Chapter 16: The Adult Patient with FA

Introduction

Good to Know

Fanconi anemia researchers in countries around the world have established programs to collect information about people with FA. This information helps researchers learn more about the condition's diagnosis, natural history, prognosis, treatment, and cancer rates.

The International Fanconi Anemia Registry (**IFAR**), the North American Survey (**NAS**), and the German Fanconi Anemia Registry (**GEFA**) are among these programs.

Thanks to a variety of factors, including increased recognition of disease diversity, greatly increased scientific understanding of Fanconi anemia (FA), improved transplant results, better supportive care options, and early detection, approximately 80% of patients with FA will survive beyond 18 years of age [1]. The median survival of all patients with FA is now greater than 30 years [previously estimated to be 33 in 2010 [2]], but it should be cautioned that patients with mutations in *FANCD1/BRCA2* have much lower median survivals. As a result, adults (≥ 18 years of age) represent an ever-increasing proportion of the FA population. Fanconi anemia is no longer an exclusive childhood illness, and diagnosis and treatment are no longer exclusively performed by pediatricians.

The major healthcare issues of the adult FA population have been described and discussed in database reports by the International FA Registry (IFAR), the National Institutes of Health (NIH)-based North American Survey (NAS), and the German FA Registry (GEFA) [3] [4] [5] [6]. However, the adult subpopulation has not been studied as a group in prospective studies published to date. Many major health issues are unique to this subpopulation of patients with FA and are just beginning to be recognized and evaluated.

This chapter will introduce the three general subgroups of adult patients with FA and describe the following concerns relevant to the adult population:

- *Solid tumors*
- *Bone marrow transplant (BMT)*
- *Gynecologic and fertility issues*
- *Transition from pediatric- to adult-oriented care*
- *Psychosocial issues*

In addition, a list of resources for adults with FA can be found at the end of this chapter.

Subgroups of Adult Patients with FA

There are three general subgroups of adult patients with FA. These groups have both common and divergent concerns, and often require different strategies for management and follow-up.

Group 1: Adult patients with FA who were diagnosed in childhood and were not transplanted

Good to Know

Iron overload is a condition that occurs when excess iron accumulates in a person's organs and tissues. Excess iron can be removed from the body through a process known as **chelation.**

Note: For post-transplant patients, phlebotomy may also be used to treat iron overload.

This population is becoming smaller due to increased success of bone marrow transplantation. 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 Group 1 who develop bone marrow failure as adults may require treatment and/or transfusions, along with frequent evaluation for the development of hematologic malignancies. They may also be at risk for iron overload and need chelation, or they may be chronically chelated and require management of chelation side effects. Importantly, with the recent advances in matched sibling and unrelated donor transplants, transplantation remains

an option for many of these adult patients. Patients and clinicians should have ongoing conversations about the potential need for a transplant in the future; these conversations should be informed by the most current transplant results and supplemented by continuing education and counseling. All adult patients with FA, including those in Group 1, are at high risk for the development of solid tumors and require aggressive surveillance by ENT and gynecology specialists. Clinicians should emphasize the need for patients to become educated about this risk.

Group 2: Adult patients with FA who were diagnosed in childhood and are transplant survivors

This population is increasing in number because of the increased success of transplantation. The major issues facing this population are the follow-up and treatment of short- and long-term transplant complications, 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. They also require aggressive surveillance for solid tumors and, in fact, may develop these tumors at a younger age than non-transplanted patients [7]. Patients with chronic GvHD of the oral mucosa are at especially high risk for the development of head and neck cancers.

Group 3: Adult patients with FA who are diagnosed in adulthood

Good to Know

Cytogenetics is the study of chromosomes—strands of DNA that contain numerous genes and other genetic material. **Cytogenetic results** such as 1q+ (additional genetic material on the long arm of chromosome 1) describe variations in the normal content of a chromosome.

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 an affected sibling 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.

Hematopoietic somatic mosaicism is a condition that occurs when one of two alleles that carry disease mutations reverts to normal. Other types of cells such as skin cells carry both mutated alleles. Mosaicism may explain some of the cases where a cancer diagnosis precedes the diagnosis of FA [9].

