

# Chapter 3: Hematologic Abnormalities in Patients with Fanconi Anemia

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## Introduction

Patients with FA generally develop some degree of bone marrow dysfunction, resulting in a deficiency in blood cells or the production of abnormal cells. Bone marrow dysfunction can cause a variety of health concerns, which can each have various signs and symptoms <sup>(1-3)</sup>.

Concerns related to the blood and marrow most commonly include:

- *Anemia: Low red blood cell count which can cause weakness and fatigue*
- *Thrombocytopenia: Low platelet count which can cause spontaneous bleeding in the skin and mucous membranes*
- *Neutropenia: Low neutrophil (also known as granulocyte or polymorphonuclear cell) – “poly” – count which can cause increased risk for serious infections*
- *Leukemia and myelodysplastic syndrome (MDS): Cancer or a pre-cancerous condition of the blood-forming cells in the bone marrow*

The hematological care team should include a **hematologist** and **hematopathologist**. This team should work in close collaboration with other FA specialists to provide comprehensive care. The involvement of multiple types of care providers in the care of patients with FA introduces the risk that diagnoses and management plans are not effectively communicated or that medications prescribed by one physician might adversely interact with those prescribed by another. Therefore, it is essential that all subspecialists communicate with the primary physician, usually the hematologist/oncologist, to coordinate care.

## Bone Marrow Dysfunction

Bone marrow dysfunction in patients with FA can range from mild, asymptomatic cytopenia to severe aplastic anemia, MDS, or acute myelogenous leukemia (AML). The absence of marrow failure, however, does

not exclude the diagnosis of FA. Most patients with FA (more than 90%) will have macrocytosis (red blood cells that are larger than normal) in infancy, childhood, or adolescence. However, macrocytosis may be mitigated by concomitant iron deficiency or an inherited blood disorder such as alpha- or beta-thalassemia minor<sup>(1-3)</sup>.

## Good to Know

The **bone marrow** produces the blood cells that our bodies need to function and fight infection.

The blood stem cells that reside in the bone marrow produce three blood cell types: **red blood cells** (erythrocytes) carry oxygen to the body's tissues; **white blood cells** (leukocytes) defend the body against infections; and **platelets** help the blood clot.

Bone marrow dysfunction can manifest in the following ways:

**Cytopenia**, a deficiency of any blood cell type

**Aplastic anemia (previously called pancytopenia)**, a deficiency of all three blood cell types

**Thrombocytopenia**, a deficiency of platelets.

**Neutropenia**, a deficiency of neutrophils.

**Myelodysplastic syndrome (MDS)**, a diverse group of bone marrow disorders characterized by abnormal production of immature and defective blood cells

**Acute myelogenous leukemia (AML)**, a rapidly progressing malignancy of myeloid blood cells predominantly expanding in the blood, spleen and bone marrow

The age of onset of bone marrow failure in patients with FA is highly variable, even among siblings. Approximately 3 out of every 4 patients develop evidence of marrow failure ranging from mild to severe within the first decade of life<sup>(4-6)</sup>. Rarely, marrow failure from FA can present in infants and small children. An analysis of 754 patients in the International Fanconi Anemia Registry (IFAR) suggested that the average age of onset is 7.6 years. However, that study analyzed patients who mainly had defects in the *FANCA*, *FANCC*, and *FANCG* genes, which are the most frequently mutated FA genes; therefore, the results may not be representative of patients with rarer gene defects<sup>(5)</sup>. In adults as compared to children, FA is less commonly diagnosed due to primary bone marrow failure; instead, the diagnosis of FA more commonly occurs as a consequence of presentation with cancer or with severe toxicity after chemotherapy treatment for a malignancy<sup>(7,8)</sup>. Severe, usually transient, bone

marrow failure can also develop in non-transplanted female patients with FA during pregnancy.

Despite its potentially misleading name, FA frequently involves the development of neutropenia (low numbers of neutrophils) and thrombocytopenia (low numbers of platelets) as well as anemia (low numbers of red blood cells). Ironically, the cytopenia that commonly leads to the diagnosis of FA is thrombocytopenia (usually with erythrocyte macrocytosis and elevated levels of fetal hemoglobin (HbF)). FA should be considered in the evaluation of any patient with hypoproliferative cytopenia.

Cytopenias in patients with FA warrant a thorough hematologic workup to rule out additional causes of cytopenias other than primary bone marrow failure. Marrow cellularity is best evaluated by bone marrow biopsy. Results must be interpreted in the context of peripheral blood counts, because marrow cellularity may be patchy and subject to sampling variation. It is helpful to follow the patient's trends in marrow cellularity and peripheral blood counts over time. Therapeutic intervention should not be based on marrow cellularity alone in the absence of clinically significant peripheral cytopenias or clear evidence (usually cytogenetic changes) of a myelodysplastic or malignant process.

