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Fanconi anemia and the development of leukemia

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Abstract

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 *FANCO*) 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.

Keywords

Fanconi anemia; leukemia; myelodysplastic syndrome; bone marrow failure; stem cell transplant

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 radii, microcephaly, microphthalmia, 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

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Conflict of Interest Statement

None.

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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 as those who had received a hematopoietic stem cell transplant. The next most frequent tumors were liver, brain, vulvar SCC, and Wilms tumor. Many of the brain and Wilms tumors were in patients whose genotypes were unknown at the time, but might have been *FANCD1/BRCA2* (see below).

The relative risk of cancer in FA is exceedingly high, when compared with the incidences expected in the general population. We combined data from four independent FA cohorts for

our analyses [4–7], and found that the observed to expected ratio of all cancers including leukemia was 48 after adjustment for age, sex, and birth cohort. Solid tumors had a relative risk of 38-, HNSCC 600-, AML 700-, vulvar SCC 3000-, and MDS 6000-fold (Fig. 5). These enormously high numbers are due to the cancers in FA occurring at much younger ages than in the general population. The peak hazard rate for severe bone marrow failure (BMF) was 5% per year at age 6.7 years, after which the annual hazard declined substantially, while the hazard for AML rose after age 10 and then plateaued in the 20- and 30-year-old patients, and the hazard for solid tumors increased after age 10 in a more than linear manner, exceeding 10% per year by age 40 (Fig. 6) [4]. MDS was analyzed separately, since it does not compete with solid tumors, and may follow BMF or precede AML; the hazard rate reached around 1% per year starting at age 10 and then plateaued, and the cumulative incidence was 40% by age 50 (data not shown). The cumulative incidence of each of the adverse events as the first event in a competing risk analysis was 60% for BMF, 15% for AML, and >20% for solid tumors, with no plateau for the latter (Fig. 6). Thus, FA in general is an extremely cancer-prone syndrome. Leukemia has been managed with chemotherapy followed by hematopoietic stem cell transplantation, with improving results over time [8]. However, solid tumors are more complicated and the prognosis less optimistic, since the major management strategy is surgery, and recurrences are frequent.

FANCD1/BRCA2

Patients with biallelic mutations in *FANCD1/BRCA2* are a special subset with unique genotype/phenotype/outcome associations [9,10]. Their physical anomalies often include many of the following: short stature, microcephaly, micro-ophthalmia, abnormal thumbs and/or radii, café au lait spots, hyper- and hypopigmented skin, imperforate anus, structural renal anomalies, and congenital heart disease; many of the features of these patients are included in the VATER association acronym [11]. The patients have very high risks of development of malignancies (Fig. 7). Leukemia, primarily AML, was reported in 17 of 36 patients, with a cumulative incidence of about 80% by age 10 years. The 6 children with a unique site for their mutation in *BRCA2*, namely IVS7, all developed leukemia before age 3, a very strong example of genotype/cancer association, although those with other mutations were also at a high risk of leukemia. Sixteen patients had brain tumors by age 5, including all 7 with one mutated allele 886delGT. Wilms tumor was the next most frequent type of cancer, reported in 8 patients, all by age 5. Overall 22 patients had solid tumors, of whom 9 had at least two malignancies (solid tumor and/or leukemia), and the cumulative incidence of any malignancy was 97% by age 7 years.

Comparison of *FANCD1/BRCA2* and other FA patients

The major adverse events are similar in all types of FA, but the frequencies and ages differ substantially (Table 2). Almost all of those with *FANCD1/BRCA2* have one or more cancers before age 7, either leukemia, brain tumor, Wilms tumor, or combinations, and very few develop severe bone marrow failure. More than half of the other patients with FA develop severe bone marrow failure, as well as solid tumors (30%) and/or leukemia (20%) by age 40–50 years. However, at least 10% and perhaps more whom we have not identified, do not develop these complications.

Management of bone marrow

The community of FA physicians has agreed on consensus guidelines for treatment of hematologic disease, namely marrow failure with hemoglobin <8 g/dL, platelets <30,000/mm³, absolute neutrophil count < 500/mm³, or overt leukemia with blasts in the blood or >20% in the marrow, or MDS with dyspoieses and cytopenias [12]. However, they have not fully addressed the concept of preemptive transplant, to preclude the development of leukemia or MDS. Patients with FA with the highest risks of AML or MDS may be identified as those with mutations in *FANCD1/BRCA2*, but may also have mutations in any of the other 15 FA genes, and the transplant decision may depend on different criteria. The definition of MDS in adults according to the World Health Organization usually involves hypercellular marrow, often with specific cytogenetic clones that have variable prognostic significance, dysplasia in one or more lineages, and an increased risk of AML. MDS in pediatrics (not necessarily FA) is most commonly refractory cytopenia of childhood (RCC), with hypocellular marrow, monosomy 7 the most frequent clone, and dyspoiesis in at least 10% of cells in one or more lineages, or “any” dyspoiesis in two or more lineages [13,14]. The FA scientific community has not fully clarified the criteria for transplant before MDS or AML, although those events increase the risk of a poor transplant outcome.

