of patients with FA should be made in consultation with an FA physician specialist.

Bone Marrow Failure

Bone marrow failure (BMF) in patients with FA can range from mild, asymptomatic cytopenia to severe aplastic anemia (AA). The absence of BMF, however, does not exclude the diagnosis of FA [2-3].

Definition of Bone Marrow Failure

Bone marrow failure is diagnosed by blood counts that are below standard age-appropriate ranges, often accompanied by macrocytosis. While many patients progress to AA, hematologic disease in patients with FA can vary widely, and some patients maintain mildly abnormal blood counts for years or even decades. Bone marrow failure is classified into three broad categories, depending on the degree of cytopenia observed (see Table 1). The classification defines points at which different clinical management options should be considered. Importantly, to meet these criteria for BMF, the cytopenia must be persistent and not transient or secondary to another treatable cause, such as infection, medication, peripheral blood cell destruction or loss, or nutritional deficiencies. The lowest value of the three cell lineages defines the severity of cytopenia.

Table 1. Severity of bone marrow failure.

Peripheral blood parameters	Mild	Moderate (or hypoplastic or aplastic anemia)	Severe (or severe aplastic anemia)
Absolute neutrophil count	< 1,500/mm^3	< 1,000/mm^3	< 500/mm^3
Platelet count	50,000-150,000/mm^3	< 50,000/mm^3	< 20,000/mm^3
Hemoglobin	≥ 8 g/dL*	< 8 g/dL	< 8 g/dL

*Less than normal for age but ≥ 8 g/dL.

Sources: references [2-3].

Age of Onset of Bone Marrow Failure

The age of onset of BMF in patients with FA is highly variable. However, the majority of patients develop evidence of at least mild BMF within the first decade of life, at a mean age of 7.6 years [3-6]. Thrombocytopenia is the cytopenia that most commonly leads to the diagnosis of FA. It is typically accompanied by red blood cell macrocytosis. More than 90% of patients with FA will have macrocytosis beginning in infancy or childhood. When a patient is diagnosed with FA, comprehensive hematologic evaluation under the direction of an FA physician specialist is necessary to rule out causes of cytopenia other than primary BMF.

Clinical Monitoring of Bone Marrow Failure

Clinical surveillance and therapeutic management are guided by the following:

- Severity of cytopenia
- Peripheral blood count trends
- Presence or development of morphologic (dysplastic) and cytogenetic bone marrow abnormalities
- Presence of potentially high-risk genotypes (see Chapter 2)

At the time of diagnosis, patients with FA should undergo a trephine unilateral bone marrow biopsy to evaluate bone marrow cellularity and architecture. Bone marrow aspiration should also be performed to assess morphology for dysplastic changes and to evaluate cytogenetics for abnormalities common to FA and myelodysplastic syndrome (MDS) (see Chapter 2). If a child is diagnosed in infancy and has normal blood counts, many clinicians will defer initial bone marrow testing until 2 years of age or later because

of the low likelihood of hematologic issues in early life. Thereafter, the frequency of evaluations is guided by the patient's clinical status and recommendations of a local FA physician specialist. Bone marrow testing should be performed by an FA physician specialist, with interpretation conducted by an experienced hematopathologist.

Recommendations for Clinical Monitoring of Bone Marrow Failure

- Peripheral blood counts, including white blood cell differentials, should be reviewed at least every 3-4 months. More frequent evaluation is recommended for patients with unexplained rising blood counts, severe cytopenia, or high-risk clonal cytogenetic anomalies. Patients with normal peripheral blood counts at diagnosis should undergo full blood count testing every 6 months [7].
- Bone marrow biopsy and aspiration with detailed testing, including cytogenetics (see Chapter 2), should be performed at least annually, with some patients requiring more frequent monitoring.
- The possibility of HCT intervention should be discussed and planned for early in the disease course, as adverse clonal progression or worsening BMF may evolve rapidly. This often includes early consultation with a physician specialist in FA, human leukocyte antigen *(*HLA)-typing of the patient, FA testing and HLA-typing of family members, and review of donor registries for potential donors.

