Chapter 13

Brief Guide to Clinical Care for Patients with Fanconi Anemia

Introduction

This chapter is a brief clinical guide that is a compendium of information provided in all other chapters in this book. It is not all-inclusive and should not take the place of reading the comprehensive information provided in other chapters. Many of the tests and procedures mentioned in this chapter will not be appropriate for every individual patient, nor does this brief guide present an exhaustive list of possible tests or treatments that each FA patient could or should undergo. Rather, it should be used at the discretion of the patient's physician and should be tailored to the needs of the individual patient and his or her family.

The brief guide covers the following areas:

- Diagnosis of FA
- General clinical care
- Bone marrow failure and hematopoietic cell transplant
- Reproductive health and gynecologic cancer
- Head and neck cancer prevention, diagnosis, and treatment
- The adult patient with FA and clinical care transition

Diagnosis of Fanconi Anemia

The following should be used as criteria to perform diagnostic testing for Fanconi anemia (FA) (see Chapter 2):

- All children with multiple anatomic abnormalities, particularly those that are grouped with the acronym PHENOS (skin Pigmentation, small Head, small Eyes, Nervous system, Otology, and Short stature) and those described in the VACTERL-H (Vertebral, Anal, Cardiac, Tracheo-esophageal fistula, Esophageal atresia, Renal, upper Limb and Hydrocephalus) association.
- All children and adults with aplastic anemia.
- All patients with a 3q gain on cytogenetic evaluation.
- All full siblings of patients with FA, regardless of whether they show physical signs or symptoms, must be tested to rule out FA and to determine whether they are matched sibling donors for hematopoietic cell transplant (HCT).
- Young adults that present at atypical ages for specific malignancies, including squamous cell carcinoma (SCC) of the head and neck or anogenital region.
- Individuals with excessive toxicity after treatment with chemotherapeutics commonly used to treat cancers such as myeloid leukemia and head and neck or anogenital SCC.

Laboratory Tests for Fanconi Anemia

Physicians who suspect that a patient may have FA should refer the patient to a hematologist and/or clinical geneticist or genetic counselor who can arrange for diagnostic testing (see Chapter 2 for complete testing guidelines).

Anyone suspected of having FA should be tested using a diepoxybutane (DEB) or mitomycin C (MMC) chromosome breakage test of blood lymphocytes. The DEB/MMC test should be performed at a clinically certified laboratory that has expertise in FA diagnostic testing.

If diagnostic test results of blood lymphocytes are negative, no further testing is necessary, unless there is strong clinical suspicion. If the result is negative, or equivocal, skin fibroblasts can be used for additional chromosome breakage testing. In addition, molecular testing for other chromosome instability or DNA repair syndromes can be performed.

If the chromosome breakage test is positive, a targeted FA gene panel and deletion/duplication analysis should be performed. If results from this test are negative, whole exome or whole genome sequencing can be performed.

General Clinical Care

Fanconi anemia (FA) leads to numerous bodily complications that require specific clinical care approaches. This section provides an overview of guidelines for monitoring and treating the body systems covered in the chapters of this guide.

Audiologic Care

Patients with FA should be examined by an otolaryngologist at diagnosis to assess for possible hearing loss or structural abnormalities of the eardrums and/or middle ear bones. If the patient has structural abnormalities, the otolaryngologist may consider possible surgical intervention to improve hearing (see Chapter 11).

An audiologist should assess the patient at the time of diagnosis to determine whether an amplification system would be useful if hearing loss is documented. These systems can be used for children as young as 4 months. The audiologist can help the family arrange for speech and language therapy, if needed, and should also contact the patient's school district to inquire about early intervention services.

If a patient with FA receives potentially ototoxic drugs (i.e., that can impair hearing), such as certain intravenous antibiotics and/or chemotherapy drugs used during hematopoietic cell transplant (HCT), the patient's auditory function should be monitored with serial audiograms.