Patients with FA are at high risk of developing MDS and AML, which are sometimes associated with recurring changes on chromosomes 1, 3, and 7 (see below) <sup>(9)</sup>. Acute lymphocytic leukemia (ALL) and lymphomas are rare in patients with FA and usually restricted to patients with genetic defects in the *FANCD1/BRCA2* gene <sup>(5,10-12)</sup>.

### **Clonal abnormalities and serial bone marrow findings**

The bone marrow of patients with FA can exhibit signs of dysplasia (abnormal development or growth), such as nuclear/cytoplasmic dysynchrony, hypolobulated megakaryocytes, and binucleated erythroid cells. These features must be distinguished from true forms of MDS. Baseline marrow dysplasia is commonly associated with the inherited marrow failure syndromes and is not necessarily a harbinger of AML. In patients with inherited marrow failure syndromes, it is often challenging to distinguish between a bone marrow with dysplastic but stable features versus new dysplasia and MDS associated with progression to AML. It is important to obtain regular bone marrow cytogenetic analyses (see below). Therefore, to avoid mistaken or premature referral of patients with FA and other bone marrow failure syndromes for allogeneic

stem cell transplantation, putative bone marrow dysplasia warrants careful evaluation by a hematopathologist with expertise in these rare syndromes.

Most hematologists agree that a patient with FA should have a bone marrow examination (which includes aspiration, biopsy, and cytogenetic analysis) at the time of diagnosis; many also perform this test annually. Compliance issues may arise when patients with FA reach adolescence or adulthood, or in situations where adherence to this regimen is simply not possible. The purpose of serial marrow examinations is to identify early signs of the development of MDS or AML. A minority of hematologists prefer to monitor the peripheral blood counts frequently and analyze chromosomes using a test known as fluorescence in situ hybridization (FISH, as outlined below and discussed in *Chapter 2*), and only perform a marrow examination if the peripheral blood counts change. Because AML in patients with FA is difficult to treat and currently is managed by going rapidly to stem cell transplantation, hematologists should strongly consider performing annual marrow examinations or regular analyses of the peripheral blood (including cytogenetic analyses), proceeding to bone marrow examination if any suspicion arises.

The marrow of a patient with FA often contains fewer cells than normal for the patient's age, even if the peripheral blood counts are normal or close to normal; therefore, marrow cellularity may not be the best parameter to indicate a need for intervention. Intervention criteria are defined below and are based upon declining blood counts (Table 1).

The morphology, or appearance, of the cells in the bone marrow may suggest early transformation of MDS into AML. However, the definition of MDS has changed with time. Adult MDS, which occurs in the absence of a genetic propensity, was initially classified according to the French-American-British (FAB) criteria. This classification scheme has been replaced by the World Health Organization (WHO) criteria, which has a specific category for pediatric MDS known as refractory cytopenia of childhood (RCC); MDS in patients with FA is classified as a secondary MDS. According to the WHO criteria, to be considered MDS, or RCC, the bone marrow should have dysplastic changes (proportion not specified) in two different myeloid cell lineages, or in more than 10% of cells in a single cell line<sup>(13)</sup>. One study, however, found that up to 25% of healthy bone marrow donors have more than 10% cells with dysplastic changes in two or more lineages<sup>(14)</sup>. Another problem with this classification is that it generally reflects MDS arising in individuals without an identified, inherited marrow failure syndrome and therefore may not be the best reflection

of what is seen and expected in individuals with FA. An analysis of 4 cohorts of patients with FA revealed that the cumulative incidence of AML was around 15-20% by age 40, and the incidence of MDS (not centrally reviewed) reached about 40% by age 50 <sup>(15)</sup>. Marrow morphology should be examined by a hematopathologist/hematologist who is experienced in the evaluation of MDS in patients with inherited bone marrow failure, in particular FA, and should be considered in the context of blood counts and cytogenetic results.

## Good to Know

A **cytogenetic clone**, or clonal abnormality, arises when a blood progenitor or stem cell acquires a mutation that provides a competitive advantage.

The presence of cytogenetic clones in a patient with FA may determine the patient's prognosis. The marrow is usually examined by evaluation of G-banded metaphase cells, although fluorescent in situ hybridization (FISH) is increasingly used to seek specific common mutations [e.g., monosomy 7 or del(7q)], and comparative genomic hybridization (CGH) has also been proposed for elucidating more details. The results of cytogenetics analyses of the marrow have revealed varying types and frequencies of clones in several reported cohorts of patients with FA. In some cases, these results led to patients being classified as having MDS/AML. An early analysis from the IFAR found that the risk of developing of MDS or AML within 3 years after the observation of a clone was approximately 1 in 3 (35%), whereas the risk for patients without a clone was 1 in 30 (3%); abnormalities in chromosomes 1 and 7 were most commonly involved <sup>(16)</sup>. In another cohort, clones were noted to disappear, appear, or reappear in serial marrow evaluations. These fluctuations were usually based on the analysis of a limited number of cells due to the aplastic nature of the marrow and therefore complicate the interpretation of the results of single marrow sample <sup>(17)</sup>.

