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Management of Fanconi anemia beyond childhood

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Fanconi anemia (FA) has long been considered a severe inherited bone marrow failure (BMF) disorder of early childhood. Thus, management of this multisystem disorder has previously been unfamiliar to many hematologists specializing in the care of adolescents and young adults (AYA). The increased diagnosis of FA in AYA patients, facilitated by widely available germline genomic testing, improved long-term survival of children with FA following matched sibling and alternative donor hematopoietic stem cell transplantation (HSCT) performed for BMF, and expanding need in the near future for long-term monitoring in patients achieving hematologic stabilization following ex vivo gene therapy are all reasons why management of FA in AYA populations deserves specific consideration. In this review, we address the unique challenges and evidence-based practice recommendations for the management of AYA patients with FA. Specific topics addressed include hematologic monitoring in AYA patients yet to undergo HSCT, management of myeloid malignancies occurring in FA, diagnosis and management of nonhematologic malignances and organ dysfunction in AYA patients with FA, and evolving considerations for the long-term monitoring of patients with FA undergoing gene therapy.

LEARNING OBJECTIVES

- Delineate the unique medical challenges facing adolescents and young adults with Fanconi anemia
- Provide updated approaches for the management of hematologic disease in adolescents and young adults with Fanconi anemia

Introduction

Fanconi anemia (FA) is an inherited bone marrow failure (BMF) disorder caused by pathogenic variants in 1 of 23 genes[1] that result in defective repair of DNA interstrand crosslinks, genomic instability, cell cycle dysregulation, and cell death or transformation. In most affected individuals, including patients with biallelic mutations in *FANCA*, *FANCC*, and *FANCG* accounting for over 80% of cases,[2] FA is inherited in an autosomal recessive pattern, although distinct inheritance patterns and specific genotype–phenotype correlations are known (Table 1).

BMF in FA results from selective attrition of CD34$^+$ hematopoietic stem cells (HSCs) that significantly precedes the development of clinical cytopenias. This pathophysiology creates a unique challenge for autologous CD34$^+$ HSC collection for gene therapy applications.[3] HSC loss results from many factors, including excess DNA damage from endogenous reactive aldehydes, inflammatory cytokines released during typical childhood infections, and abnormal telomere shortening.[4,5] Recently, natural killer cell-mediated immune destruction through FA HSC upregulation of natural killer group 2 D ligand expression has been implicated as a key mechanism driving HSC attrition.[6]

Early studies suggested that 75% of patients with FA were diagnosed due to evolving BMF in the first decade of life, leading to initial impressions that FA was primarily an early pediatric disorder.[7] However, these studies mostly comprised patients with classic, severe *FANCA*, *FANCC*, and *FANCG* mutations. Recently expanded use of next-generation sequencing (NGS) to identify germline predisposition in adolescents and young adults (AYA) with BMF and myeloid malignancies (MMs) is now diagnosing FA in older patients with distinct phenotypes. Improvements in long-term survival following matched sibling and alternative donor HSC transplantation (HSCT) in children with FA and the advent of gene therapy that ameliorates but does not fully correct hematologic deficits have led to the need for increasing education and practice guidelines for hematologists specializing in the care of AYA patients with FA.

CLINICAL CASE

A 20-year-old man presents to the student health center at his university with increased fatigue and bruising. Medical history is significant for a ventricular septal

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Table 1. Genes associated with Fanconi anemia

Gene	% of FA cases	Inheritance	Population distribution and unique phenotypes
FANCA	45–60	AR	Founder mutations: Middle Eastern, North African, Spanish Romani, Afrikaner, Sicilian Mutation-specific disease severity
FANCC	10–15	AR	Founder mutations: Ashkenazi, Saudi, northern Europe Exon 15 mutations: more severe phenotype c.67delG: milder phenotype
FANCG	5–10	AR	Founder mutations: Sub-Saharan Africa, Japan, Korea Severe hematologic disease
FANCB	1–2	XL	VACTERL-H common
FANCD1/BRCA2	1–4	AR	High leukemia risk: myeloid and lymphoid Early childhood solid tumors: brain, Wilms, neuroblastoma Aplastic BMF uncommon Carriers: risk of breast, ovarian, prostate, pancreatic cancer
FANCD2	3–5	AR	Sequencing challenging due to pseudogenes
FANCI	1–4	AR	VACTERL-H common
FANCJ/BRIP1	1–4	AR	Carriers: increased breast/ovarian cancer risk
FANCL	1–2	AR	Founder mutations: India, Pakistan VACTERL-H common
FANCM	<2	AR	Lower risk of congenital anomalies and BMF Early-onset cancer risk
FANCN/PALB2	<2	AR	Severe clinical presentation High leukemia risk Early childhood solid tumors: brain, Wilms, neuroblastoma Carriers: breast and pancreatic cancer risk
FANCQ/ERCC4	<2	AR	Overlap with xeroderma pigmentosum
FANCR/RAD51	<2	AD	Congenital anomalies common BMF and cancer not yet reported
FANCS/BRCA1	<2	AR	Severe solid tumor and leukemia risk Congenital anomalies BMF not yet reported Carriers: risk of breast, ovarian, prostate, pancreatic cancer
FANCE, *FANCF*, *FANCO*, *FANCP*, *FANCT*, *FANCU*, *FANCV*, *FANCW*, *FANCY*	<2	AR	Rare cases only