Dermatologic Care

Patients with suspicious nevi or other abnormal skin lesions should be examined by a dermatologist (see Chapter 8). All patients with FA should limit sun exposure and wear sunscreen to reduce the risk of skin cancer. Post-HCT patients should limit sun exposure to reduce the risk of cutaneous chronic graft-versus-host disease.

Endocrine Care

Many children and adults with FA have endocrine problems, including growth hormone deficiency, hypothyroidism, pubertal delay, or diabetes (see Chapter 10). To ensure optimal care, the patient should consult with an endocrinologist or pediatric endocrinologist.

At diagnosis and annually, each FA patient should receive a thorough baseline endocrine evaluation to monitor the following:

- **Growth.** Nutritional and medical causes for poor growth should be identified as early as possible for optimal treatment. Growth in children with FA should be followed clinically. Height, determined on a stadiometer, should be plotted on a growth chart at least annually.

- **Puberty.** Onset of puberty, which is often delayed in individuals with FA, should be evaluated by at least annual physical examinations to evaluate stage and progression. After age 12, pubertal hormone concentrations should be obtained at least every two years as needed to assess pubertal progression.
- **Glucose tolerance.** A 2-hour oral glucose tolerance test (OGTT) with insulin levels should be obtained and repeated as determined by the endocrinologist.
- **Diet and exercise.** All persons diagnosed with FA should engage in regular exercise and consume a healthful diet that provides adequate calories and follows the guidelines of the American Diabetes Association. Concentrated sweets should be avoided.

Gastrointestinal Care

Patients with gastrointestinal or hepatic concerns should be seen by a gastroenterologist. A number of patients with FA have gastrointestinal symptoms, such as poor oral intake, nausea, abdominal pain, and/or diarrhea resulting in a failure to thrive. These problems may affect nutrition and/or quality of life in patients with FA. The physician should ask the patient and family about gastrointestinal symptoms during routine clinic visits, as patients often do not disclose these concerns voluntarily (see Chapter 9). The hepatic complications of androgens also are a concern in patients with FA. Liver enzymes should be monitored every 3-6 months in patients receiving androgens, and a liver ultrasound every 6-12 months is recommended.

Hand and Arm Abnormalities

Patients with hand or arm abnormalities should be assessed at the time of diagnosis by an orthopedic surgeon with specific experience in congenital limb anomalies. It is very important that the surgeon hold a Certificate of Added Qualification in Hand Surgery. Early referral of the patient to an orthopedic upper extremity specialist is important to obtain the best possible functional and cosmetic outcome for arm and thumb abnormalities that are common in FA.

Oral Care

All patients with FA should have regular dental examinations at least every six months by a dentist who is well versed in FA head and neck squamous cell carcinoma risks. The examination should include a thorough screening for possible oral cancer. Digital dental x-rays provide limited radiation exposure and may be required to monitor for cavities and diagnose gum and bone diseases that cannot be detected by visual inspection. However, because patients with FA have increased sensitivity to radiation, use of dental x-rays should be limited as much as possible.

Other dental procedures (e.g., braces) should be discussed with the FA hematologist. Bone marrow failure (BMF) contributes to significant oral health problems, including increased

bacterial, viral, and fungal infections. Oral care is essential for treating and managing oral complications for patients with FA both pre and post-HCT. Patients with FA should not have dental cleaning, extraction, or other invasive procedures after HCT until the immune system has recovered. If urgent care is required, supportive care may be needed (see Chapter 6).

Polypharmacy

Patients with FA often take several different prescription medication simultaneously throughout their lives. The involvement of multiple subspecialists introduces the risk that medications prescribed by one physician will interact adversely with those prescribed by another or that the use of non-prescription drugs may interact adversely with prescribed medication. It is extremely important that all subspecialists communicate with the primary physician or hematologist to coordinate care. The patient should share all prescription and non-prescription drugs, dietary supplements, and homeopathic agents used with the primary physician and subspecialists.