Clonal Evolution

Patients with Fanconi anemia (FA) have a significantly elevated risk of clonal disease evolution, and myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML) can occur in the context of bone marrow failure (BMF) or in patients with normal blood counts [8].

Clonal Abnormalities

The purpose of serial bone marrow examination and cytogenetic analysis is to identify clonal evolution to MDS or AML in the context of peripheral blood count changes or physical examination findings. Despite the presence of clonal abnormalities, some patients may have stable hematopoiesis and a relatively favorable long-term prognosis, while other patients may be at high risk for rapid progression to MDS or leukemia. Regular bone marrow examinations with detailed testing before blood counts change offer the best opportunity for early diagnosis of marrow progression and time to discuss treatment options. The interpretation of specific chromosomal abnormalities indicative of clonal

progression to MDS or AML is discussed in detail in Chapter 2. The decision regarding how to proceed with treatment should be made in consultation with an FA physician specialist. In addition to karyotype analysis to screen for chromosomal abnormalities, many centers now employ next-generation sequencing to screen for clinically significant myeloid molecular alterations suggestive of clonal evolution. Additionally, in some circumstances, patients with FA develop reversion of a germline *FANC* mutation in a hematopoietic cell that promotes a proliferative advantage, leading to somatic mosaicism (see Chapter 2). This unique situation also warrants discussion with an FA physician specialist.

Treatment Guidelines for Patients with Myelodysplastic Syndrome or Acute Myeloid Leukemia

Hematopoietic cell transplantation (HCT) offers the only curative therapy for MDS or leukemia, and treatment should be conducted at centers experienced with FA. As chemotherapy prior to HCT may cause severe, prolonged, or even irreversible myelosuppression in patients with FA, it should not be initiated until a potential stem cell donor has been identified, if possible. For patients who present with MDS or AML at the time of FA diagnosis, low-intensity chemotherapy may be used in preparation for transplantation. Published reports of chemotherapy regimens for AML in patients with FA are sparse and limited by a lack of longitudinal follow-up. It remains unclear whether chemotherapy prior to transplantation improves or worsens outcomes [9].

Management Options for Hematopoietic Disease

Minimizing Transfusion Support

The onset of cytopenia in patients with Fanconi anemia (FA) is typically insidious. Peripheral blood counts should be monitored closely so that treatment (specifically, hematopoietic cell transplantation [HCT]) may be instituted before transfusions are required. Treatment of anemia should be considered when the hemoglobin level is consistently below 7 g/dL or the patient has heart or lung disease requiring higher hemoglobin. Treatment of thrombocytopenia and neutropenia should be considered for platelet counts consistently less than 10,000/mm^3 and absolute neutrophil counts consistently less than 500/mm^3, respectively. Transfusions should be avoided, if possible, to maximize the success of HCT; however, they should not be withheld if the blood counts are dangerously low. Additionally, long-term transfusions with red blood cells and platelets may become a lifeline for patients for whom HCT is

not possible. All transfused products should be irradiated and cytomegalovirus-negative. Antibacterial and antifungal prophylaxis also should be considered in neutropenic patients.

Hematopoietic Cell Transplantation

The only curative option for bone marrow failure (BMF), myelodysplastic syndrome (MDS), or acute myeloid leukemia (AML) in patients with FA is HCT. Survival outcomes following HCT have dramatically improved for patients with FA primarily because of earlier referral for HCT prior to the onset of MDS or AML, refinements in treatment plans, human leukocyte antigen-matching between patients and donors, and better supportive care before, during, and after HCT. Various sources of donor stem cells can be used, including bone marrow, mobilized peripheral blood, and umbilical cord blood. Decisions regarding donor and conditioning options should be made by an FA physician specialist, in discussion with the patient and their family.