Data derived from Fanconi Anemia Clinical Care Guidelines.[2]

AD, autosomal dominant; AR, autosomal recessive; VACTERL-H, vertebral, anal, cardiac, tracheoesophageal fistula, esophageal atresia, renal, limb, hydrocephalus; XL, X-linked.

defect repair in early childhood and what he describes as slightly low blood counts detected on a sports clearance evaluation when he was 16 years old. Physical exam reveals only short stature (height 63 inches/160 cm) and a white patch on his left buccal mucosa. Laboratory evaluation reveals a normal white blood cell count and differential, macrocytic anemia (mean corpuscular volume [MCV], 105 fL; hemoglobin, 8.5 g/dL) and thrombocytopenia (platelets, 33 000/μL). He is admitted to the nearby university hospital, where hematology performs a bone marrow aspirate and biopsy, revealing hypocellularity (20%) multilineage dysplasia and no excess blasts by morphology. Metaphase cytogenetics and fluorescence in situ hybridization reveal a gain of chromosome 3q (20% by fluorescence in situ hybridization). Chromosome stress testing reveals increased breakage upon exposure to diepoxybutane. NGS revealed biallelic pathogenic mutations in *FANCA*.

Diagnosis of FA in adolescence and young adults

Any AYA patient (up to age 40 years) who presents with BMF or MM associated with 1q, 3q, or 7q copy number abnormalities/translocations or unusual solid tumors for age (oral, head/neck, genital) should undergo a diagnostic evaluation for FA. Screening should include at minimum a chromosome stress test performed on peripheral blood lymphocytes exposed to DNA crosslinking agents diepoxybutane and mitomycin C. This screening by chromosomal stress test remains the gold standard in diagnosing FA. A positive test should trigger NGS testing and

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Table 2. Factors that should trigger high clinical suspicion for FA in adolescent and young adult patients presenting with bone marrow failure or myeloid malignancies

Clinical features
• Positive family history of bone marrow failure • Long-standing cytopenias • Characteristic congenital abnormalities including VACTERL-H, café au lait, short stature, microcephaly • Myeloid malignancy with +1q, +3q, or −7/del7q cytogenetics or FISH • Excessive toxicity with chemotherapy • Unusual solid tumor for young adults (oral, head/neck, liver, stomach, genital)

FISH, fluorescence in situ hybridization.

sensitive copy number analysis of the 23 genes associated with FA. Notably, 1 mechanism resulting in delayed onset of hematologic abnormalities in patients who present with FA at older ages is revertant hematopoietic clonal evolution resulting in elimination of 1 FA-associated mutation.[8] Such mosaicism can result in equivocal or even normal results on blood-based chromosome stress and NGS testing. Thus, in AYA patients with a high clinical suspicion for FA (Table 2) but in whom peripheral blood screening is normal or equivocal, screening results should be confirmed using skin fibroblasts. Once a mainstay of FA classification, complementation group testing is now used only in situations where NGS is equivocal in assigning subclassification due to variants of uncertain significance.

