Malignant hematological diseases in the presence of Fanconi anemia

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Find out more about the diagnosis of malignant hematological diseases in the presence of Fanconi anemia (FA) and learn more about prognosis and therapy.

Diagnostic recommendation

Method	Anticoagulant	MDS Recommendation for FA	AML Recommendation for FA
Cytomorphology	EDTA	mandatory	mandatory
Immunophenotyping	EDTA or Heparin	optional	mandatory
Chromosome analysis	Heparin	mandatory	mandatory
FISH	EDTA or Heparin	optional	optional
Molecular genetics	EDTA or Heparin	optional	optional

Background

Pathogenesis and clinical appearance of Fanconi anemia
Fanconi anemia is based on germline mutations in *FA/BRCA* DNA repair genes and is the most common genetic cause of bone marrow failure. FA patients typically develop pancytopenia in the first decade of life, which usually begins with thrombocytopenia and leukopenia. The fact that all hematopoietic lines are affected suggests a dysfunction of the hematopoietic stem cells (HSCs). This theory is supported by the low proportion of CD34-positive cells in the bone marrow of young Fanconi anemia patients, a cell fraction that is enriched with HSCs. Therefore, a prenatal defect of HSCs in Fanconi anemia patients is assumed.

Due to chromosomal instability, the risk of cancer is generally increased in Fanconi anemia patients. Most frequently Fanconi anemia patients develop myelodysplastic syndromes (MDS) or acute myeloid leukaemias (AML); often already in early childhood with a cumulative risk of disease in the further course (30%-40% at the age of 40 years) (Kutler et al. 2003, Quentin et al. 2011). Close monitoring of haematopoiesis is therefore necessary. For this purpose, a bone marrow analysis is recommended at the time of Fanconi anemia diagnosis and in the further course of the disease. This should include bone marrow aspiration, (biopsy) and a cytogenetic examination (Peffault de Latour et al. 2016, Frohnmayer et al. 2014).

Diagnosis of Fanconi anemia
In Germany, analyses to confirm the diagnosis of Fanconi anemia are carried out at the Institutes of Human Genetics at the Universities of Würzburg and Berlin and at the University of Düsseldorf, among others.

The diagnosis of Fanconi anemia is classically made by means of a chromosome break test. Chromosomal breaks are induced in lymphocytes from peripheral blood via DNA cross-linking using mitomycin C (MMC) or diepoxybutane (DEB). Fanconi anemia cells show an increased number of chromosomal breaks compared to wild-type cells. Another diagnostic test is cell cycle analysis after MMC treatment by flow cytometry (FACS), whereby Fanconi anemia cells show accumulation in the G2 arrest compared to wild type cells (Auerbach 2009).

Nowadays, Fanconi anemia diagnostics is substantially supported by sequence analyses of the genes that make up the 16 known genetic subtypes of Fanconi anemia (Longerich et al. 2014). The respective Fanconi anemia genotype is clinically relevant, since e.g. the genetic subtypes Fa-D1 (*BRCA2* mutation) and Fa-N (*PALB2* mutation) are associated with severe phenotypic expression of Fanconi anemia and are associated with early development of leukemia (median 2.2 years) and pediatric cancer (Gille et al. 2012).

A peculiarity that may occur in Fanconi anemia patients is somatic reversion in part of the blood and bone marrow cells (mosaic), whereby the Fanconi anemia gene defect is corrected, which gives this cell population an enormous growth advantage. In these cases a chromosome break test in fibroblasts of the skin is necessary to confirm the diagnosis.

Therapy of Fanconi anemia
Clinical measures in Fanconi anemia patients are treatment with androgens or blood transfusions to stabilize the blood count. Due to their defective DNA repair, Fanconi anemia patients show a hypersensitivity to DNA damage and thus to most chemotherapies. The only curative therapy is hematopoietic stem cell transplantation (HSCT) with a long-term survival rate of 30%-40%. However, HSCT is associated with a high mortality rate, especially in the first decade of life.