Recent Advances in Hematopoietic Cell Transplantation

- Results after HCT for adult patients have improved in recent decades, especially for patients undergoing transplantation during the aplastic phase [7, 10-11].
- It is essential that patients undergo HCT at an FA center of excellence or an institution specializing in the care of patients with FA.
- Survival rates after HCT continue to improve for patients with HLA-matched siblings, as well as for those with alternative donors [12].
- T-cell depletion has improved outcomes by decreasing the risk of graft-versus-host disease (GvHD), especially when an unaffected HLA-matched sibling donor is not available and an alternative donor is used.
- Reduced-intensity conditioning is now recommended, and HCT regimens that do not require radiation are successful under certain conditions.

Patients with FA have an increased risk of cancer following HCT if chronic or acute GvHD occurs and if genotoxic conditioning or radiation were used as part of the treatment regimen [1]. Various strategies are being used to reduce the likelihood of developing GvHD, including improved donor HLA-matching and T-cell depletion. T-cell depletion can be accomplished using ex-vivo graft manipulation (e.g., $CD34^+$ cell enrichment and $TCRaB^+$ T-cell depletion) or in vivo strategies (e.g., post-transplantation cyclophosphamide and serotherapy). Additionally, radiation-free conditioning protocols using reduced-dose busulfan and anti-CD117 antibodies are being explored. Long-term follow-up after HCT at an FA

center of excellence or an institution that specializes in the care of patients with FA is essential for lifelong monitoring.

Indications for Hematopoietic Cell Transplantation

The eligibility criteria for considering sibling or alternative donor HCT are as follows:

- Severe aplastic anemia (hemoglobin consistently < 8 g/dL or absolute neutrophil count consistently < 500/mm^3 or platelet count consistently < 20,000/mm^3)
- Advanced MDS or AML
- Suitable donor [8-9]

Long-Term Follow-Up Care after Hematopoietic Cell Transplantation

Long-term follow-up after hematopoietic cell transplantation (HCT) must be viewed as an indispensable part of routine medical care for patients with Fanconi anemia (FA). Guidelines for the long-term care of survivors of childhood cancer have been developed by the Children's Oncology Group [13]. In addition, the American Society of Blood and Marrow Transplantation, the European Group for Blood and Marrow Transplantation, and the Center for International Blood and Marrow Transplant Research recently developed joint recommendations, which include suggested screening and preventive practices for adult survivors of HCT [14]. Many of these recommendations apply to patients with FA who have undergone HCT.

All patients treated with HCT, including those with FA, are subject to health complications known as "late effects," which may develop long after the procedure. These adverse effects include late graft failure, as well as recurrent acute and chronic graft-versus-host disease (GvHD) and secondary malignancies. Other late effects after HCT, such as short stature and sterility, have not been formally evaluated in patients with FA since these can be pre-existing problems. Late effects of HCT can negatively impact the patient's physical and mental health, quality of life, growth, development, education, and employment (Table 2). Therefore, patients should be monitored regularly for the development of these effects [15-23].

Table 2. Possible long-term adverse effects of Fanconi anemia or hematopoietic cell transplantation.

Organ or system	Adverse effects
General	Short stature
	Primary or secondary cancers
Skin	Variable pigmentation
	Dryness
	Thickening
Eyes	Cataracts
	Dry eyes
Ears, nose, and throat	Chronic sinusitis
	Hearing loss
	Dry mouth
Heart	Congenital anomalies
	Iron overload
Lungs	Pulmonary scarring
Liver	Chronic liver disease
	Iron overload from transfusions
Kidneys and genitourinary system	Congenital anomalies
	Chronic renal insufficiency
Gastrointestinal tract*	Congenital anomalies
	Failure to thrive
	Functional problems (e.g., malabsorption)
Endocrine	Diabetes
	Hypothyroidism
Gonadal	Masculinization from androgen therapy
	Infertility
	Early menopause
Musculoskeletal	Hand and arm anomalies
	Hip anomalies
Psychological	Psychosocial issues (e.g., anxiety, depression)
Systemic	Malignancies†

Sources: references [15-23].