The role of aberrations of chromosome 3 was first reported in a study of 53 German patients, 18 of whom had chromosomal abnormalities (partial trisomies or tetrasomies) involving the long (q) arm of chromosome 3. In this group of patients, the 3-year risk of MDS/AML was 9 in 10 (90%), compared with 1 in 10 (10%) for patients without aberrations in chromosome 3 <sup>(9)</sup>. In other studies, the prognostic implications have been more difficult to establish. Of a group of 119 patients who were referred for a bone marrow transplant in Minneapolis, Minn., 32% had clonal aberrations and 20/119 had

a clonal gain of chromosome 3q<sup>(18)</sup>. However, many of the participants were referred to Minneapolis for a diagnosis of MDS and because the gain of 3q and the diagnosis of MDS were simultaneous in most reported patients<sup>(18)</sup>, the prognostic implications of 3q could not be evaluated. Among 20 patients who had a gain of 3q, 4 had MDS, 2 were borderline, 3 did not have MDS, and 11 had additional clones and had MDS. A group from India did not find any 3q aberrations in 10 FA patients that progressed to MDS or AML. Five of these patients developed other clones<sup>(19)</sup>. In a group of patients from Cincinnati, 4 of 64 without MDS and 6 of 13 with MDS/AML had gain of 3q, but when time of follow up was taken into account, there was no significant association of aberrations in chromosome 3 with the risk of MDS/AML<sup>(20)</sup>. Finally, a French study of 57 patients with FA detected gain of 3q in 12 of 29 patients with MDS/AML and in none of 20 with aplastic anemia<sup>(21)</sup>. It is important to note that the methodology used in cytogenetic analysis differed in these reports, and the optimal methodology for detecting, confirming and following aberrations is not firmly established. Taken together, the results of these studies suggest that the gain of 3q may be associated with MDS/AML, although its prognostic significance is not entirely clear, particularly when it occurs in isolation.

As in non-FA settings, the appearance of monosomy 7 and most 7q deletions is generally held to portend a poor prognosis with high risk of developing MDS/AML whereas trisomy of 1q has not been convincingly shown to associate with prognosis. However, longitudinal prospective studies of larger numbers of patients are required to clarify the prognostic role of specific types of clones and specific combinations of aberrations. An ongoing prospective study in Berlin is using interphase FISH to compare the occurrence and detection of chromosomal aberrations on chromosome 1, 3, and 7 in both the bone marrow and peripheral blood. The results of this study are eagerly awaited and certainly will influence the standards of care for patients with FA in the future<sup>(22)</sup>.

In summary, based on our current knowledge, physicians must be cautious and assess the latest literature when treating a patient who has a clone but lacks other abnormalities of blood counts or myelodysplastic changes in the marrow. Despite the presence of a clone, the patient may have stable hematopoiesis (production of blood cells) and possibly a relatively favorable long-term prognosis; in such cases, a stem cell transplant may subject the patient to an unwarranted risk of morbidity and mortality.

### Definition of bone marrow failure

Bone marrow failure manifests clinically by blood counts that are below age-appropriate norms due to decreased production of effective blood cells. While many patients progress to frank aplastic anemia, others may maintain mildly abnormal blood counts for years and even decades. Clinical surveillance and therapeutic management are guided by the severity of the cytopenia(s), the stability of the blood counts, the presence of morphologic and cytogenetic marrow abnormalities, the presence of potentially high-risk genotypes as described in *Chapter 1*; Table 3, the patient's quality of life, and the wishes of the patients and their families.

Bone marrow failure can be classified into three broad categories, depending upon the degree of cytopenia(s) observed (Table 1). These definitions are more than semantic as they also define points at which different clinical management options should be considered.

**Table 1.** Severity of bone marrow failure.

	Mild	Moderate	Severe
Absolute neutrophil count (ANC)	<1,500/mm <sup>3</sup>	<1,000/mm <sup>3</sup>	<500/mm <sup>3</sup>
Platelet count	150,000-50,000/mm <sup>3</sup>	<50,000/mm <sup>3</sup>	<30,000/mm <sup>3</sup>
Hemoglobin (Hb) level	≥8 g/dL*	<8 g/dL	<8 g/dL

\*Less than normal for age but ≥ 8 g/dL.

Importantly, to meet these criteria for marrow failure, the cytopenias must be persistent and not transient or secondary to another treatable cause, such as infection, medication, peripheral blood cell destruction/loss, or nutritional deficiencies.