Adult patients should be screened for FA if they have any of the following conditions:

- *Aplastic anemia (AA) or severe cytopenias not responding to standard therapy*
- *Myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML) associated with unusual cytogenetic results such as 1q+ or 3q+* [10] [11] [12]
- *Solid tumors that develop at a younger than expected age, in patients without known risk factors*
- *Severely delayed blood count recovery or aplasia after chemotherapy* [13]
- *Unusual sensitivity to radiation therapy* [14] [15]
- *Decreased fertility or early menopause*

Solid Tumors in Adult Patients with FA

Solid tumors are the most significant health issues facing the adult patient with FA. In particular, squamous cell cancers of the head and neck, as well as cervical and vulvar cancers in women, occur at remarkably high rates and at younger than expected ages. It is estimated that one-third of patients with FA will develop a solid tumor by the age of 48, most likely in the second and third decades of life [5]. These cancers may occur at an even earlier age in transplanted patients [7]. The HPV vaccine is prophylactic, not therapeutic, and is currently recommended by the United States Centers for Disease Control and Prevention for males and females, ages 9 to 26. The HPV vaccine may help prevent HPV infections in the cervix and oropharynx, as well as prevent subsequent cancers in these locations. Adults with FA should avoid cigarettes and alcohol, and practice good oral hygiene.

Surveillance for solid tumors is **essential** in all adult patients with FA. Surveillance should include:

- *Head and neck exam at least every 6 months*
- *PAP smear yearly (for females)*
- *GYN exam yearly (for females)*

- *Dental exam every 6 months*
- *Skin exam yearly*
- *Breast cancer screening (MRI and mammography) beginning at age 25 (for females); see* Chapter 6
- *Esophagoscopy (this surveillance recommendation is controversial because it requires anesthesia)*

Patients must be continually re-educated about the potential for solid tumor development, and should be screened by oncologists specializing in head and neck cancer (see *Chapter 14*.) FA specialists should be consulted when these tumors are diagnosed, as treatment may require different modalities than are used for the same cancers in non-FA patients. Previous reports of the treatment of solid tumors in patients with FA are generally limited to single case reports. The literature contains no prospective studies to date. The largest retrospective study of patients with FA with HNSCC describes the treatment of only 13 patients [16]. In general, only early-stage cancers are treatable. Treatment of advanced-stage tumors has been associated with severe toxicity and poor outcomes. Targeted therapies such as Erbitux for head and neck cancers are being studied in patients with FA and may allow for less toxicity and better cancer control [17].

Several FA-related genetic mutations (*FANCD1/BRCA2, FANCJ, FANCN, FANCO, FANCP,* and *FANCQ)* in heterozygotes (FA carriers) are associated with breast and ovarian cancers. These cancers have been reported in individuals with FA, but the exact risk of developing these cancers in patients with any FA mutation is not known.

Bone Marrow Transplant in the Adult Patient with FA

In patients with FA, transplants yield 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. At Memorial Sloan-Kettering Cancer Center (MSKCC), 12 adult patients with FA have received stem cell transplants since April 2001 [18]. The patients ranged in age from 18 to 36 years (median 24

years). Six of the 12 patients (50%) were post-transplant disease-free survivors, 4 of whom had AML at transplant. However, 2 of the 6 post-transplant, disease-free survivors succumbed to secondary cancers 5 and 8 years after transplant. Although these preliminary data explore a small number of transplants, the results are promising and suggest that BMT for FA adults is a possible therapeutic option.

Gynecologic and Fertility Issues in the Adult Patient with FA

Discussions of fertility and life expectancy are obviously quite different in adults with FA, particularly those diagnosed in adulthood, than in younger patients. Adult women with FA frequently experience early menopause, require high-risk management of pregnancies, and have an increased risk of gynecologic malignancies. Adult FA men are generally azoospermic, meaning that they do not produce measurable levels of sperm, and are therefore infertile. That said, it is important to note that advances in assisted reproduction techniques have led to new possibilities for the prevention and treatment of infertility. Early referral to a fertility clinic may be warranted. A complete discussion of gynecologic and fertility issues in adult patients with FA can be found in *Chapter 6.*

Transition of Care

The transition from pediatric- to adult-oriented care is an important issue facing young adults with 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 [19-21]. Effective transition programs have been developed for patients with other chronic illnesses, such as cystic fibrosis, diabetes, juvenile idiopathic arthritis, and sickle cell anemia. European countries with comprehensive state-supported healthcare systems have often taken the lead in the development of these transition systems.

Transition of healthcare is particularly important for two reasons. In most centers, patients outgrow pediatric services and are unable to be treated by pediatric subspecialists or in pediatric inpatient facilities. This is obviously dependent on the center and location, and policies vary widely. Furthermore, the transition to adult care is an important step because it helps young adults develop independence and assume a personal responsibility for their healthcare.

Timing is an important issue in the transition to adult care. This transition must be seen as a process, not as an abrupt transfer of services. Current evidence indicates that the most successful transitions are those initiated during the late teenage years, and accompanied by family and patient education about the future transition [19, 22]. As this process proceeds and adolescents take on more healthcare responsibilities, the patients should become involved in educational opportunities and decision-making. The timing of this transition should be individualized and not dependent on age, but rather situation-dependent. It would be inappropriate to transition a rapidly deteriorating patient who is facing the end of life, for example.