*Beginning at approximately 10 years of age.

†May be due to the underlying Fanconi anemia or triggered or accelerated by hematopoietic cell transplantation (see Chapters 4 and 5).

Practical Considerations for Long-Term Follow-Up Care

General guidelines for pre-HCT evaluation and long-term follow-up of all patients with FA (regardless of HCT status) are outlined in Tables 3 and 4 [15, 24-28]. Long-term care plans should be tailored to the

specific needs of each patient under the supervision of a long-term care team consisting of the HCT physician, primary hematologist, and a multidisciplinary team of specialists at an FA center of excellence or an institution that specializes in the care of patients with FA. Furthermore, patients with biallelic *FANCD1*/*BRCA2* mutations should undergo more extensive evaluation (i.e., annual brain magnetic resonance imaging and renal ultrasound monitoring) and be followed by an FA physician specialist.

Table 3. Pre-hematopoietic cell transplantation evaluation guidelines for patients with Fanconi anemia.

Physical exam and history: Obtain a complete patient and family history and perform a detailed physical examination.
Multidisciplinary evaluation: Conduct visual, hearing, endocrine, nutritional, and neuropsychological evaluations in all patients. Perform a thorough oral examination (by a dentist) and detailed skin examination. Perform other evaluations as needed, such as gastrointestinal endoscopy or nasolaryngoscopy screening.
Hematologic evaluation: Determine the disease phase (single or multilineage cytopenias, MDS, AML). Check CBC, fetal hemoglobin, α-fetoprotein, bone marrow aspirate and biopsy, cytogenetics, flow cytometry, and FISH for chromosomes 3 and 7.
Previous transfusions (risk of iron overload): Check number of transfusions, chelation history, and ferritin levels. Consider T2*-weighted MRI to assess iron overload of the liver or heart. Check for alloimmunization and the presence of DSA.
Prior use of androgens: Describe the type, duration, and dose. Check for signs of virilization, growth problems, and liver dysfunction. Check abdominal ultrasound, liver function, lipid metabolism, and bone age.
Prior use of glucocorticoids: Describe the type, duration, and dose. Check for signs of Cushing's syndrome (hyperglycemia, hypertension, metabolic syndrome, avascular necrosis) and adrenal insufficiency.
Adult evaluation: Focus special attention on genitourinary and gynecologic issues. Address fertility and options available for pre-HCT cryopreservation. Early detection via cancer screening is crucial for all patients with FA (see Chapters 4, 5, and 7).
Lifestyle issues: Recommend complete abstinence from smoking and alcohol, good oral hygiene, sunscreen use, healthy diet, and exercise.
Evaluate congenital abnormalities (e.g., head, heart, skeletal, genitourinary, gastrointestinal).
Evaluate central nervous system (brain): Obtain MRI for children with multiple defects (to evaluate the pituitary gland).
Evaluate endocrine problems: Identify short stature, elevated glucose, and abnormalities of thyroid function, gonadal function, or lipid metabolism.
Post-pubertal patients: Evaluate fertility.

Sources: references [15, 24-28].

AML, acute myeloid leukemia; CBC, complete blood count; DSA, donor-specific antibodies; FA, Fanconi anemia; FISH, fluorescence in situ hybridization; MDS, myelodysplastic syndrome; MRI, magnetic resonance imaging.

Table 4. General and post-hematopoietic cell transplantation long-term follow-up guidelines for patients with Fanconi anemia.