Diagnosis of malignant hematological diseases in the presence of Fanconi anemia

Cytomorphology

MDS in Fanconi anemia is often characterized by refractory cytopenia with multilineage dysplasia with or without excess of blasts. A certain level of dyserythropoiesis can be observed almost constantly in Fanconi anemia patients, which is why mild dyserythropoiesis is not used as a criterion for MDS in Fanconi anemia. AML can be diagnosed primarily or after an MDS phase. For the diagnosis of AML a cytomorphological assessment is mandatory.

Immunophenotyping

Particularly against the background of dysplasia frequently occurring in Fanconi anemia, the cytomorphological differentiation from MDS represents a diagnostic challenge (Frohnmayer et al. 2014). The immunophenotypic detection of aberrant antigen expression patterns can contribute to the reliability of an MDS diagnosis. In case of AML in Fanconi anemia, flow cytometry allows the immunological characterization of the leukemic cells. The determination of the leukemia-associated aberrant immunophenotype (LAIP) lays the background for monitoring in the course of therapy and the determination of measurable residual disease (MRD).

Chromosome analysis

Cytogenetic aberrations are common in both MDS and AML in Fanconi anemia. Characteristic is the absence of typical AML associated cyto- and molecular genetic subtypes - instead chromosomal gains and losses are observed (Butturini et al. 1994, Quentin et al. 2011, Peffault de Latour et al. 2016). Among the most common aberrations are gains of the long arm of chromosome 1 (+1q; minimal region 1q23 to 1q32), monosomy 7/7q and gains of the long arm of chromosome 3 (+3q; minimal region 3q25 to 3q29, including *MECOM/EVI1*). Less frequent are deletions of 5q, 11q, 13q, and 20q, and gains of 9p or a trisomy 8 (Peffault de Latour et al. 2016, Quentin et al. 2011). Changes often involve the *RUNX1* gene on chromosome 21q22, including *RUNX1* translocations or *RUNX1* mutations (Peffault de Latour et al. 2016).

Fluoreszenz in situ Hybridisierung

While 1q gains and 7q deletions are easy to identify in conventional chromosome analysis, cytogenetically cryptic 3q gains or *RUNX1* aberrations may occur (Quentin et al. 2011, Cioc et al. 2010, Tönnies et al. 2003, Peffault de Latour et al. 2016). In the case of cryptic changes, FISH diagnostics can optimally complement chromosome analysis. This also applies to the clarification of complex changes (e.g. by 24-colour FISH). Due to its high sensitivity FISH can also contribute to the detection of small clones (Peffault de Latour et al. 2016).

Molecular genetics

With the exception of acquired *RUNX1* mutations, somatic gene mutations are rare (Peffault de Latour et al. 2016). Due to the high sensitivity of molecular genetic methods, molecular genetic analysis allows the detection of small clones in the presence of molecular markers (Peffault de Latour et al. 2016).

Prognosis and staging

Chromosomal aberrations in Fanconi anemia patients, especially +3q, -7/7q- and *RUNX1* aberrations, are usually associated with MDS/AML and indicate an unfavorable prognosis. In contrast, +1q represents an early event and is found in all stages of Fanconi anemia and therefore cannot be associated with malignant transformation. Other aberrations such as 5q-, 11q- or 20q- are found in the same way as in non- Fanconi-anemia-associated MDS cases, but less frequently, and are not considered to indicate an unfavourable prognosis (Fig. 1). If such non-predictive chromosomal aberrations with no or slight cytopenia are detected, close monitoring of the bone marrow (morphology and cytogenetics) is recommended (Fig. 1).

Once high-risk bone marrow staging is present, HSCT is indicated (Fig. 1). Due to the high toxicity of DNA-damaging agents to Fanconi anemia patients, reduced-intensity conditioning (RIC) is applied as standard prior to stem cell transplantation (Fig. 1).

Due to the high risk of secondary malignancies as well as chronic Graft-versus-Host Disease (GvHD), long-term monitoring with regular examinations in Fanconi anemia patients is strongly recommended (Fig. 1).