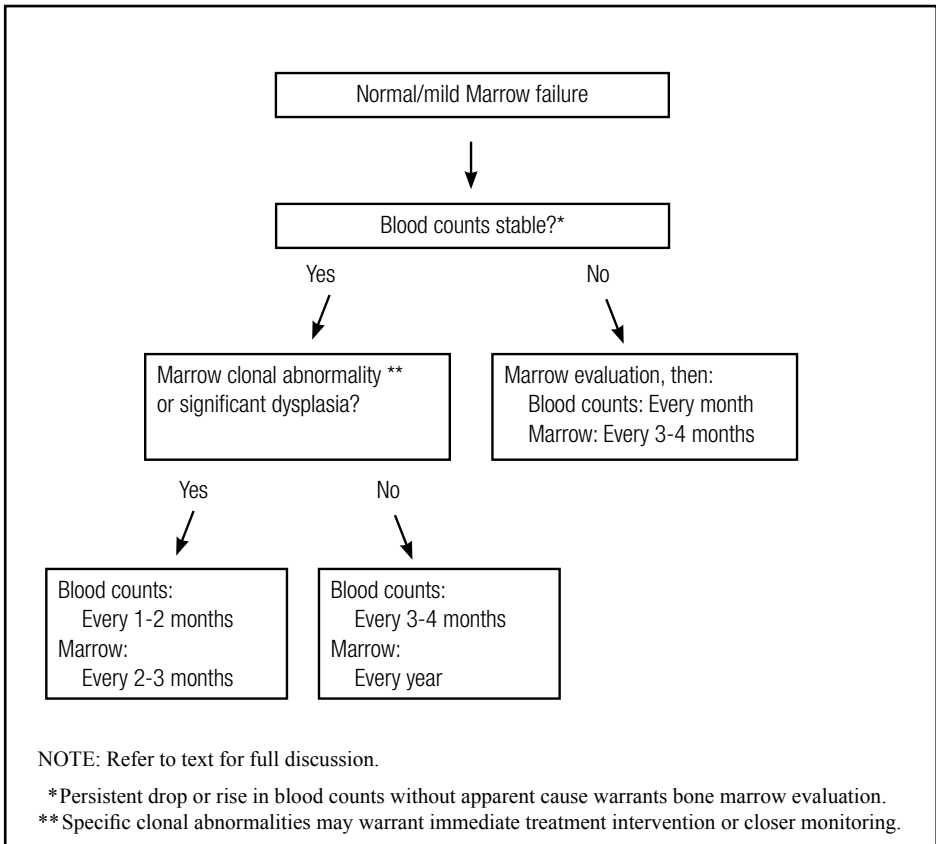
### Clinical monitoring of bone marrow failure

Current guidelines for monitoring bone marrow failure are summarized below. These recommendations may be modified as new data become available, and patients are urged to consult with a hematologist with expertise in FA. Testing should be individualized as indicated.

At a minimum, bone marrow examination should consist of an aspirate to assess morphology and cytogenetics with G-banding and FISH (where available) to look for chromosomal abnormalities that are commonly associated with MDS and AML in patients with FA. A bone marrow trephine biopsy provides valuable information regarding marrow architecture and cellularity.

Periodic monitoring is important to assess the significance of a clonal cytogenetic abnormality and the onset of MDS or frank leukemia, and to identify the presence of cytogenetic abnormalities that may suggest immediate intervention or at least initial consideration for transplantation. Annual evaluation of the bone marrow, beginning at age 2, allows for comparison of a patient's marrow to previous specimens from the same patient. The availability of serial marrow specimens facilitates assessment of the progression of that patient's marrow and enables informed decisions about the significance of a clonal abnormality. Interphase FISH cytogenetic analysis in peripheral blood cells with specific probes for MDS/AML in FA may reduce the frequency of bone marrow examinations to longer than 1 year; however, this technique may not be widely available, and the efficacy of such an approach has not yet been published.

**Box 1.** Clinical monitoring of bone marrow failure.





Recommendations for clinical monitoring of bone marrow failure (Box 1) include the following:

- ***Peripheral blood counts stable in the normal to mild marrow failure range and NO clonal cytogenetic abnormalities***

For patients with normal counts and no cytogenetic clonal marrow abnormalities, a peripheral blood count and differential white blood cell count should be reviewed approximately every 3 to 4 months and a bone marrow aspirate and biopsy with cytogenetics considered yearly. A similar monitoring regimen is recommended for patients with mildly abnormal but stable peripheral blood counts without any associated clonal marrow abnormalities.