Recommendations for evaluation	Year 1	Year 2	Year 3	Year 4	Year 5	After 5 years
Regular check-ups (including history and physical examination)	X	X	X	X	X	Yearly
Patient recommendation to maintain a healthy diet, regular exercise, good oral hygiene, and use of sunscreen	X	X	X	X	X	Yearly
Patient recommendation to completely abstain from alcohol and smoking (including vaping)	X	X	X	X	X	Yearly
HEMATOLOGY						
Complete blood count	X	X	X	X	X	Yearly
Bone marrow aspiration (including chimerism testing and cytogenetic studies)	If clinically indicated	If clinically indicated	If clinically indicated	If clinically indicated	If clinically indicated	
Ferritin and iron levels (perform T2*-weighted 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						
Immune phenotype and function	X	Repeat if previous test was abnormal	Repeat if previous test was abnormal			
IgG, IgA, and IgM levels	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	
Immunizations (including HPV vaccine)	X	As per schedule				Administer boosters as needed
CARDIAC						
Fasting lipid profile (including total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides)	X	Repeat if previous test was abnormal	X	Repeat if previous test was abnormal	X	Repeat if previous test was normal
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 normal
Echocardiography	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 normal

	Year 1	Year 2	Year 3	Year 4	Year 5	After 5 years
PULMONARY						
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	
GASTROINTESTINAL						
Colonoscopy (yearly, starting at age 30 years)	If age ≥ 30 years	If age ≥ 30 years	If age ≥ 30 years	If age ≥ 30 years	If age ≥ 30 years	Yearly, If age ≥ 30 years
HEPATIC						
Liver function panel analysis	X	X	X	X	X	Yearly
Liver biopsy: if liver function panel values are high, consider the need for liver biopsy	Only if previous test was abnormal					
Ferritin and iron levels tested (perform T2*-weighted MRI if ferritin levels are high)	If clinically indicated	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						
Electrolytes, BUN, and urinary creatinine analysis	X	X	X	X	X	Yearly
Urinalysis	X		X		X	
ENDOCRINE and METABOLISM						
Oral glucose tolerance test	X	X	X	X	X	Yearly
Lipid metabolism evaluation	X	X	X	X	X	Yearly
Gonadal function testing	X	X	X	X	X	Yearly
TSH and FT4 level testing	X	X	X	X	X	Yearly
FSH and LH levels tested if age < 10 years, estradiol level tested in females ≥ 10 years of age, and testosterone level tested in males ≥ 11 years of age	X	X	X	X	X	As needed
IGF-1 and IGFBP-3 testing (if age < 18 years)	If clinically indicated	If clinically indicated	If clinically indicated	If clinically indicated	If clinically indicated	

	Year 1	Year 2	Year 3	Year 4	Year 5	After 5 years

25-OH vitamin D and calcium levels tested	X	X	X	X	X	Yearly
Bone age determination (if 5-18 years of age)	If clinically indicated	If clinically indicated	If clinically indicated	If clinically indicated	If clinically indicated	
Bone mineral density assessment	X	X	X	X	X	
DXA scan (adjusted for height)	If clinically indicated	If clinically indicated	If clinically indicated	If clinically indicated	If clinically indicated	If clinically indicated
GROWTH and DEVELOPMENT						
Plot height and weight on a growth chart	X	X	X	X	X	Yearly
Neuropsychological evaluation, with special focus on neurocognitive issues (especially if developmental delay)	If clinically indicated	If clinically indicated	If clinically indicated	If clinically indicated	If clinically indicated	
HEAD and NECK						
Ophthalmology evaluation	X	If clinically indicated	If clinically indicated	If clinically indicated	If clinically indicated	As needed
Screening for head and neck cancers (performed by a head and neck specialist)	At least every 6 months	At least every 6 months	At least every 6 months	At least every 6 months	At least every 6 months	At least every 6 months
Visual and hearing evaluations	X		As needed		As needed	
Biannual dental evaluation (may be unnecessary if ear, nose, and throat evaluations are performed); also encourage monthly oral self-examination	Every 6 months	Every 6 months	Every 6 months	Every 6 months	Every 6 months	Every 6 months
GYNECOLOGIC						
Ensure HPV vaccination	X	X	X	X	X	Yearly
General gynecologic evaluation and cancer screening (in females > 13 years of age)	X	X	X	X	X	Yearly
DERMATOLOGY						
Evaluation of nevi and possible skin cancers	X	X	X	X	X	Yearly
Evaluation for GvHD of the skin	X	X	X	X	X	Yearly

Sources: references [15, 24-28].

