

REVIEW

Hematopoietic stem cell transplantation in childhood inherited bone marrow failure syndrome

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Aplastic anemia is a rare disease in children that is most commonly idiopathic and less often a hereditary disorder. Hereditary bone marrow failure (BMF) syndromes, however, should be considered both in children and in adults before any attempt at treatment. Precise diagnosis is important because it will modify prognostic treatment options and the results of bone marrow transplantation. In this review, we will report recent results of treatment of Fanconi anemia and other hereditary BMF syndromes.

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Introduction

Aplastic anemia (AA) is a rare disease in children that is most commonly idiopathic and less often a hereditary disorder. Hereditary bone marrow failure (BMF) syndromes, however, should be considered both in children and in adults before any attempt at treatment. While new genetic tests are being developed, these are not widely available. Genomic instability in the presence of clastogenic agents is the hallmark of Fanconi anemia (FA). In contrast, marked telomere dysregulation is a characteristic of dyskeratosis congenita. Mutations affecting ribosome assembly and function are associated with dyskeratosis congenita, Shwachman–Diamond syndrome and Diamond–Blackfan anemia.¹ The principal characteristics of these diseases are detailed in Table 1.

Hematopoietic cell transplantation in FA

Fanconi Anemia is a rare autosomal recessive disease characterized by congenital abnormalities, progressive BMF, spontaneous and induced chromosome breakage, and cancer susceptibility. At least 13 genes have been implicated in the disease, as resultant products functionally interact within the FA/BRCA biochemical pathway of DNA repair.² FA patients often have skeletal, thumb or limb abnormalities and abnormal skin pigmentation (café au lait spots). Other organ systems involved include cardiac, renal and auditory systems. Low birth weight and growth retardation are frequent.

The hematological consequences of FA often develop in the first years of life, but sometimes the diagnosis is made only later in life because of the absence of any obvious morphologic malformation and, in some cases, due to somatic mosaicism. Death often results from complications of aplastic anemia or occurrence of malignancy. Acute myeloid leukemia is the most common hematological malignancy, and squamous cell carcinomas of the esophagus, head and neck, and urogenital tract are the most common solid tumors.

Due to the marked variation in the clinical manifestations of FA as well as its rarity, the diagnosis is most often missed until there are hematological manifestations. Even in those with a BMF syndrome, FA is frequently not considered unless there are classic morphological features, such as radial ray or renal defects. Importantly, other constitutional forms of AA may have similar congenital abnormalities of FA, and FA patients may have no obvious constitutional anomalies. Several diagnostic tests have been developed including the following:

- Demonstration of increased chromosome breaks with tri- or quadri-radial figures on exposure of peripheral blood lymphocytes or cultured fibroblasts to clastogenic agents, such as nitrogen mustard, diepoxybutane or mitomycin C. This test is reliable and has a long track record although it needs validation in well-trained laboratories.
- Demonstration of cell cycle G2/M arrest on exposure to clastogenic agents.
- Demonstration of FANCD2 ubiquitination, which is both sensitive and specific for most FA patients but does

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Table 1 Principal characteristic of hereditary bone marrow failure syndromes

<i>Disease</i>	<i>Mutations</i>	<i>Diagnostic tests</i>	<i>Clinical expression</i>
Fanconi anemia	<i>FANCA</i> <i>FANCB</i> <i>FANCC</i> <i>FANCD1/BRCA2</i> <i>FANCD2</i> <i>FANCE</i> <i>FANCF</i> <i>FANCG/XRCC9</i> <i>FANCI</i> <i>FANCI/BACH1/BRIP1</i> <i>FANCL/PHF9/POG</i> <i>FANCM/Hef</i> <i>FANCN/PALB2</i>	MMC, DEB chromosomal breakage in lymphocytes FANCD2 monoubiquitination	Aplastic anemia, malformations: thumbs, <i>café au lait</i> spots, microcephaly, short stature, kidney, heart, etc. Malignancies: acute leukemia (AML), squamous cell carcinoma of head and neck, urogenital tract, liver and other organs
Dyskeratosis congenita	<i>DCK1</i> <i>TERC</i> <i>TERT</i>	Telomere length	Aplastic anemia, malformations, cancer
Seckel syndrome	<i>SCKL1</i> , 2, 3	None	Malformations, bird-head, dwarfism, mental retardation, pancytopenia
Shwachman–Diamond	<i>SBDS</i>	Decreased serum trypsinogen and/or pancreatic isoamylase	Aplastic anemia, pancreatic exocrine deficiency
Kostmann	<i>Neutrophil elastase ELA2</i>	None	Chronic neutropenia, leukemia
Diamond–Blackfan	<i>RSP19</i>	Elevated adenosine deaminase	Erythroblastopenia, malformations
Congenital amegakaryocytic thrombocytopenia	<i>c-Mpl</i>	None	Amegakaryocytosis, aplastic anemia

Abbreviations: DEB = diepoxybutane; MMC = mitomycin C; AML = acute myeloid leukemia.

not permit diagnosis in those rare patients with mutations in FA genes downstream of FANCD2.