- ***Peripheral blood counts stable in the normal to mild marrow failure range AND clonal cytogenetic abnormalities present***

For patients with a cytogenetic clonal marrow abnormality (in the absence of morphologic MDS) together with normal or mildly low, but stable, blood counts, more frequent surveillance of counts and bone marrow examinations should be considered (as indicated by the patient's clinical status) to monitor for progression to MDS or leukemia. It would be reasonable to examine the blood counts every 1 to 2 months and the bone marrow every 1 to 6 months initially to determine if the blood counts are stable or progressively changing. Cytogenetic abnormalities and marrow morphologic changes should be similarly monitored. If the blood counts are stable, then the interval between bone marrow exams may be increased. Appropriate plans for stem cell transplantation—including HLA typing of family members, clarification of donor status and availability, contact with a HSC transplant center, and communication with the insurance company—should be in place, as adverse clonal progression or worsening marrow failure may evolve rapidly. However, in some cases clones have remained stable for more than a dozen years without transplantation.

- ***Peripheral blood counts falling or rising***

Patients with progressively changing blood counts without a clinically apparent underlying cause (e.g., transient response to an acute infection or suppression secondary to medication) require immediate evaluation with a complete blood count and bone marrow examination with cytogenetics. Rising peripheral blood counts can be due to either the development of MDS/AML (for which stem cell transplantation would be a potential urgent undertaking) or, rarely, reversion of a germ-line mutation in a

stem cell, which repopulates the marrow with normal cells (somatic stem cell mosaicism). Such patients warrant continued close monitoring with complete blood counts at least every 1 to 2 months and a marrow exam with cytogenetics every 1 to 6 months. Appropriate plans for intervention should be in place, as adverse clonal progression or worsening marrow failure may evolve rapidly.

## Treatment Options for Bone Marrow Failure

Available treatments for bone marrow failure in patients with FA are described below. The risks and benefits of each treatment are discussed. A suggested treatment algorithm is presented under “Management Guidelines for Bone Marrow Failure” in this chapter.

### **Hematopoietic stem cell transplant**

Hematopoietic stem cell transplantation (HSCT; described in detail in *Chapter 11*) is currently the only curative treatment for bone marrow failure, although it does not cure non-hematopoietic complications of FA. Patients with FA generally experience undue toxicity from the chemotherapy and radiation used in standard transplant conditioning regimens due to their underlying defect in DNA repair. Excellent results for matched sibling donor transplants have been achieved in the last 15 years using the chemotherapy drug fludarabine and modified transplant regimens<sup>(23,24)</sup>. Compared with past regimens, the currently available alternative donor regimens appear to have markedly improved results so far, representing a new opportunity for patients<sup>(25-27)</sup>. These regimens for alternative or unrelated donor transplantation will continue to evolve over the coming years and need to be discussed on an individual basis with a physician experienced in transplants for patients with FA.

Because the best transplant outcomes are associated with young patients who have not yet developed medical complications from their bone marrow failure, patients and families who opt to pursue transplantation are generally encouraged to proceed early in the course of the disease. However, issues regarding timing of transplant are complicated by the up-front risk of transplant-related morbidity and mortality and the unknown long-term side effects of transplantation in patients with FA. Most importantly, as it is currently not possible to predict for the vast majority of patients who will progress to severe marrow failure and who will not, transplantation prior to the development of significant marrow failure may unnecessarily subject a subset of patients to both early and late transplant-related morbidity and mortality.

The effect of current transplant approaches on long-term transplant-related risks such as increased risk of solid tumor development remains unknown. For example, graft-versus-host disease (GvHD) was identified as a major risk factor for oral squamous cell carcinoma in patients with FA <sup>(28,29)</sup>, but several innovations have decreased the rate of GvHD. Ongoing dialogue with an FA transplant specialist should be initiated early after the diagnosis of FA.

### **Androgens**

Synthetic androgens have been widely used for the treatment of cytopenias in patients with FA for more than 50 years. The beneficial effects of androgens are most pronounced in the red cells and platelets, but neutrophil counts may also improve <sup>(30,31)</sup>. The mechanisms by which androgens raise peripheral blood counts and bone marrow cellularity in patients with FA are unclear. The advantages of androgens include the absence of short-term, and low long-term, risks of therapy-related mortality and the long history of experience with their use. Side effects have been well documented and are related to the absolute dose of androgens given per kilogram (kg) of body weight. The major potential side effects associated with androgen therapy are listed in Table 2. More than half of patients with FA that are treated with androgens will respond at least transiently. Although a subset of patients who initially respond may become refractory over time, it appears as if as many as 10-20% of patients receiving continuous low dose androgen therapy might never need a transplant, unless MDS/AML develops. Thus, androgen treatment may delay a transplant for months and even years in responsive patients. This is particularly important for patients and families who decline immediate HSCT, patients without a suitable donor, cases in which hematopoietic stem cell transplant facilities do not exist, and patients for whom transplant would be associated with very high risk.