BUN, blood urea nitrogen; DXA, dual x-ray absorptiometry; EKG, electrocardiogram; FT4, free thyroxine; GvHD, graft-versus-host disease; HDL, high-density lipoprotein; HPV, human papillomavirus; Ig, immunoglobulin; IGF-1, insulin-like growth factor-1; IGFBP-3, insulin-like growth factor binding protein 3; LDL, low-density lipoprotein; MRI, magnetic resonance imaging; TSH, thyroid-stimulating hormone.

Alternative Management of Hematologic Disease in Fanconi Anemia

To date, hematopoietic cell transplantation (HCT) is the only known cure for bone marrow failure (BMF), myelodysplastic syndrome (MDS), and acute myeloid leukemia (AML). However, some patients with BMF and severe cytopenia (Table 1) are unable to undergo HCT, so alternative therapies should be considered in these cases. Therapies being explored for the treatment of mild or moderate cytopenia (e.g., androgens, granulocyte colony-stimulating factor, eltrombopag, metformin, or quercetin [8, 29-34]) may help maintain blood counts, stabilize FA hematopoietic disease, and improve quality of life, but they have potential inherent risks and are unlikely to fully prevent hematopoietic disease progression.

Gene Therapy

Gene therapies are being tested for various diseases with a hematopoietic component, including FA [35-38]. The first clinical trials of stem cell gene therapy for FA used retroviruses to deliver *FANCA* or *FANCC* genes. These early protocols, however, resulted in no or only transient correction of hematopoietic cells, an observation consistent with only short-term functional gene complementation [39-42]. Lessons learned from earlier gene therapy clinical trials and preclinical animal model studies cumulatively led to the development of improved clinical trial protocols [42-45].

The first successful gene therapy trial for patients with *FANCA* variants evaluated lentiviral-mediated hematopoietic gene transfer into mobilized peripheral blood hematopoietic progenitor stem cells from patients with FA, followed by infusion without conditioning into these same patients. This approach led to partial engraftment and expansion of *FANCA* gene-corrected cells [46]. Additional clinical gene therapy trials for patients with *FANCA* variants are ongoing, with promising results reported in a subset of patients, especially those treated early in the disease course, when their bone marrow reserve was still robust [47-48]. Such treatment may ultimately prove to be a preventive and curative therapy for the hematologic aspects of FA disease, but additional research is required to understand the full risks and benefits of this treatment.

Conclusion

Fanconi anemia (FA) is a genetic disorder characterized by DNA repair defects that adversely affect the stability of hematopoietic stem cells. This results in a high likelihood that patients with FA will develop bone marrow failure (BMF) or clonal progression to myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). The only cure for BMF at present is hematopoietic cell transplantation (HCT). Recommendations for clinical monitoring of BMF are based on the stability of peripheral blood counts and the presence of clonal abnormalities observed in serial bone marrow examinations. The decision to proceed with HCT in patients with FA who have BMF, clonal abnormalities, MDS, or AML should be made in consultation with an FA physician specialist. Recent advances in HCT protocols have led to continuing improvements in survival rates. These advances include, but are not limited to, recognition that HCT without total body radiation is successful in most patients; ex-vivo T-cell depletion is safe and may reduce the incidence of graft-versus-host disease; and HCT from mismatched related, unrelated, and haploidentical donors may be successful for patients with no other donor options [8]. Hematopoietic cell transplantation, in general, confers an increased risk of early-onset cancer because of graft-versus-host disease, conditioning regimens, and long periods of immunosuppression. This highlights the need for close follow-up during long-term care following HCT. Finally, there is emerging evidence that gene therapy holds promise as a curative option for BMF in patients with FA.

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