- In rare cases, negative or borderline blood tests may reflect marked somatic mosaicism in the lymphocyte population and necessitate skin fibroblast testing in those where there is a strong suspicion of FA.

Once the diagnosis of FA has been confirmed, annual marrow examinations are recommended to identify clonal cytogenetic abnormalities, most commonly involving chromosomes 7 (7– or 7q–) and 8 (trisomy), and balanced or unbalanced translocations involving portions of chromosomes 1, 3 or 11. While there have been reports of transient clonal abnormalities, presence of cytogenetic abnormalities necessitates more frequent monitoring.

Results of HLA-identical sibling donor hematopoietic cell transplantation

Currently, BMT is the only treatment that definitively restores normal hematopoiesis. As FA cells are hypersensitive to DNA crosslinking agents, FA patients exhibit marked sensitivity to exposure to genotoxic agents, including CY, Bu or irradiation. In addition, GVHD itself induces severe tissue damage with delayed or absent tissue repair relative to non-FA patients.³

Most reports over the past decade have demonstrated good results. In our series of 117 FA patients, conditioned with low-dose CY and total lymphoid irradiation, 5-year survival was 85%. In general, most series have reported younger patient age, higher pretransplant platelet counts, absence of previous treatment with androgens, normal pretransplant liver function tests and limited malformations as factors associated with better survival after transplantation.⁴ Unfortunately, a rising risk of cancer has been observed in long-term survivors, particularly cancers of the head and neck.⁵ In an analysis of 700 patients with FA ($n=79$) or AA ($n=621$) treated with allogeneic hematopoietic cell transplantation (HCT) in Seattle or Paris, the Kaplan–Meier estimate for developing any malignancy by 20 years after transplantation was 14%.⁶ Among patients with FA, a single hazard peak for solid tumors occurred between 8 and 9 years after HCT. The Kaplan–Meier estimate of developing any malignancy by 20 years after HCT was 42% (95% confidence interval, 10–74%), with all being solid tumors. In the multivariate analysis of the 700 patients with marrow failure (FA and non-FA), the diagnosis of FA (relative risk (RR) 2, $P=0.0001$) and treatment with azathioprine (RR 11.7, $P=0.0001$) were independent predictors of secondary malignancy. Absence of irradiation in the conditioning regimen did not abolish the risk of secondary tumors.

As solid tumors occur in FA patients without prior exposure to chemotherapy and radiation, it is clear that cancer is at least in part related to the specific genetic defect present and environment, as shown by different phenotypic expressions of the disease in homozygous twins.

In an attempt to reduce the potential impact of irradiation and GVHD on the risk of late effects, including cancer, newer regimens have replaced total lymphoid irradiation with fludarabine in combination with low-dose CY as well as used T-cell depletion to reduce the risk of GVHD. While limited in number and follow-up, early results are encouraging.⁷ It is too early to tell if there is any impact on cancer risk at this time.

Nonetheless, the good results of HLA-identical sibling HCT raise several questions regarding the optimal timing of BMT and the best conditioning regimen. Concerning the former, there is a general agreement that HLA-identical sibling hematopoietic stem cell transplantation should be performed as first-line therapy, without first using androgens or corticosteroids, which have considerable side effects. When blood counts fulfill the criteria of severe AA (Hb < 8 g/100 ml, neutrophils < 0.5 × 10⁹/l or platelets < 20 × 10⁹/l), transfusions and infections are more likely, making this a suitable time to perform HCT. During the waiting period, it is important to regularly perform bone marrow aspiration and cytogenetic analysis for detection of clonal abnormalities or of leukemic transformation. Results show that transplants performed late (after a long period of aplasia or during leukemic transformation) are associated with markedly poorer results. Most patients treated for acute leukemia do not tolerate standard-dose chemotherapy and have a very poor prognosis, although some long-term survivors have been reported after HCT. In terms of the best conditioning regimen, the aims are to (1) avoid rejection in a population of patients who have received multiple transfusions, (2) limit early and late toxicities and (3) minimize risk of GVHD. Several combinations have been used in a limited number of patients; fludarabine-containing regimens in combination with low-dose CY or Bu and ATG appear to be well tolerated.