Hematologic status of AYA patients with FA

In a recent single-institution study of young adults with FA (age range 18-37 years at last follow-up), Wang et al.[9] demonstrate that AYA patients with FA have quite variable hematologic function. Of 52 adults, 8 (15%) had normal blood counts without prior HSCT, and 31% of the total cohort overall had not required HSCT. Patients with *FANCA* mutations had decreased likelihood of requiring HSCT compared to those with other genotypes (57% vs 83%),[9] consistent with known mild phenotypes and later onset of malignancies conveyed by some *FANCA* mutations.[10] Twenty-seven (52%) had undergone HSCT for BMF at a median age of 10.5 years, and 9 (13%) had undergone HSCT for MM at a median age of 15.4 years.[9] While the trend toward higher likelihood of presentation with MM vs BMF in AYA patients is consistent with earlier registry studies, the increased percentage of AYA patients who have maintained normal blood counts or exhibit only mild BMF in the Wang et al.[9] cohort without ever requiring HSCT may reflect improved diagnosis of patients with milder phenotypes.[9-11]

These findings emphasize that HSCT is not necessarily inevitable in FA and should not be performed in the absence of BMF or MM. This lack of inevitability also creates a challenge for ex vivo gene therapy, because while autologous collection for FA gene therapy is ideally performed at a young age prior to onset of HSC attrition and subsequent severe BMF,[12] proceeding to gene-modified autologous HSC infusion should not be done prior to BMF onset as some patients will not ultimately require stem cell therapy. This temporal disconnect between collection and infusion will make reimbursement models for commercialization of FA gene therapy challenging. For AYA patients with FA who have not undergone successful HSCT, adherence to hematologic malignancy screening is recommended as outlined in the Fanconi Anemia Clinical Guidelines[2] and in Table 3.

Therapy for severe BMF in AYA patients with FA

Several groups have published data demonstrating inferiority of HSCT outcomes for AYA vs young children with FA for BMF indications. In European Society for Blood and Marrow Transplantation (EBMT) published outcomes of adults with FA undergoing HSCT through 2014,[13] 4-year overall survival (OS) for the 64 patients receiving HSCT for BMF was only 48%, much inferior to outcomes in younger pediatric cohorts where OS now exceeds 80% to 90%.[1] These findings are comparable to prior Center for International Blood and Marrow Transplant Research and multicenter analyses of matched sibling donor and alternative donor outcomes,[14] as well as a prospective multicenter study of low-dose busulfan base conditioning for alternative donor HSCT,[15] which all demonstrate poorer outcomes for patients ≥10 vs those under 10 years old.

One practice-changing consequence of this age-based dichotomy in HSCT outcomes is a recommendation to avoid giving therapies long term that forestall onset of severe bone marrow failure but do not definitively fix hematopoiesis, as the consequence of delaying HSCT until the AYA period may result in poorer outcomes. Thus, strategies such as androgen therapy,[16] metformin,[17] and eltrombopag (NCT03206086) should be used in young children only as bridging therapy while completing diagnostics and identifying optimal HSCT donors, or in patients ineligible for HSCT due to lack of feasible donors or comorbidities. In contrast, use of these supportive strategies is reasonable for new-onset BMF occurring in AYA patients, as these individuals are already at high age-based risk for HSCT complications. While early data on use of metformin and eltrombopag hold promise, data supporting the use of androgen therapy are the most extensive. Indeed, AYA patients with FA may exhibit stable hematopoietic function on androgen therapy for many years.[18] For AYA patients with FA unresponsive to these approaches with good organ function, novel HSCT strategies testing risk-adapted alkylator dosing are currently in clinical trials (NCT02143830) to reduce rates of severe toxicities responsible for poor OS in AYA patients.

Hematologic malignancy management in patients with FA

Most myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) cases that arise in patients with FA occur in AYA patients.[19] Rarely, cases of lymphoma and T-cell acute lymphoblastic leukemia have also been seen,[20,21] although these are mostly limited to rare genetic subtypes. MDS/AML in FA has characteristic cytogenetic abnormalities, although not all abnormalities are clear indicators of malignant transformation.[22] Gain of chromosome 1q is the most common abnormality in FA and was once thought to not necessarily represent MDS transformation.[2] Recently, however, +1q has been shown to trigger a specific pathway driving leukemogenesis (Figure 1), starting with MDM4 triplication, which downregulates p53 pathways that in turn rescues BMF but also drives clonal dominance enabling AML development.[23] Prognostic significance of the similarly common chromosome 3q gain remains controversial, whereas chromosome 7q loss represents a late step, signaling imminent AML transformation.[24] In general, gene-specific somatic mutations are less commonly seen in FA compared to other BMF syndromes, although

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Table 3. Screening recommendations for adolescent and young adult patients with Fanconi anemia