Skeletal Health

Hematopoietic cell transplantation may increase the risk of osteoporosis/osteopenia for any patient regardless of underlying diagnosis. The pre-transplant recommendation for FA patients is to obtain a bone density screening (DXA scan) at age 14, with follow-up as needed. For patients who have undergone a transplant, a DXA scan should be obtained one year post-transplant, with ongoing monitoring as needed. Independent of transplantation, premature menopause is a high-risk factor for reduced bone mass and gynecological experts who treat adult female patients with FA recommend careful monitoring of bone health. Long-term treatment with corticosteroids also increases the risk of osteoporosis/osteopenia in both male and female patients with FA.

Bone Marrow Failure

Most patients with Fanconi anemia (FA) will develop bone marrow failure (BMF); however, the age of onset can be highly variable, even among affected siblings. The absence of BMF does not exclude the diagnosis of FA, however. All patients with FA should be monitored by a hematologist with experience in FA, regardless of whether the patient has bone marrow involvement. Chapter 3 provides a detailed overview for clinical monitoring of BMF in patients with FA.

Hematopoietic Cell Transplantation

Hematopoietic cell transplantation (HCT) is currently the only therapy available to cure patients with FA of marrow aplasia and prevent progression to myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML).

Pre-Transplant Precautions for Patients with Fanconi Anemia

The FA diagnosis must be confirmed before proceeding to HCT. The donor, if related to the patient, must be tested to rule out the possibility of FA. The physician should take ample time to discuss childbearing options with the patient and family before HCT, as the procedure may affect future fertility.

After Transplant Care

Table 2 in Chapter 3 provides a comprehensive schedule of the long-term follow-up examinations needed for FA patients after HCT. Long-term care plans should be tailored to the specific needs of each individual FA patient under the supervision of a long-term care team comprised of the HCT physician, primary hematologist, and a multi-disciplinary team of specialists. Early complications, such as graft-versus-host disease (GvHD), graft failure, organ toxicity, and infections should be monitored. Abnormal liver enzymes and blood counts should be monitored. Testing for viruses should be performed early on as well. Late complications should be monitored and include chronic GvHD, organ toxicity (i.e., cardiac, pulmonary, renal), endocrinopathies (i.e., diabetes, hypothyroidism, gonadal dysfunction, growth failure), osteoporosis, avascular necrosis, infertility, and cancer.

Most transplant centers will expect patients to remain near the facility for a minimum of 100 days, during which time the patient is at highest risk for developing immunologic complications (i.e., graft rejection, GvHD, and opportunistic infections) associated with HCT. Patients with FA should be screened for immune reconstitution one year after HCT. The primary care physician should discuss the exact timing of immunizations with the patient's transplant physician. All patients and their family household members should receive the intramuscular formulation of the influenza vaccine on an annual basis. After HCT, the patient's hematologist will determine how often blood counts and bone marrow tests are needed (see Chapter 3).

Myelodysplastic Syndrome and Acute Myelogenous Leukemia

Patients with FA are at high risk of developing MDS and AML and should be monitored closely to assess for possible onset. Serial marrow examination and cytogenetic analysis should be performed annually in patients who have not undergone HCT to identify clonal evolution to MDS or AML. There is no standard therapy for FA patients with MDS or AML. Treatment options include HCT with or without prior induction chemotherapy.

Hematopoietic Cell Transplant in Adult Patients with Fanconi Anemia

In patients with FA, HCT yields the best results when performed in the first decade of life and before the onset of myeloid malignancies, solid tumors, or transfusions. Increasingly, however, adult patients with FA are undergoing transplant, made possible by advances such as reduced intensity cytoreduction regimens and T-cell depletion methods designed to decrease the incidence of GvHD. To date, there are no published trials of adult FA transplant; however, data are slowly becoming available. A multicenter retrospective analysis of 199 adult patients with FA transplanted between 1991 and 2014 was recently published [1]. Non-relapse mortality at 96 months was 56% with an overall survival of 34%, which improved with more recent transplants.