The use of androgens to delay transplantation may be associated with the following risks:

- *Androgens do not prevent progression to AML, which, once developed, may significantly increase the risks associated with transplant.*
- *Patients will be older when transplantation may be necessary, or may have acquired viral infections, which will be problematic at transplant.*

The decision about whether to use androgens to delay transplantation can be very difficult for patients with FA and their families, and may require time and consultations with more than one specialist and/or center.

**Table 2.** Possible side effects of androgens.

Androgen use has been associated with ...
<ul style="list-style-type: none"><li>• Virilization, including acne, facial hair growth/scalp hair loss, deepening of voice, development of pubic hair, enlargement of penis or clitoris, and priapism (painful erection) in young boys</li><li>• Growth spurt followed by premature closure of epiphyses (the regions of bones involved in skeletal growth) and exacerbation of short adult stature</li><li>• Hyperactivity and behavioral changes such as puberty and aggressiveness</li><li>• Cholestatic jaundice or transaminitis</li><li>• Hepatic adenoma (benign) or hepatocellular carcinoma (malignant)</li><li>• Peliosis hepatis (the development of blood-filled cavities in the liver)</li><li>• Hypertension</li></ul>

The major outcome of androgen therapy is increased/stabilized hemoglobin levels, although it may also improve/stabilize the platelet count. Androgen therapy should be considered when the patient's hemoglobin drops below 8 g/dL or the platelet count falls below 30,000/mm<sup>3</sup> (classified as severe AA in Table 1). Because there is no evidence (i.e., no trial has been performed/ reported) that androgens can forestall bone marrow failure, treatment should begin when blood counts drop to clinically significant levels, but before the marrow becomes completely devoid of hematopoietic stem cells for androgens to stimulate (this may be the point at which patients/parents wish to start some active treatment).

The most commonly used androgen since 1961 is oxymetholone<sup>(30,31)</sup>. The starting dose of oxymetholone should be ~2 mg/kg/day (but doses as high as 5 mg/kg may be required) rounded to the nearest ¼ tablet (50 mg tablets are usually available but can be broken). Most patients respond within 3 months to the initial dose with a stabilization or an increase in the hemoglobin or platelet levels. If a response occurs, then the general strategy is to slowly taper the daily dose of oxymetholone in 10-20% decrements every 3 to 4 months until an effective dose with minimal side effects is obtained. Over time, the side effects of accelerated linear growth (ultimately with premature closure of the growth plates) and weight gain effectively reduce the individual's dose per kilogram body weight; therefore, the patient's dose per kg should be recalculated prior to making dose adjustments.

The patient and family should be counseled about the possible side effects of oxymetholone and the child, especially teenagers, should be forewarned about

them. Every effort should be made to minimize the side effects by tapering the dose to the minimum effective dose whenever possible. Aggressive acne treatment with topical benzoyl peroxide and topical antibiotics (clindamycin or erythromycin) may make the treatment more tolerable. Long-term androgen usage may lead to shrinkage/impaired development of the testis in males due to suppression of the hypothalamic-pituitary-gonadal axis (a complex hormone-based system that regulates many bodily functions, including the function/sex hormone production of gonads). An appropriate discussion of the masculinizing side effects of androgen therapy is very important. However, critical marrow failure is life-threatening and all parties must weigh the side effects for both male and female patients versus the potential benefits.

If no response is seen after 3 to 4 months, then—in the absence of other causes of cytopenias such as viral or bacterial infection—oxymetholone should be discontinued, although there are anecdotal reports of patients responding after 6 or more months. Improvements in hemoglobin levels may be seen earlier than improvements in platelet counts, and white cell responses may occur later or be nonexistent.

Oxymetholone was the first androgen approved by the Food and Drug Administration (FDA) for the treatment of aplastic anemia. It is noteworthy, however, that bodybuilders consider oxymetholone to be the strongest and most effective oral steroid with extremely high androgenic and anabolic effects. It has been utilized widely in bodybuilders, athletes, and also racehorses. Other synthetic androgens are also used in patients with FA worldwide. For example, stanozolol has been used in Asia, and oxandrolone has been used recently in Cincinnati, Ohio<sup>(32,33)</sup>; however, these two androgens have strong anabolic and androgenic effects and, like oxymetholone, are banned from usage in athletes.

A few reports<sup>(34-36)</sup> in the literature show that both male and female FA patients may benefit from treatment with danazol, an attenuated synthetic androgen that produces fewer virilizing effects than oxymetholone. A recent retrospective study demonstrated the effectiveness of danazol in 7 of 8 patients with FA (starting dose 3.5-7.7 mg/kg/day): Three patients (2 females and 1 male) were treated successfully for more than 3 years and 1 female for more than 10 years without exhibiting progressive marrow failure requiring stem cell transplantation<sup>(36)</sup>. The comparative efficacy of danazol versus oxymetholone to treat marrow failure in patients with FA is unknown. Danazol has been used at doses of 200-800 mg/day (3.3-13.3 mg/kg for a 60 kg woman) for months

in women to treat endometriosis and is still used as long-term prophylaxis for hereditary angioedema at a dose of approximately 5 mg/kg/day<sup>(37)</sup>.