As an increasing number of patients with FA reach adulthood, the management and development of transition of health care services is becoming increasingly important and must be addressed on a national level. In recent studies, focus groups have identified a number of barriers to the transition to adult care [19] [21, 23-25], including:

- *Reluctance of patients and their families to leave trusted healthcare providers and comfortable clinical settings*
- *Differences in pediatric versus adult approaches to the chronically ill (i.e., family-oriented medicine with support from art therapists, social workers, and psychologists versus the expectation of adult independence and self-reliability)*
- *Concerns about the experience, knowledge base, and quality of care that will be offered by adult medical specialists in childhood-onset diseases*
- *Physician reluctance to transition*
- *Lack of continuing healthcare insurance coverage in the young adult*
- *Lack of an organized detailed history of the chronic complex illness*

The key element to a successful transition is continuous preparation and the identification of a willing and appropriate adult-oriented physician who can become the primary coordinator of healthcare issues. The patient's new and prior teams should work to define necessary subspecialist providers who either have experience in FA or are willing to become educated about the needs of this complicated patient population. Because of the rarity of FA, however, this is often not a realistic option, in which case it is essential that an FA specialist remain involved in the patient care decisions and be available for consultation, especially regarding the screening and treatment of secondary cancers. Patients with FA who have been transplanted at larger centers may have an option to be

followed in long-term survivor clinics, where much of their healthcare needs will be coordinated.

Psychosocial Issues in Adult Patients with FA

The appropriate development of a child through adolescence into adulthood is a monumental process that is complicated significantly by chronic disease. There is a potential risk of parental over-protectiveness given the competing issues of requisite attention to safety and the age-appropriate pursuit of adolescence independence. The inability to fully participate in childhood activities (e.g., school, sports, and leisure) may isolate FA children and delay development of peer relationships. 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 limited activities compared with their siblings [26]. In addition, rates of marriage, college graduation, employment, and health insurance coverage were all lower compared with 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. High-risk behaviors, such as alcohol and drug use, are common in patients with chronic illness, just as they are in the general population, and present major challenges for adults with FA [27]. Medical compliance may also become a problem, 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.

The magnitude of these psychosocial problems has not been assessed in FA adults, and should be assessed in contemporary patient cohorts in the future. A complete discussion of psychosocial issues in patients and families affected by FA can be found in *Chapter 18*.

Summary

Resources for Adults with FA

Meeting for Adults with FA: The Fanconi Anemia Research Fund (FARF) sponsored its fifth Meeting for Adults with FA in March 2014 in Baltimore, MD. Forty-two adults ages 18 to 61 attended. The previous meeting in 2012 was attended by 25 adults with FA. The meeting is held approximately every 18 months.

FA Family Meeting: The Fanconi Anemia Research Fund holds its annual FA Family Meeting at Camp Sunshine every summer. Adult patients with FA are well-represented at this event.

Facebook Support Group: The FARF also offers an online support group specifically for adults with FA through the social networking site, Facebook.

Today, most patients with FA will survive well into adulthood. This is likely due to earlier diagnosis, improved BMT outcomes, particularly in the area of alternative transplants (non-sibling donors), and better education of patients, their families, and medical staff regarding surveillance for myeloid malignancies and solid tumors.

There is a growing emphasis by the FA community on quality of life, particularly with regards to education, socialization and relationships, and work issues. However, the growing population of adult patients with FA represents a new challenge to FA care providers. These patients have not been studied prospectively, and many of their issues may be poorly defined or understood. The physicians caring for adults with FA must be educated about the nature of the disorder and the particular needs of this patient population. The responsibility lies with the pediatric FA specialist to educate patients and adult care providers, coordinate transitional care, and direct future research to improve outcomes.