Reproductive Health

Female patients with FA may experience a variety of gynecologic issues, including structural abnormalities, delayed puberty, decreased fertility, early menopause, and a high risk of squamous cell carcinoma (SCC) of the lower genital tract, which includes cervical, vaginal, vulvar, and anal cancers. Male patients with FA may have numerous structural abnormalities of the reproductive system and extremely low sperm count that affect fertility.

Gynecologic Cancer

Proper prevention, surveillance, and treatment of anogenital SCC in female patients with FA are essential. Beginning at age 13, female patients with FA should have annual examinations by a gynecologist for visual inspection of the external genitalia. Once sexually active, or by age 18, female patients with FA should receive comprehensive annual gynecologic exams with cervical cytology testing. Clinical experts recommend screening for gynecological cancer every 6-12 months because squamous intraepithelial lesions (SIL) can rapidly progress to cancer. Anal pap smears and anoscopy may be considered in female patients with FA who have vulvar disease.

As with the general population, colposcopy is appropriate in the setting of abnormal cytology or suspicious lesions noted on examination. Suspicious genital tract lesions should be biopsied. Female patients diagnosed with anogenital SCC should be referred immediately to a gynecologic oncologist. Early referral may enable surgical treatment of the cancer, thereby avoiding the risks associated with chemotherapy or radiation for patients with FA (see Chapter 7 for complete guidelines on gynecologic cancer).

Human Papillomavirus Vaccination

It is recommended that patients with FA follow the current guidelines from the U.S. Centers for Disease Control and Prevention, which recommends routine HPV vaccination for both females and males. The currently available vaccine protects against acquiring the nine HPV types that are most commonly associated with cervical, vaginal, and vulvar cancer, and genital warts. Ideally, the vaccine should be given before the patient is exposed to HPV through oral sex or sexual intercourse. It is recommended that patients with FA be vaccinated starting at age 9. Regardless of prior HPV vaccination, patients with FA should be vaccinated after hematopoietic stem cell transplantation (HCT), when deemed appropriate (see Chapter 7).

Primary Ovarian Insufficiency

Primary ovarian insufficiency (POI) is common in female patients with FA. It is characterized by a spectrum of low ovarian reserve, declining ovarian function, reduced fertility, and estrogen deficiency. It is recommended that female patients with FA be treated either with oral contraceptive pills (if the patient is sexually active and pregnancy is not desired) or postmenopausal hormone therapy, which consists of low to physiologic doses of estrogen and progestins. Either approach is superior to no therapy regarding the effects on bone and other aspects of health.

Fertility and Pregnancy

Pregnancies have been reported in female patients with FA, in both those who were treated with HCT and those who were not. Physicians should discuss childbearing options with female patients with FA before HCT, as the transplant may further affect the patient's future fertility. The patient should not take androgens during pregnancy. While pregnancy for women with FA who have not been transplanted is not life-threatening, it nonetheless likely will impact onset or severity of bone marrow failure, requiring intensified surveillance. The pregnancy should be considered high risk and should be co-managed by a maternal/fetal medicine specialist and a hematologist. Pregnancies after HCT have occurred, but they are rare.

Menopause

Female patients with FA usually experience premature menopause. Thus, the physician should consider the patient's risk of post-menopausal conditions such as osteoporosis, cardiovascular disease, breast cancer, and the management of hot flashes using hormone therapy.

Breast Cancer Screening

Five of the genes implicated in Fanconi anemia (FA) are breast cancer susceptibility genes: *FANCD1/BRCA2*, *FANCJ/BRIP1*, *FANCN/PALB2*, *FANCO/RAD51C*, and *FANCS/BRCA1*. However, breast cancer risk for individuals with FA who harbor variants in these genes or other FA genes has not been established; therefore, more research is needed to develop guidelines for breast cancer screening for female patients with FA (regardless of their specific FA variant). It is unclear whether the current mammography screening recommendations for carriers also apply to individuals with FA, as FA patients have an elevated sensitivity to radiation exposure due to their underlying genetic defects in DNA repair. The long-term risks of radiation exposure must be weighed against the benefits of early detection.