Graft-versus-host disease must be prevented, as it is more likely to be severe in FA patients because of the underlying DNA repair defect and because lichen planus lesions associated with chronic GVHD may be a precursor to squamous cell carcinoma. CsA and mycophenolate mofetil are being used more frequently as methods of GVHD prophylaxis with some groups incorporating T-cell depletion of sibling donor marrow.

Results of unrelated donor adult volunteer HCT

The European Group for Blood and Marrow Transplantation (EBMT) working party on AA has analyzed the outcome of alternative donor HCT in 67 FA patients. The median 2-year survival was 28 ± 8%. Causes of death included infection, hemorrhage, acute GVHD, chronic GVHD, liver venoocclusive disease and multi-organ failure.⁸

The CIBMTR analyzed 98 patients transplanted with unrelated donor marrow (excluding those with peripheral

blood or umbilical cord blood (UCB) grafts) between 1990 and 2003.⁹ Probabilities of neutrophil (89 vs 69%, $P=0.02$) and platelet recovery (74 vs 23%, $P<0.001$) were higher after fludarabine- than non-fludarabine-containing regimens. Risks of acute (RR 2.95, $P=0.003$) and chronic GVHD (RR 3.30, $P=0.03$) were significantly higher in recipients of non-T-cell-depleted than T-cell-depleted grafts. Day 100 mortality rate was significantly higher after non-fludarabine- than fludarabine-containing regimens (65 vs 24%, respectively; $P<0.001$). Corresponding 3-year-adjusted overall survival rates were 13 vs 52% ($P<0.001$), with best survival in those treated with a fludarabine-based regimen (Figure 1). In addition, mortality was higher in recipients who were older (>10 years), CMV seropositive and >20 blood product transfusions pre-BMT. Based on these results, significant practice changes were suggested: use of a fludarabine-containing conditioning regimen in the context of T-cell-depleted marrow allografts and earlier referral with transplantation prior to excessive transfusions.

Results of related and unrelated donor UCB transplantation

In the circumstance where an HLA-identical sibling donor is available, cord blood transplant (CBT) and BMT give similar results in terms of survival. However, reports comparing the two demonstrate a reduction in the frequency and severity of acute and chronic GVHD related to the relative immaturity of neonatal T cells.

However, the majority of patients do not have an HLA-matched sibling donor. Eurocord analyzed the results of unrelated CBTs in 93 FA patients (Figure 2).¹⁰ The incidence of neutrophil recovery at 60 days was 60 ± 5%. In addition to high cell dose, fludarabine-containing regimens (as in marrow recipients)⁹ were associated with better neutrophil engraftment. The incidence of acute and chronic GVHD was 32.5 and 16%, respectively. Overall survival was 40 ± 5%. In multivariate analysis, factors associated with favorable outcome were use of fludarabine, high number of cells infused and negative recipient CMV serology.

To date, there has been no formal comparison of outcomes in recipients of unrelated cord blood and

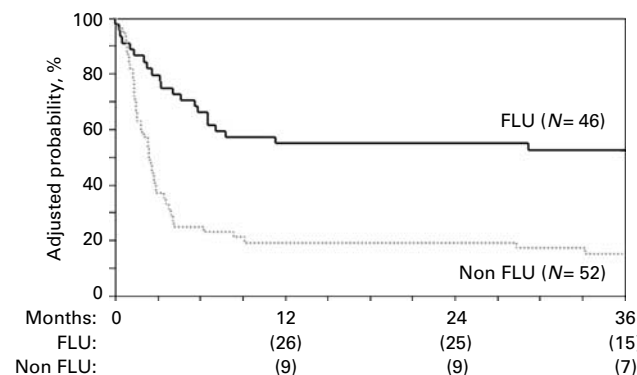


Figure 1 Impact of fludarabine on survival in patients with FA treated with unrelated donor BMT. This research was originally published in *Blood*. Wagner JE, Eapen M, MacMillan ML, Harris RE, Pasquini R, Bouldad F *et al*. Unrelated donor bone marrow transplantation for the treatment of Fanconi anemia. *Blood* 2007; **109**: 2256–2262.