There are no data to support the provocative notion of using low doses of prednisone to prevent androgen toxicity. Furthermore, prednisone therapy carries a risk of additional bone toxicities, such as avascular necrosis or osteoporosis. Therefore, its use is no longer recommended in patients with FA. Among potential toxicities, hepatic toxicities are one for which routine surveillance should be initiated. Patients taking androgens should be monitored for liver tumors and undergo regular liver function tests (LFT) for abnormalities. Blood tests for LFTs should be performed every 3 to 6 months, and a liver ultrasound should be performed every 6 to 12 months. Liver-derived  $\alpha$ -fetoprotein has been used as an early marker for hepatocellular carcinomas<sup>(32)</sup>. Unfortunately, the levels of transaminases in the blood do not always correlate with the degree of liver inflammation determined by liver biopsy. If the levels of liver transaminases increase to 3 to 5 times above normal, the androgen dose should be tapered until the blood tests improve. Androgen-associated liver adenomas may develop with long-term androgen treatment and are predominantly due to the cellular liver toxicities of the  $17\alpha$ -alkylated androgens (which include oxymetholone, oxandrolone, stanazolol, and others, but not danazol). Liver adenomas may resolve after androgens are discontinued, but some may persist for years after androgen therapy has ended. Liver adenomas are not a contraindication for transplantation. If screening tests raise a concern for hepatocellular carcinoma, a liver biopsy using a technique appropriate to the patient's bleeding risk should be considered. Even without additional risk factors, malignant transformations may occur after years of androgen treatment<sup>(32)</sup>.

### **Cytokines**

Several cytokines have been evaluated for their capacity to stimulate the failing bone marrow in patients with FA, but none have proven entirely successful. The cytokines granulocyte colony-stimulating factor (G-CSF)<sup>(38)</sup> and granulocyte-macrophage colony-stimulating factor (GM-CSF)<sup>(39)</sup> can indeed improve the neutrophil count in patients with FA. GM-CSF is no longer available for clinical use. Importantly, low absolute neutrophil counts that occur in isolation and are not associated with bacterial infections are not an indication for cytokine treatment. Treatment with other cytokines has not shown any benefit in patients with FA. However, newer agents such as thrombopoietin-mimetic drugs have not been tested in patients with FA.

Treatment with G-CSF may be considered if the neutropenia is associated with recurrent or serious infections, particularly if the neutrophil count is persistently below  $500/\text{mm}^3$  or as a short-term bridge to transplant. Historically, a few patients have also shown improvements in hemoglobin levels or platelet counts while on G-CSF; these effects are most likely due to the treatment of or reduction in infections. Long-term follow-up has not been published. G-CSF is typically started at a low dose of  $5 \mu\text{g}/\text{kg}/\text{day}$ ; one published study on G-CSF<sup>(38)</sup> reported that no patients with FA required a higher dose to maintain an absolute neutrophil count (ANC) of greater than  $1,000/\text{mm}^3$ . Patients have been maintained on lower doses given less frequently (e.g., every other day or 2 to 3 times per week), and the dose should be tapered to the lowest effective dose. Treatment should generally be discontinued if the neutrophil count fails to improve after 8 weeks of G-CSF therapy. Recently, long-acting preparations of G-CSF have become available and offer the advantage of decreased injection frequency (a particularly appealing prospect for thrombocytopenic patients); however, there are no reports of their use in patients with FA.

A bone marrow aspirate/biopsy with cytogenetics is recommended prior to the initiation of cytokine treatment, given the theoretical risk of stimulating the growth of a leukemic clone. It is reasonable to monitor the bone marrow morphology and cytogenetics every 6 months while patients are treated with cytokines. In the setting of a compelling clinical indication for cytokine therapy, there is no literature to mandate withholding cytokines from patients with clonal abnormalities. In such cases, the use of hematopoietic cytokines should be pursued in consultation with experts in the care of patients with FA.