Specialty/type of screening	Frequency of follow-up screening
Hematology CBC monitoring Bone marrow biopsy/aspirate with cytogenetics	Pre-HSCT: Every 3–4 months Post-HSCT: At least annually Pre-HSCT: Yearly* Post-HSCT: only if clinically indicated
Endocrinology Endocrinology consultation Thyroid function Growth axis 25-OH vitamin D and calcium DXA scan Fasting glucose Oral glucose tolerance test Lipid profile Gonadal function monitoring	Yearly Yearly if normal Screen young adolescents with short stature Yearly Every 5 years Yearly If indicated based on fasting glucose Every 3 years if normal Yearly
Head/neck cancer screening Dental/oral surgery assessments Nasolaryngoscopy Audiology	Every 6 months Every 6 months Based on symptoms
Dermatologic cancer screening	Yearly. Initiate by age 18
Gynecologic screening External and cervical exams	Yearly. Initiate by age 13
Breast cancer screening Mammogram, ultrasound, or MRI	Yearly. Age of initiation depends on genotype
Gastroenterology screening Esophagogastroduodenoscopy Colonoscopy	Only if indicated based on symptoms
Hepatology Liver function tests Liver ultrasound MRI for liver iron concentration	Yearly Every 3–5 years if normal If history of chronic red cell transfusions
Pulmonary Spirometry, diffusing capacity	Every 1–2 years post-HSCT

Based on the Fanconi Anemia Clinical Care Guidelines.[2]

CBC, complete blood count; DXA, dual-energy X-ray absorptiometry; MRI, magnetic resonance imaging.

*More frequent bone marrow (BM) screening recommended in patients with high-risk acquired cytogenetic lesions.

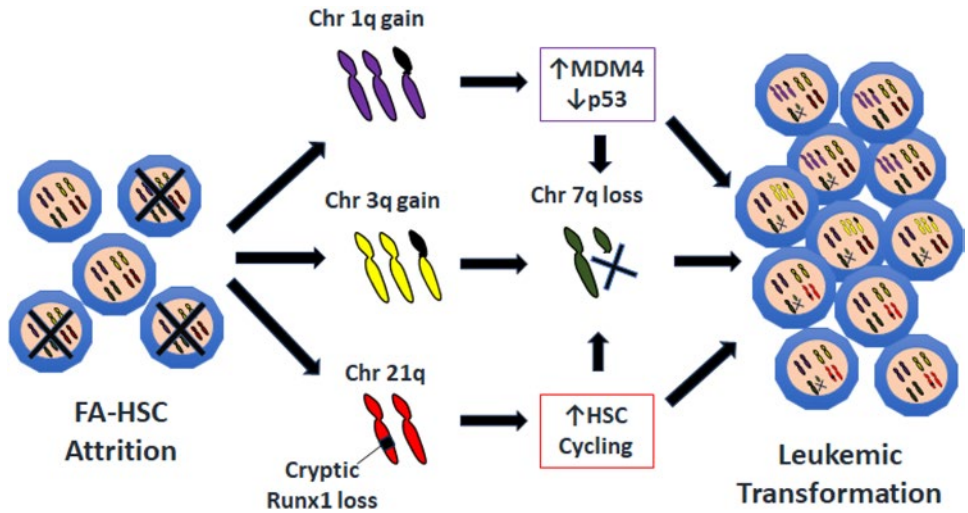

Figure 1. Schematic of leukemic transformation pathways in patients with Fanconi anemia.

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Table 4. Recent studies reporting hematopoietic stem cell transplant outcomes for patients with Fanconi anemia and pre-HSCT evolution to myeloid malignancies

Reference	Patients (n)	Era of HSCT	Conditioning	Survival
Mitchell et al. (2014)[35]	MM: 21	1988–2011	Various	All MM: 5-year OS 33%
Bierings et al. (2018)[13]	Total: 199 MM: 54	1991–2014	Various	MDS: 4-year OS 48% AML: 4-year OS 17%
Giardino et al. (2020)[32]	MM: 74	1999–2016	Various	All MM: 5-year OS 42% 5-year EFS 39%
Bernard et al. (2021)[33]	Total: 82 MM: 11	1999–2018	Most fludarabine + cyclophosphamide	All MM: 5-year OS 40%
Mehta et al. (2017)[15]	Total: 45 MM: 11	2009–2014	Low-dose busulfan + cyclophosphamide, fludarabine, ATG	MDS: 3-year OS 63.6%
Chattopadhyay et al. (2023)[34]	Total: 60 MM: 10	1990–2021	Low-dose busulfan + fludarabine	All MM: 5-year OS 46%