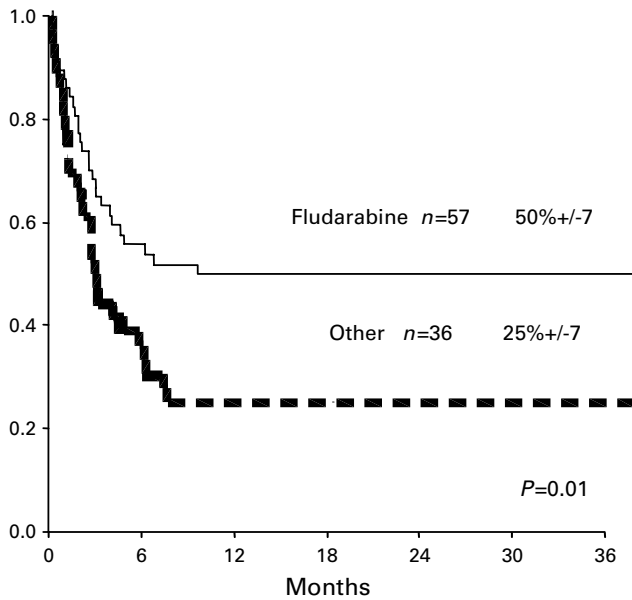


Figure 2 Impact of fludarabine on survival in patients with FA treated with unrelated umbilical cord blood transplantation. This research was originally published in *Biol Blood Marrow Transplant*. Gluckman E, Rocha V, Ionescu I, Bierings M, Harris RE, Wagner J *et al*. Results of unrelated cord blood transplant in Fanconi anemia patients: risk factor analysis for engraftment and survival. *Biol Blood Marrow Transplant* 2007; 13: 1073–1082.

marrow. However, the results demonstrate that fludarabine is associated with better survival regardless of stem cell source in patients with FA. This suggests that fludarabine, a potent immune suppressive agent, enhances engraftment without paying the price of extramedullary toxicity. In the future, studies may help us determine the place of UCB. For now, UCB is clearly indicated in those FA patients for whom an HLA-A, -B, -C and DRB1 allele-matched unrelated volunteer donor cannot be identified.

Preimplantation genetic diagnosis to select an embryo produced by *in vitro* fertilization that is both unaffected by a heritable genetic disease and HLA-identical to the affected recipient has been performed. Clearly, this approach is controversial,¹¹ with marked differences in its acceptance by different countries worldwide. Globally, the strategy has been most often used for couples at high risk of having children with thalassemia. However, the first successful use of preimplantation genetic diagnosis for a specific HLA type was for a child with FA. With this approach, the couple can avoid the risk of having additional affected children (and the consequent consideration of abortion) and also have a healthy child that will be an HLA-identical match with the existing child needing HCT. In these cases, it is typical for UCB to be collected at birth, eliminating risk to the newborn child. In the United States, the use of the technology is expanding. To date, five transplants have been successfully performed in patients with FA.

Post-HCT monitoring in FA

Patients with FA require particular attention because of their sensitivity to toxic agents, various organ dysfunctions

due to congenital malformations and increased risk of developing malignancies. This should include at least yearly endocrinological and growth follow-up, bone marrow cytogenetic and oral follow-up. Patients with oral lichen planus should be biopsied regularly and lesions removed.

Other congenital cytopenias

Dyskeratosis congenita

Dyskeratosis congenita, also known as Zinsser–Engman–Cole syndrome, is a rare, progressive BMF syndrome characterized by the triad of reticulated skin hyperpigmentation, nail dystrophy and oral leukoplakia. Evidence exists for telomerase dysfunction, ribosome deficiency and protein synthesis dysfunction in this disorder. Early mortality is often associated with BMF, infections, fatal pulmonary complications or malignancy. Results of HCT are disappointing because of severe late effects, including diffuse vasculitis and lung fibrosis.¹²

Conditioning with fludarabine-containing non-myeloablative regimens are being explored and may give better short-term results. Very few results are available to make any general recommendations.

Seckel syndrome

Seckel syndrome is a rare autosomal recessive disorder with growth retardation, microcephaly with mental retardation and a characteristic bird-headed facial appearance. Two gene loci have been identified. Very few transplants have been reported in the literature. In our experience, in one case, late pulmonary fibrosis occurring 2 years after HCT was the cause of death despite an early favorable outcome.

Shwachman–Diamond syndrome

Shwachman–Diamond syndrome is an autosomal recessive disorder with clinical features that include pancreatic exocrine insufficiency, skeletal abnormalities and pancytopenia.¹³ AML transformation has been observed. Very few patients have been treated by allogeneic HCT.