Reproductive Issues in Male Patients with Fanconi Anemia

Developmental anomalies of the genital tract are more frequent in male patients with FA than in the general population. Many male patients with FA may have the following reproductive issues:

- Delayed puberty
- Undescended testicles and hypospadias, a condition where the urethra opens on the underside of the penis
- Small testes for their age and pubertal status, most likely reflecting reduced Sertoli cell mass and spermatogenesis
- Testicles fail to descend
- Low levels of sex hormone production due to underlying problems with the pituitary gland or hypothalamus
- Azoospermia

Head and Neck Squamous Cell Carcinoma

Patients with FA are at extremely high risk for developing cancer at an early age, and in particular, head and neck squamous cell carcinoma (HNSCC). Therefore, implementation of early and lifelong surveillance, regardless of whether the patient has undergone a bone marrow transplant, is essential.

Prevention

- Maintain good oral hygiene and visit a dentist and an expert in head and neck cancer detection every six months.
- Minimize exposure to dietary alcohol and do not use mouthwashes containing alcohol.
- Avoid smoking and exposure to second-hand smoke; vaping also should be avoided.

- Receive the human papillomavirus (HPV) vaccination series, beginning at age 9 for both male and female patients with FA (see Chapter 7 for full guidelines).

Surveillance and Treatment

- Beginning at age 10, patients with FA should be examined every six months by an otolaryngologist, oral surgeon, or other doctor who is experienced in head and neck cancer detection and is familiar with FA. The exam should include a careful exploration of the nasopharynx, oropharynx, hypopharynx, and larynx.
- Suspicious lesions in the oral cavity should be brushed immediately using a brush biopsy. If pre-cancerous or cancerous lesions are identified via brush biopsy, incisional biopsy must be performed to confirm the diagnosis.
- Malignant lesions must be treated immediately, as cure can best be achieved via early surgical removal. Treatment should be discussed with a hematologist/oncologist with experience in FA.
- Aggressive monitoring by the treating surgeon is required for those previously treated for head and neck cancer.

Adult Patients with Fanconi Anemia

Fanconi anemia (FA) is no longer an exclusive childhood illness. Increased recognition of disease diversity, improved hematopoietic cell transplant (HCT), better supportive care options, and early detection have improved the likelihood that patients with FA will live into adulthood. It is now estimated that approximately 80% of patients with FA will survive beyond 18 years of age [2, 3]. The major healthcare issues of the adult FA population have been described and discussed in database reports by the International Fanconi Anemia Registry, the National Institute of Health (NIH)-based North American Survey, and the German Fanconi Anemia Registry [4-7]. However, the adult population with FA has not been studied as a patient subgroup in any prospective studies published to date. Many major health issues unique to this subpopulation of patients with FA are just beginning to be recognized and evaluated.

Subgroups of Adult Patients with Fanconi Anemia

The three general subgroups of adult patients with FA have both common and divergent concerns, and often require different strategies for management and follow-up. All adult patients with FA, regardless of which subgroup they are in, are at high risk for the development of head and neck squamous cell carcinoma or anogenital SCC (female patients) and require aggressive surveillance (see Chapters 5 and 7). The three subgroups of FA adult patients are summarized as follows:

Adult Patients Diagnosed in Childhood Who Have Not Had a Transplant

Although a few of these patients have not developed bone marrow failure or hematologic malignancies (and may not do so in their lifetime), all of these patients require scheduled hematologic evaluations. Patients in this group who develop bone marrow failure as adults may require an HCT.

Adult Patients Diagnosed in Childhood Who Have Had a Transplant

This population is increasing in number because of the increased success of HCT. The major issues facing this population are the follow-up and treatment of non-hematologic FA issues and short- and long-term complications of HCT, such as the treatment of chronic graft-versus-host disease (GvHD). These patients face a relatively small risk of hematologic relapse, for which they require continued hematologic evaluation.