ATG, antithymocyte globulin; EFS, event-free survival.

the exceptions are cryptic RUNX1 mutations, occurring in up to 20% of patients with FA, that reverse HSC quiescence through abrogating cell cycle checkpoints, resulting in restored hematopoietic output but promotion of malignant transformation.[25,26]

For patients with early-stage MDS without excess blasts such as the one in our case, most centers recommend proceeding directly to HSCT with best available donor.[27] Prior to the year 2000, even early-stage MDS conveyed dismal prognosis in FA, with 5-year OS <25%.[28] Subsequently, improved outcomes have been made possible by T-cell depletion strategies such as CD34 selection and TCRαβ depletion to limit graft-versus host disease (GvHD) and by use of low-intensity regimens to reduce organ toxicity.[29,30] Posttransplant cyclophosphamide has also proven to be an effective method of in vivo T-cell depletion for patients with FA undergoing HSCT with haploidentical donors.[31] Unfortunately, 5-year OS for patients with MDS/AML (30%-50%) remains considerably lower than for patients with BMF (Table 4) in recent studies owing notably not just to relapse but also to ongoing high rates of nonrelapse mortality.[13,32-34] Whether increased nonrelapse mortality is driven by distinct pathophysiology of MDS/AML in FA or is confounded because MDS/AML occurs in AYA patients, whereas BMF occurs in younger patients, remains uncertain.

Pretransplant cytoreduction in patients with FA and advanced MDS/AML remains controversial. Intensive AML therapy has been associated with prolonged aplasia and significant toxicity,[35] although 1 recent series suggests improved outcomes in patients exhibiting pre-HSCT complete remission.[32] Sequential strategies of fludarabine/cytarabine-based chemotherapy followed by HSCT several weeks later regardless of aplasia status may improve relapse-free survival.[27] Combination azacytidine/venetoclax as pretransplant cytoreduction is currently being tested in a combined safety/efficacy basket trial that includes patients with FA and MDS/AML (NCT05292664).

Hematologic monitoring in patients with FA who have received prior gene therapy

Ex vivo autologous gene therapy may soon be a commercially available option for patients with FA, although to date, trials have been limited to patients with a *FANCA* genotype. The tremendous potential of this approach is tied to the elimination of conditioning from this platform.[12] If efficacious, autologous HSC gene correction avoids not only GvHD but also long- and short-term chemotherapy radiation toxicities seen after allogeneic HSCT. However, while effects on restoring health of HSC based on in vitro assays have been promising,[36] hematopoietic restoration in clinical trials has been somewhat inconsistent. In the FANCOLEN-1 study,[12] despite impressive percentages of gene-corrected leukocytes, gene therapy did not halt progressive thrombocytopenia. In a recent presentation of 12 patients under age 6 at the time of treatment on the RP-L102 study, hematopoietic stabilization was achieved in 7 of 12 patients, but blood counts failed to normalize in any patient.[37] Thus, for AYA patients who receive this therapy on clinical trials or if made commercially available, we would continue to recommend annual bone marrow (BM) screening and routine complete blood count (CBC) monitoring, as patients may remain at risk for developing severe BMF or MM.

CLINICAL CASE (continued)

After undergoing unrelated donor stem cell transplant with TCRαβ depletion, our patient remains engrafted with 100% donor chimerism and no evidence of relapse 3 years post-HSCT. He is planning to transition care to an adult hematology center in another city. At his final visit, he asks about his malignancy risks and about other subspecialty care he needs to reestablish.

Solid tumors in AYA patients with FA

Most solid tumors in patients with FA will occur between age 20 and 40 years, although exceptions include liver tumors associated with androgen use that have been seen in younger patients and childhood cancers (Wilms, brain, neuroblastoma) associated with rare *FANCD1* and *FANCN* subtypes.[2] Notably, nearly one-third of AYA patients are diagnosed with FA because of a preceding malignancy diagnosis.[2]

AYA patients should thus undergo routine screening as recommended in the FA clinical care guidelines (Table 3). Recent