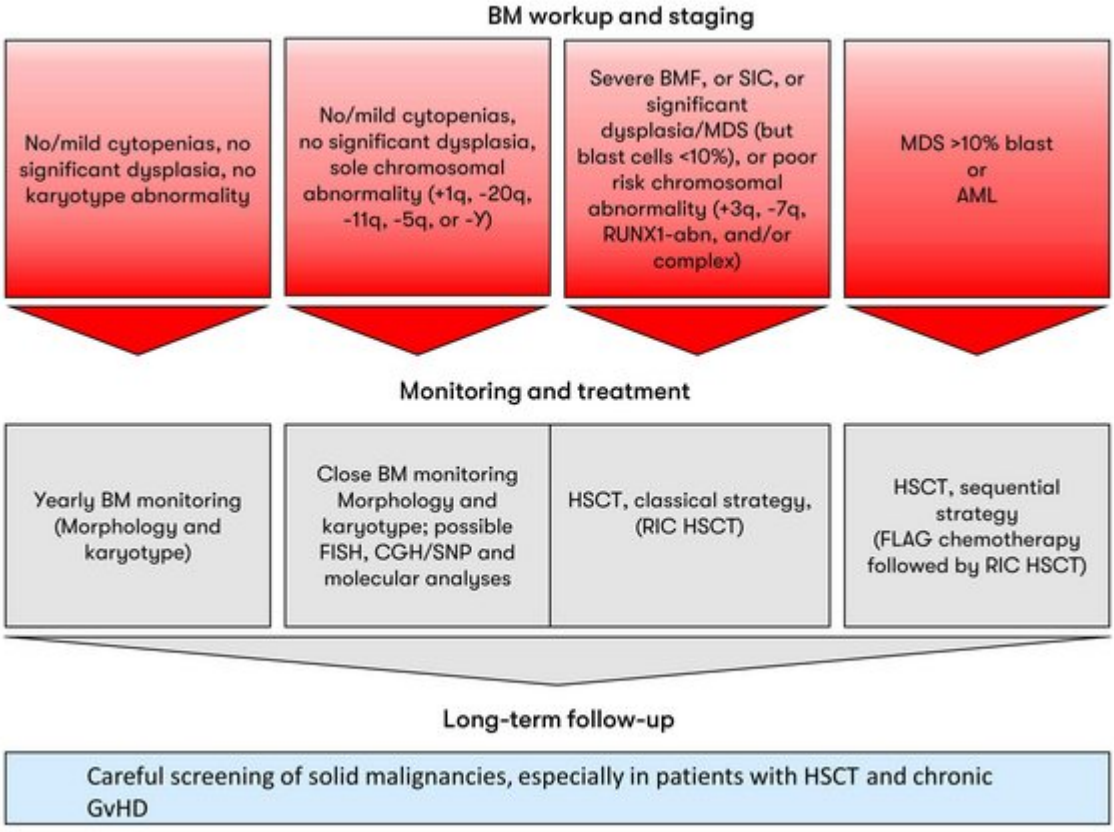

Figure 1:Staging and management of MDS and AML in Fanconi anemia **patients.**
FA, fanconi anemia; CGH, comparative genomic hybridization; FLAG, fludarabine/cytarabin/granulocyte colony-stimulating factor; GvHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; AI, bone marrow insufficiency; BM, bone marrow; SIC, severe isolated cytopenia; SNP, single nucleotide polymorphism (according to Peffault de Latour et al. 2016).

Related literature

Deutsche Fanconi-Anämie-Hilfe e.V. Fanconi Anämie: Ein Handbuch für Eltern, Patienten und ihre Ärzte; auf dem Original von Lynn und Dave Frohnmayer basierende und ergänzte deutsche Überarbeitung. 2005. ISBN 3-00-015621-6.
Download unter: https://fanconi.de/informationen-zur-fa/

Frohnmayer D et al. Fanconi Anemia: Guidelines for Diagnosis and Management. Fourth Edition. Fanconi Anemia Research Fund, Inc 2014.
Download unter: https://www.fanconi.org/explore/clinical-care-guidelines

References

You can find the corresponding references here:
https://www.mll.com/en/diagnostic-offer/others/malignant-hematological-diseases-in-the-presence-of-fanconi-anemia.html#references