Myelodysplastic Syndrome, Acute Myeloid Leukemia, and Cancer Surveillance in Fanconi Anemia

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KEYWORDS

- Bone marrow failure • Myelodysplastic syndrome • Leukemia
- Exquisite therapeutic sensitivity • DNA repair • BRCA1/2 • Fanconi complex
- Fanconi anemia

KEY POINTS

- Fanconi anemia is a DNA damage repair syndrome caused by pathogenic variants in key components of the Fanconi DNA repair complex.
- Patients with Fanconi anemia are at very high risk of bone marrow failure, myelodysplastic syndrome, leukemia, head and neck squamous cell carcinoma, and other malignancies.
- Treatment of patients with Fanconi anemia and cancer must be carefully tailored because of exquisite sensitivity to ionizing radiation and alkylating drugs.

INTRODUCTION TO FANCONI ANEMIA

Fanconi anemia (FA; MIM 607139) is a rare, cancer-prone inherited bone marrow failure syndrome with a wide range of clinical presentations, including radial ray anomalies, short stature, microcephaly, café au lait spots, and other medical problems. The condition is eponymous for Dr Guido Fanconi, who originally described the syndrome in 1927. At present, there are more than 2000 patients reported in the literature.[1] Advances in supportive care, including hematopoietic cell transplantation (HCT), have improved the lifespan for patients with FA, but cancer, HCT-related complications,

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and other complex medical problems remain significant causes of mortality. Herein, the authors review the underlying biology and clinical manifestations of FA as well as the current recommendations for cancer surveillance and management.

The Biology of Fanconi Anemia

FA is a chromosomal instability disorder caused predominantly by autosomal recessive inheritance of pathogenic variants in key components of the DNA damage response.[2,3] There is one gene, *FANCB*, associated with X-linked recessive inheritance.[4] Germline mutations (ie, pathogenic variants) in at least 22 genes are associated with FA. There is consensus in the field regarding 18 genes (*FANCA*, *B*, *C*, *D1*, *D2*, *E*, *F*, *G*, *I*, *J*, *L*, *N*, *P*, *Q*, *T*, *U*, *V*, and *W*)[4–26] (**Table 1**).[27] An additional 4 genes (*FANCM*, *FANCO*, *FANCR*, and *FANCS*) are considered FA-like, because they have not been described in patients with bone marrow failure (BMF).[25,28,29] *FANCM* is not considered a bonafide FA gene, because it only has only occurred in a patient also reported to harbor biallelic *FANCA* mutations. Biallelic pathogenic variants in *FANCA* are the most common cause of FA, with 65% of patients harboring mutations in this gene. *FANCC* (14%) and *FANCG* (9%) follow *FANCA* for genes most frequently mutated in Fanconi Anemia patients with all other only reported rarely[30] (see **Table 1**).

The proteins of the FA pathway create a biochemical circuit that function in DNA repair, DNA damage response, and other cellular processes. As DNA is replicated, nucleotide incorporation and processing of the replication fork are prone to errors including wrong nucleotides, damaged bases within the DNA, abnormal DNA-protein complexes, creation of DNA-RNA hybrids (R-loops), and aberrant DNA structures, such as G quadraplexes.[31] The specific role of proteins in the Fanconi pathway is removal of DNA interstrand cross-links. Interstrand cross-links may arise from endogenous and exogenous compounds, such as aldehydes and platinum drugs, respectively. Interstrand cross-links prevent DNA strand separation and can act to block the DNA replication process and/or transcription. These aberrant DNA strands, if left intact, promote cell death.[32]

Clinical Manifestations

Clinical characteristics of FA may vary significantly from patient to patient. Typical FA findings include radial ray abnormalities with missing or unusual thumbs, café au lait macules, and typical "Fanconi" facies. Abnormal thumbs are an important differentiating feature of FA and differentiate this syndrome from thrombocytopenia absent radius syndrome in which thumbs are present.[33] Other significant FA-associated anomalies include kidney and urinary tract malformations, vertebral anomalies, esophageal atresia, hydrocephalus, short stature, and small eyes. Almost all organ systems may be involved with the highest number of congenital malformations associated with the *FANCD1/BRCA2* genotype.[34] Clinical features of FA may significantly overlap with those of the VACTERL-H association: VACTERL-H is the acronym for vertebral anomalies, anal atresia, cardiac anomalies, trachea-esophageal fistula, esophageal or duodenal atresia, renal structural anomalies, limb deformities, and hydrocephalus.[35] Additional manifestations of FA may include metabolic abnormalities, endocrinopathies, and hearing impairments. Although patients with FA may exhibit the VACTERL-H phenotype, it is not specific to FA. Alter and Giri[36] distinguished PHENOS (Pigmentation, small Head, small Eyes, central Nervous system [not hydrocephalus], Otology, and Short stature) as an acronym that includes the major dysmorphic features of FA as an aid to identify FA patients within the VACTERL-H phenotype.

Patients with FA are at very high risk of BMF, myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), head and neck squamous cell carcinoma (HNSCC),