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updates from the US National Cancer Institute FA cohort show that the cumulative incidence of solid tumors by late adulthood (age 60) is 18% to 24%, with head/neck squamous cell carcinoma (SCC) being the most common type, followed by basal cell and SCC skin cancers, and vulva/vaginal/cervical cancers in females.[38] Median age of onset for these malignancies was over 30 years of age, a full decade later than the median age of leukemia onset. Head/neck and skin cancers were the only solid tumors seen in adolescents. These findings parallel those seen in Wang et al.,[9] where 19% of patients developed solid tumors, 80% of which were SCC. In the National Cancer Institute cohort, earlier onset of solid malignancies was seen in patients with prior HSCT. Whether HSCT is the driver of earlier cancer occurrence or earlier tumor onset simply parallels earlier onset of BMF, necessitating HSCT in patients with more severe phenotypes, remains uncertain. Supporting the hypothesis that genotype may be the primary driver of age of tumor onset, 60% patients with severe *FANCA* variants impacting function of exons 27 through 30 developed a solid tumor by age 40 years.[38]

Prevention of solid tumors in FA is a critical focus of ongoing research. New brush biopsy techniques measuring aneuploidy have shown high sensitivity/specificity in diagnosing early oral dysplasia in FA.[39] A long-enrolling study (NCT03476330) with data yet to be released is assessing whether daily supplementation of the flavonoid quercetin, which possesses antioxidant, anti-inflammatory, and antineoplastic properties, can achieve the primary end point of reducing buccal micronuclei formation, a marker of malignant transformation risk. In vitro studies suggest combination therapy of quercetin and mammalian target of rapamycin (MTOR) inhibition may provide synergistic reduction in DNA damage.[40] Skin cancer prevention strategies include basic sun avoidance, avoidance of GvHD post-HSCT, and avoidance of medications such as voriconazole that may increase skin cancer risk. Whether human papillomavirus (HPV) drives development of head/neck and anogenital cancer in FA has long been debated. While we still recommend HPV vaccination to eliminate this risk factor, a recent comprehensive sequencing study of FA-associated SCC vs sporadically occurring SCC demonstrates that unlike in sporadic SCC, most FA-SCCs arise in the absence of HPV genome marking. Instead, FA-SCCs arise from TP53 loss and copy number alterations in other SCC driver mutations.[41]

Organ dysfunction monitoring in AYA patients with FA

In young children with FA, surgical intervention is often required for congenital anomalies, including the vertebral, anal, cardiac, tracheoesophageal fistula, esophageal atresia, renal, limb/digit, and hydrocephalus complex; hypospadias; and structural ear abnormalities. AYA patients with FA may need ongoing postsurgical follow-up for these congenital anomalies.

In addition, all AYA patients with FA need ongoing endocrinology care because of high rates of anatomic pituitary stalk abnormalities and other hormone changes. Short stature in FA may be driven in up to 25% of cases by growth hormone (GH) deficiency. GH replacement can help patients with FA achieve adequate adult height, and although early literature raised malignancy risk concerns, such risks for GH use in FA have not been proven. AYA patients with FA also have high rates of hypothyroidism (30%-40%) and osteoporosis (up to 50%), and diabetes (both type 1 and 2) occurs in 10% to 17% of patients.[9,38] In contrast, few patients have pulmonary complications unless induced by HSCT.

Finally, reproductive health remains an unmet challenge in FA. Both delayed and precocious puberty may occur and require hormonal intervention. Testicular failure and premature ovarian failure occur in over 40% of adults with FA.[2] Most males have a reduction in sperm counts, and women often reach menopause in their 20s or 30s, even without prior HSCT. A large retrospective study of gonadal function post-HSCT in FA demonstrates that longitudinal tracking of inhibin B levels in males and anti-Mullerian hormone in females may be better predictors of testicular and ovarian failure than traditional markers like follicle-stimulating hormone.[42] Biologic pathways that could be exploited to provide new approaches to improve fertility in patients with FA are only beginning to be explored.[43]

Conclusions

Improved outcomes for pediatric patients with FA and increased diagnosis of FA in older patients with late symptom onset are driving an increased need for multispecialty providers for AYA patients with FA. Increased recognition of patients with later-onset hematologic manifestations and the advent of gene therapy, which stabilizes but does not fully restore hematopoietic function, mean that many AYA patients with FA may not require allogeneic HSCT but will still need long-term hematologic monitoring. Furthermore, new techniques to prevent, diagnose, and treat solid malignancies will hopefully soon lead to decreased morbidity and mortality. The complex, long-term screening and treatment needed by AYA patients with FA require enhanced care models centered on a medical home with FA expertise, ensuring efficient and durable access to care.

Conflict-of-interest disclosure

Timothy S. Olson: no competing financial interests to declare.

Off-label drug use

Timothy S. Olson: All uses of medications discussed in this article are off-label, as there are no approved medications for use in Fanconi anemia.

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