Diamond–Blackfan anemia

Diamond–Blackfan anemia is characterized by chronic constitutional aregenerative anemia with absent or decreased erythroid precursors in the BM. Both autosomal dominant and recessive inheritances are described. Most patients present with anemia in the neonatal period or in infancy. Approximately 30% patients have a variety of physical anomalies, including thumb, upper limb, craniofacial, heart and urogenital malformations, which can overlap with the FA phenotype.

Usually, the patients are treated with transfusions and steroids and more recently CsA, with responses in at least 50% of patients. Allogeneic HCT is an option in steroid-resistant patients. In a report from the DBA Registry, 354 patients were registered and 20 underwent HCT. The 5-year survival in recipients of HLA-identical sibling grafts was 87.5%. In contrast, results were poor in recipients with alternative donors. CIBMTR reported results in 61 Diamond–Blackfan anemia patients transplanted from

1984 to 2000. Most patients (67%) were transplanted with HLA-identical sibling donors. The 3-year probability of overall survival was 64%. Results were better in HLA-identical sibling transplants.¹⁴

Kostmann syndrome

Kostmann syndrome is an inherited disorder with severe neutropenia and early onset of severe bacterial infections. More than 90% of the patients respond to r-HuG-CSF but approximately 10% develop myelodysplastic syndrome (MDS)/AML, regardless of their treatment or response.

Allogeneic HCT is the treatment of choice in patients refractory to G-CSF or with acute leukemia.¹⁵ In the French Chronic Neutropenia Registry, including 101 patients, 9 patients were transplanted, 7 with an unrelated donor and 2 with an HLA-identical sibling donor. Four patients had leukemia; four were refractory to G-CSF and one had BMF. The overall survival at 5 years was 61%. While numbers of patients are small, these data suggest that HCT should be considered in these patients even if there is no HLA-identical sibling donor.

Inherited thrombocytopenia

Congenital amegakaryocytic thrombocytopenia

Affected infants are identified within days or weeks of birth. Its transmission is autosomal recessive. Despite optimal supportive care, severe AA develops leading to death in the absence of HCT, which is the only chance of cure in this disease. Anecdotal reports suggest that engraftment may be more difficult to achieve in this patient population as compared to those with idiopathic severe AA. However, most cases were performed prior to the general use of fludarabine.

Thrombocytopenia with absent radii

Thrombocytopenia with absent radii syndrome includes shortened or absent forearms due to the absence of development of the bilateral radii, associated with severe thrombocytopenia at birth. Skeletal anomalies are also seen in other bones but do not affect the hands and fingers. Usually, the degree of thrombocytopenia is greatest at birth, requiring transfusions; however, thrombocytopenia becomes less severe during the first year of life and most patients do not require platelet transfusion after infancy. HCT is generally not recommended.

Other rare inherited BMF syndromes

Nijmegen breakage syndrome

Nijmegen breakage syndrome is a rare autosomal recessive condition of chromosomal instability that is clinically characterized by microcephaly, a distinct facial appearance, short stature, immunodeficiency, radiation sensitivity and a strong predisposition to lymphoid malignancy. Mutations in the *NBS1* gene located in band 8q21 are responsible for Nijmegen breakage syndrome. hematopoietic stem cell transplantation can be considered in some patients. This

procedure has been used for a patient with Nijmegen breakage syndrome who was initially diagnosed with atypical FA, to correct his severe immunodeficiency.¹⁶

Pearson syndrome

Pearson syndrome is currently recognized as a rare, multisystemic, mitochondrial cytopathy. Its features are refractory sideroblastic anemia, pancytopenia, defective oxidative phosphorylation, exocrine pancreatic insufficiency, and variable hepatic, renal and endocrine failure. Death often occurs in infancy or early childhood due to infection or metabolic crisis. Patients may recover from the refractory anemia. Older survivors have Kearns–Sayre syndrome, which is a mitochondriopathy characterized by progressive external ophthalmoplegia and weakness of skeletal muscle.

DNA ligase IV deficiency

DNA ligase IV deficiency is a rare autosomal recessive disorder caused by hypomorphic mutations in the DNA ligase IV gene (*LIG4*). The clinical phenotype shows overlap with a number of other rare syndromes including Seckel, Nijmegen and FA. Thus, the diagnosis is often delayed. In one successful HCT, the diagnosis was made by cellular radiosensitivity in the absence of manifestation of ataxia telangiectasia confirmed by compound mutations in the *LIG4* gene. The patient had progressive marrow failure; he was successfully treated with a matched sibling donor hematopoietic stem cell transplantation using a fludarabine-based conditioning.¹⁷

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