Adult Patients Who Are Diagnosed in Adulthood

This is a small but growing population due to increased recognition of the disease diversity. At least 10% of patients with FA are 16 years or older at the time of diagnosis [8]. Occasionally, an adult is diagnosed with FA when the family members of a newly diagnosed individual are screened. More commonly, an adult is diagnosed with FA because of a clinically atypical cancer diagnosis or an abnormal response to cancer chemotherapy or radiation therapy. One study found that in more than 20% of patients with FA who developed solid tumors, the diagnosis of FA in these patients was made only after the appearance of their cancer [9]. Many of these patients were diagnosed as adults and very often had no, or minor, phenotypic abnormalities and normal blood counts. Mosaicism may explain some of the cases where a cancer diagnosis precedes the diagnosis of FA [9].

Transitioning to Adult Clinical Care

The transition from pediatric- to adult-oriented care is an important issue facing young adults with many complex and chronic illnesses. Although the authors are not aware of specific transition programs for young adults with FA, there is ample evidence to support the benefits of an anticipated and coordinated transition process [10-12] that is outlined as follows:

- This transition must be seen as a process, not as an abrupt transfer of services.
- Successful transitions are often initiated during the late teenage years, and accompanied by family and patient education about the future transition [11, 12].
- Transition timing should be individualized and not dependent on age.
- Pediatric FA specialists may remain involved in long-term patient care decisions, especially regarding the screening and treatment of secondary cancers.
- Patients transplanted at larger centers may be followed in long-term survivor clinics where healthcare needs are addressed by a multi-disciplinary team.

Creating an Adult Clinical Care Plan

The adult clinical care plan should include surveillance and treatment of all aspects of FA, including:

- Preventive healthcare and wellness check-ups.
- Ongoing hematological evaluation of patients who have not undergone an HCT.
- Continuation of rigorous cancer prevention and surveillance, especially of head and neck and anogenital SCC.
- Screening for vascular and cardiac disease after HCT.
- Screening for endocrine-related conditions, such as abnormal thyroid function, diabetes mellitus, reduced fertility, and osteoporosis.
- Screening for effects of treatment that manifest later in life, such as cataracts.
- Complete all standard vaccinations including human papillomavirus vaccination to prevent SCC.
- Gynecological consultations to screen for and prevent cancer, to monitor menses, and to manage fertility and menopause issues.

Psychosocial Issues in Adult Patients with Fanconi Anemia

The magnitude of potential psychosocial problems has not been assessed in FA adults and should be assessed in patient cohorts in the future. However, a recent follow-up study of adult survivors of childhood acute lymphoblastic leukemia reveals that these patients experienced more functional impairments in mental health, and engaged in limited activities compared with their siblings [13]. In addition, rates of marriage, college graduation, employment, and health insurance coverage were all lower in FA patients in comparison to controls. It is expected that FA adults may experience similar issues. For these reasons, the adult FA patient may need extensive vocational, educational, and psychosocial support and guidance. Medical compliance also may become a challenge, particularly during the transition period. For individuals who are newly diagnosed in adulthood, the ramifications of the diagnosis on established relationships (with spouses, parents, employers, etc.) may be extreme.

Summary

The brief clinical guide for patients with FA is an overview of clinical recommendations provided in all other chapters in this book. It should be used as a guide only and is not intended to provide comprehensive clinical care guidelines for each unique patient with FA. Fanconi anemia is a heterogenous disease that affects all bodily systems. The complexity of the disease requires a holistic approach to wellness and treatment for each patient. Multi-disciplinary clinical care is essential for patients with FA and should be offered in a coordinated fashion by a team with expertise in FA. This is particularly important for adult patients with FA, who are quickly becoming the largest subpopulation of FA patients. Adults with FA have a unique set of clinical challenges that are still not well understood. Research on this subgroup is desperately needed in order to improve their clinical care.

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