Chapter Committee

K. Scott Baker, MD, MS, Farid Boulad, MD, Alfred Gillio, MD, and Eva Guinan, MD*
**Committee Chair*

References

1. Alter BP (2003) Nathan and Oski's hematology of infancy and childhood. *In:* Orkin SH, Nathan DG, Eds. 6th ed., Philadelphia: WB Saunders Co, pp 280-365.
2. Alter BP*, et al.* (2010) Malignancies and survival patterns in the National Cancer Institute inherited bone marrow failure syndromes cohort study. *Br J Haematol* 150(2):179-188.
3. Butturini A*, et al.* (1994) Hematologic abnormalities in Fanconi anemia: an International Fanconi Anemia Registry study. *Blood* 84(5):1650-1655.
4. Kutler DI*, et al.* (2003) A 20-year perspective on the International Fanconi Anemia Registry (IFAR). *Blood* 101(4):1249-1256.
5. Rosenberg PS, Greene MH, Alter BP (2003) Cancer incidence in persons with Fanconi anemia. *Blood* 101(3):822-826.
6. Rosenberg PS, Alter BP, Ebell W (2008) Cancer risks in Fanconi anemia: findings from the German Fanconi Anemia Registry. *Haematol* 93(4):511-517.
7. Rosenberg PS, Socie G, Alter BP, Gluckman E (2005) Risk of head and neck squamous cell cancer and death in patients with Fanconi anemia who did and did not receive transplants. *Blood* 105(1):67-73.
8. Alter BP (2005) Bone marrow failure: A child is not just a small adult (but an adult can have a childhood disease). *In:* American Society of Hematology Education Program Book.
9. Alter BP, Joenje H, Oostra AB, Pals G (2005) Fanconi anemia: adult head and neck cancer and hematopoietic mosaicism. *Arch Otolaryngol Head Neck Surg* 131(7):635-639.
10. Cioc AM, Wagner JE, MacMillan ML, DeFor T, Hirsch B (2010) Diagnosis of myelodysplastic syndrome among a cohort of 119 patients with Fanconi anemia: morphologic and cytogenetic characteristics. *Am J Clin Pathol* 133(1):92-100.
11. Quentin S*, et al.* (2011) Myelodysplasia and leukemia of Fanconi anemia are associated with a specific pattern of genomic abnormalities that includes cryptic *RUNX1/AML1* lesions. *Blood* 117(15):e161-170

12. Rochowski A*, et al.* (2012) Patients with Fanconi anemia and AML have different cytogenetic clones than de novo cases of AML. *Pediatr Blood Cancer* 59(5):922-924.

13. Rochowski A*, et al.* (2012) Estimation of the prevalence of Fanconi anemia among patients with de novo acute myelogenous leukemia who have poor recovery from chemotherapy. *Leuk Res* 36(1):29-31.

14. Bremer M*, et al.* (2003) Fanconi's anemia and clinical radiosensitivity report on two adult patients with locally advanced solid tumors treated by radiotherapy. *Strahlenther Onkol* 179(11):748-753.

15. Tan IB*, et al.* (2011) Fanconi's anemia in adulthood: chemoradiation-induced bone marrow failure and a novel *FANCA* mutation identified by targeted deep sequencing. *J Clin Oncol* 29(20):e591-594.

16. Masserot C*, et al.* (2008) Head and neck squamous cell carcinoma in 13 patients with Fanconi anemia after hematopoietic stem cell transplantation. *Cancer* 113(12):3315-3322.

17. Wong WM*, et al.* (2013) Squamous cell carcinoma of the oral tongue in a patient with Fanconi anemia treated with radiotherapy and concurrent cetuximab: A case report and review of the literature. *Head Neck* 35(10):E292-298.

18. Boulad F (Personal communication).

19. McLaughlin SE*, et al.* (2008) Improving transition from pediatric to adult cystic fibrosis care: lessons from a national survey of current practices. *Pediatrics* 121(5):e1160-1166.

20. McDonagh JE, Kelly DA (2003) Transitioning care of the pediatric recipient to adult caregivers. *Pediatr Clin North Am* 50(6):1561-1583, xi-xii.

21. Reiss JG, Gibson RW, Walker LR (2005) Health care transition: youth, family, and provider perspectives. *Pediatrics* 115(1):112-120.

22. Boyle MP, Farukhi Z, Nosky ML (2001) Strategies for improving transition to adult cystic fibrosis care, based on patient and parent views. *Pediatr Pulmonol* 32(6):428-436.

23. Scal P, Evans T, Blozis S, Okinow N, Blum R (1999) Trends in transition from pediatric to adult health care services for young adults with chronic conditions. *J Adolesc Health* 24(4):259-264.

24. Flume PA, Anderson DL, Hardy KK, Gray S (2001) Transition programs in cystic fibrosis centers: perceptions of pediatric and adult program directors. *Pediatr Pulmonol* 31(6):443-450.

25. Flume PA, Taylor LA, Anderson DL, Gray S, Turner D (2004) Transition programs in cystic fibrosis centers: perceptions of team members. *Pediatr Pulmonol* 37(1):4-7.

26. Mody R*, et al.* (2008) Twenty-five-year follow-up among survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. *Blood* 111(12):5515-5523.

27. Gillio AP (Personal communication).