The decision to perform a hematopoietic stem cell transplant (SCT) is not clearcut, and requires shared decision making between physicians and families. The components of the decision include information regarding the risk of not surviving the procedure, the possibility of post-SCT complications, which could include graft-versus-host disease, immune dysfunction, and endocrine disorders, as well as subsequent development of solid tumors. These tumors could be the ones that occur with very high frequency in patients with *FANCD1/BRCA2* and are independent of transplant, or HNSCC for which the very high risk in patients with FA is even higher after SCT [9,15]. A recent survey of parents of participants in the Fanconi Anemia Research Fund registry indicated that the decision is not easy, associated with uncertainty due to the indeterminacy of the outcome risks, as well as ambiguity of the risk estimates related to conflicting evidence, conflicting opinions, and lack of information. Families seek expert opinions, but may delegate the ultimate decision to their physicians [16]. It must be emphasized, however, that almost half of the patients with FA may never need a transplant, and a challenge for the physicians is to identify those patients.

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Figure 1.

Chromosome breakage. Metaphases from blood T-lymphocytes following culture with phytohemagglutinin and a DNA crosslinking agent such as diepoxybutane or mitomycin C. Figure shows breaks, gaps, rearrangements and endoreduplications.

Adapted from Leiden Open Variation Database, <http://chromium.liacs.nl/LOVD2/FANC/home.php>

Figure 2.

Fanconi anemia genes, indicating the majority are FANCA, followed by FANCC and FANCG, and others less frequent. The ones marked with an asterisk are associated with breast cancer in heterozygotes, and FA when mutations occur in both alleles. Adapted from Leiden Open Variation Database, <http://chromium.liacs.nl/LOVD2/FANC/home.php>.

Figure 3.

FA/BRCA DNA damage response pathway. Following DNA damage, the proteins represented by A, B, C, E, F, G, L and M form the core complex, which is required for ubiquitination of the I and D2 proteins, which are in turn required for the downstream complex of D2-ubi, I-ubi, and D1/BRCA2, J/BRIP1, N/PALB2, BRCA1, O/RAD51C, P/SLX4, Q/ERCC4, and BRCA1 to form DNA repair foci. Only BRCA1 has not yet been proven to be a Fanconi gene. Adapted from Shimamura and Alter [1].

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188 leukemias and 286 solid tumors in 413/2190 people with FA;
47 had 2-4 cancers.

Figure 4.

The types and frequencies of cancer in FA reported in the literature from 1927 through 2012. There were 188 cases of leukemia, of which 84% were acute myeloid leukemia, and 286 solid tumors, in 413 of 2190 people with FA. Forty-seven had 2-4 cancers.

Data from North American Survey, Germany, Israel, and NCI

Figure 5.

The relative risk of cancer compared with the general population (using SEER data) in a combination of four independent cohorts. The Y axis shows the observed/expected ratio on a log scale. The risk of any cancer was ~50-fold, solid tumors ~40-fold, HNSCC ~550-fold, vulvar 3000-fold, AML 700-fold, and MDS 6600-fold. Data from [4–7].

Alter et al, BJH, 2010

Figure 6.

Annual hazard rate and cumulative incidence of competing adverse events by age in patients with Fanconi Anaemia (FA). Adverse events are severe bone marrow failure (BMF, blue), leukemia (AML, black), or solid tumors (ST, red). Results are combined from the cohorts cited in Figure 5. Left, Annual hazard rate in percent per year. Right, cumulative incidence by age (cumulative percentage experiencing each event as initial cause of failure) and 95% confidence intervals (CI) (shaded areas). From Alter et al [4].

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Adapted from Alter et al JMG 2007

Figure 7.

Outcomes in patients with FA due to mutations in FANCD1/BRCA2. **(A)** Probability of any type of leukemia. **(B)** Probability of a brain tumor, associated with a mutation in 886delGT compared with other mutations. The relative hazard due to 886delGT is 4 (CI 2 – 12). **(C)** Probability of any solid tumor. **(D)** Probability of leukemia associated with a mutation in IVS7 compared with other mutations. The relative hazard due to IVS7 is 4 (CI 1.3 – 13). **(E)** Probability of Wilms tumor. **(F)** Probability of any cancer is 97% by age 7 years. Adapted and updated from Alter et al [9,10].

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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

^a At diagnosis.

^b Acute myeloid leukemia.

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

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Table 2

Comparison of patients with *FANCD1/BRCA2* and other mutations.

Adverse Event	<i>FANCD1/BRCA2</i>	Other Genes
By age, years	7	40
Leukemia	50%	20%
Solid Tumor	80%	30%
Any Cancer	97%	50%
Severe bone marrow failure	<5%	50%
No adverse event	<5%	<10%