Best Practice & Research Clinical Haematology 27 (2014) 214–221

Contents lists available at ScienceDirect

Best Practice & Research Clinical Haematology

journal homepage: www.elsevier.com/locate/beha

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Fanconi anemia and the development of leukemia

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Keywords:
Fanconi anemia
leukemia
myelodysplastic syndrome
bone marrow failure
stem cell transplant

Fanconi anemia (FA) is a rare autosomal recessive cancer-prone inherited bone marrow failure syndrome, due to mutations in 16 genes, whose protein products collaborate in a DNA repair pathway. The major complications are aplastic anemia, acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and specific solid tumors. A severe subset, due to mutations in *FANCD1/BRCA2*, has a cumulative incidence of cancer of 97% by age 7 years; the cancers are AML, brain tumors, and Wilms tumor; several patients have multiple events. Patients with the other genotypes (*FANCA* through *FANCQ*) have cumulative risks of more than 50% of marrow failure, 20% of AML, and 30% of solid tumors (usually head and neck or gynecologic squamous cell carcinoma), by age 40, and they too are at risk of multiple adverse events. Hematopoietic stem cell transplant may cure AML and MDS, and preemptive transplant may be appropriate, but its use is a complicated decision.

Introduction

Fanconi anemia (FA, MIM 607139) is one of the rare inherited bone marrow failure syndromes (IBMFS) with a very high cancer-predisposition, including leukemia. It is primarily autosomal recessive (except *FANCB* which is X-linked), due to mutations in more than 16 genes, whose gene products collaborate in a DNA repair pathway. The majority of known patients have a variety of physical anomalies, including short stature, café au lait spots and hyper/hypopigmentation, abnormal thumbs, absent

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http://dx.doi.org/10.1016/j.beha.2014.10.002
1521-6926/Published by Elsevier Ltd.

radii, microcephaly, micro-ophthalmia, structural renal anomalies, and other findings. It was first described in 1927 by Dr Guido Fanconi, and more than 2000 cases have been reported in the literature. Many patients are recognized because of the development of aplastic anemia, which has a peak at around 7 years of age [1]. The age at diagnosis ranges from in utero to over 50 years, and includes adults with no physical findings who present with aplastic anemia, leukemia, or solid tumors; the number of undiagnosed adults who are spared these complications and lack birth defects is unknown. FA is one of several IBMFS, which share hematologic changes leading to the diagnosis, such as pancytopenia or single lineage cytopenias, very high risks of leukemia, primarily acute myeloid leukemia (AML), and extremely high risks of specific solid tumors. The molecular pathways are very different, however (Table 1).

The usual diagnostic test for FA involves detection of an increased amount of chromosomal breakage in peripheral blood T lymphocytes cultured with a clastogenic agent such as diepoxybutyrate or mitomycin C (Fig. 1). This widely used labor intensive assay is very sensitive and specific. The only limitation is the identification of patients with hematopoietic somatic mosaicism, in whom a hematopoietic stem cell may have undergone a genetic correction by several mechanisms (eg, gene conversion), leading to marrow and blood cells that have a selective growth advantage. Testing of skin fibroblasts may be required if there is insufficient chromosomal breakage to clearly diagnose FA but it is suspected clinically [2].

Genetics

There are 16 known FA genes, of which *FANCA* is the most frequent, followed by *FANCC* and *FANCG*; *FANCB* is a rare X-linked recessive gene, while all the others are autosomal recessive (Fig. 2). The FA/BRCA2 DNA repair pathway begins when DNA damage occurs. The genes for *FANCA*, *FANCB*, *FANCC*, *FANCE*, *FANCF*, *FANCG*, *FANCL*, and *FANCM* are activated, produce RNA, which then leads to proteins that combine into the core complex (Fig. 3). This complex is necessary for the ubiquitination of the FANCD2 and FANCI proteins, which form the ID complex, which then permits DNA repair foci to form, including the downstream gene products, J/BRIP1, D1/BRCA2, N/PALB2, O/RAD51C, P/SLX4, and Q/ERCC4 [3]. Biallelic mutations in any of these genes prevent the repair pathway from operating. Patients with biallelic mutations in *FANCD1/BRCA2* have a unique phenotype and cancer risk (see below).

Leukemia and solid tumors

More than 400 among over 2000 cases with FA were reported to have some type of malignancy (Fig. 4). There were 188 leukemias and 286 solid tumors described in 413 patients by the end of 2012; 47 had 2–4 cancers. Eighty-four percent of the leukemias were AML, which is more typical of adults than children, where acute lymphoblastic leukemia is much more common. The most frequent solid tumors were head and neck squamous cell carcinoma (HNSCC), among untransplanted patients as well

Table 1
Inherited bone marrow failure syndromes.

Syndrome	Hematology[a]	Leukemia	Solid tumors	Pathway
Fanconi anemia	Aplastic anemia	AML[b]	SCC[c]	DNA repair
Dyskeratosis congenita	Aplastic anemia	AML	SCC	Telomere biology
Diamond-Blackfan anemia	Anemia	AML	Osteosarcomas	Ribosome biogenesis
Shwachman-Diamond syndrome	Neutropenia	AML	–	Ribosome biogenesis
Severe congenital neutropenia	Neutropenia	AML	–	Neutrophil differentiation
Amegakaryocytic thrombocytopenia	Thrombocytopenia	AML	–	Mutations in thrombopoietin receptor
Thrombocytopenia absent radii	Thrombocytopenia	AML	–	exon–junction complex subunit Y14 at 1q21.1

Reprinted from Blood Reviews, Volume 24/Edition 3, Shimamura A, Alter BP, Pathophysiology and management of inherited bone marrow failure syndromes, Pages 101-22, 2010, with permission from Elsevier.

[a] At diagnosis.

[b] Acute myeloid leukemia.

[c] Squamous cell carcinomas, particularly head and neck and gynecologic. Adapted from Ref. [1].