### **Transfusion of blood products**

Transfusions of red cells or platelets may be needed prior to surgery or in the following clinical situations:

- *To manage the symptoms of anemia*
- *For patients with significant bleeding (thrombocytopenia)*
- *For patients with progressive marrow failure who fail to respond to androgen or G-CSF therapy*
- *For patients with marrow failure who have no prospect of early transplant (due to the lack of an acceptable transplant, comorbidities, socio-economic situations that preclude transplant and or lack of interest in pursuing transplantation as a therapy)*

Long-term transfusions with red cells and platelets may become a lifeline for patients for whom no other treatment options are available. Transfusions may be required as frequently as once per week. Complications of long-term transfusions include iron overload (see below) and allosensitization, both of which may complicate HSCT, as well as allergic reactions. However, physicians at most FA transplant centers believe that receiving fewer than 10-20 transfusions does not increase the risk for transplantation.

### **Investigational protocols**

Investigational protocols for new therapies should be considered in all patients with FA and their families who want to participate. It might be especially important for patients who fail to respond to androgens or cytokines, who have no acceptable transplant donor, or who have an unacceptably high transplant risk (see *Chapter 11*).

## **Management Guidelines for Bone Marrow Failure**

Because FA is a rare disease, prospective randomized trials comparing different treatment approaches are not available to guide therapeutic decisions. For this reason, the risks and benefits of the available treatment options need to be discussed with hematologists who are experienced with FA. A suggested treatment algorithm is presented below (Box 2).

### *At the time of diagnosis with FA:*

- Patients should be referred to a hematologist with expertise in FA for medical monitoring and management.
- Patients with any degree of bone marrow failure should be referred immediately to a transplant center with expertise in FA to initiate a discussion of available treatment options and to assess potential transplant options. This will give families the opportunity to initiate transplant at a time that is optimal for the patient and also the family. If the patient has no hematologic abnormalities at the time of diagnosis, it is reasonable to defer referral to a transplant center. The physician should take a detailed family history and perform high-resolution HLA-typing of the patient, parents, and siblings to assess the availability of tissue-matched bone marrow donors for the patient (likely donors should undergo additional testing to



rule out FA). In consanguineous families or families with unusual HLA types, members of the extended family may undergo HLA typing.

- Some families may wish to conceive children without FA who can serve as a tissue-matched donor for a sibling with FA (see *Chapters 11 and 17*). Such families should be referred for appropriate medical/genetic counseling.

*Guidelines for patients with normal blood counts or mild bone marrow failure:*

- Physicians should monitor the patient's blood counts, bone marrow morphology, and cytogenetics as described previously until further therapeutic intervention is warranted. Because transplant risk is lowest in patients younger than age 10, a few physicians have proposed that transplants might be offered to young patients with FA prior to the potential development of marrow failure. However, this suggestion, known as preemptive transplantation, remains controversial, because some patients who might never progress to significant marrow failure would be unnecessarily subjected to both early and late risks of morbidity and mortality associated with transplant. Further, transplantation may minimize the risk of marrow malignancy but increase the risk of other malignancies in patients with FA. Research is ongoing to elucidate the factors that can be used to identify the patients with FA who might benefit from a transplant at a young age. Families interested in this investigational approach should have a careful discussion with a hematologist and a transplant physician.

*Guidelines for patients with moderate marrow failure:*

- Physicians should consider allogeneic stem cell transplantation for patients who have an HLA-identical sibling; otherwise, if the patient is asymptomatic, continue monitoring blood counts, bone marrow morphology, and cytogenetics.
- Some patients and families may not feel ready for transplant despite having an ideal HLA-identical sibling donor, and may prefer to delay the transplant by using androgens (sometimes at a reduced dose). In such cases, individual counseling is important; contact with other families and family support groups may also be very helpful.
- Patients who lack an HLA-identical sibling should consult with a transplant center to plan for a possible future transplant from an unrelated donor (see "Guidelines for patients with severe marrow failure" below). Management should include high-resolution HLA typing and a preliminary search through the National Marrow Donor Program (or other national and

international donor registries/organizations) for a free, preliminary screen of potential HLA-matched donors. Selection of a donor requires additional confirmatory testing as well as a determination of donor availability. This process accrues a substantial charge and should not be undertaken until active plans for transplant are underway. Information regarding the number of potential donors available is helpful in estimating the amount of time that will likely be required to complete a full donor search if the marrow failure progresses and an imminent need for transplant emerges.

- Patients who do not wish to proceed to transplant at all, or who have risk factors that strongly increase the risks associated with transplant, should receive androgens and/or transfusions if the hemoglobin levels fall below 8 g/dL, if the platelets are under 20,000-30,000/mm<sup>3</sup>, or if clinical signs of anemia or bleeding are present.

*Guidelines for patients with severe marrow failure:*

- Eligible candidates should consider a hematopoietic stem cell transplant from a related or unrelated donor.
- Patients who have risk factors that confer an unacceptable transplant risk or who do not wish to proceed to transplant should consider treatment with androgens, cytokines, and/or transfusions.

*Guidelines for patients with severe marrow failure that is unresponsive to androgens/cytokines and who have unacceptable transplant risks or lack an appropriate donor:*

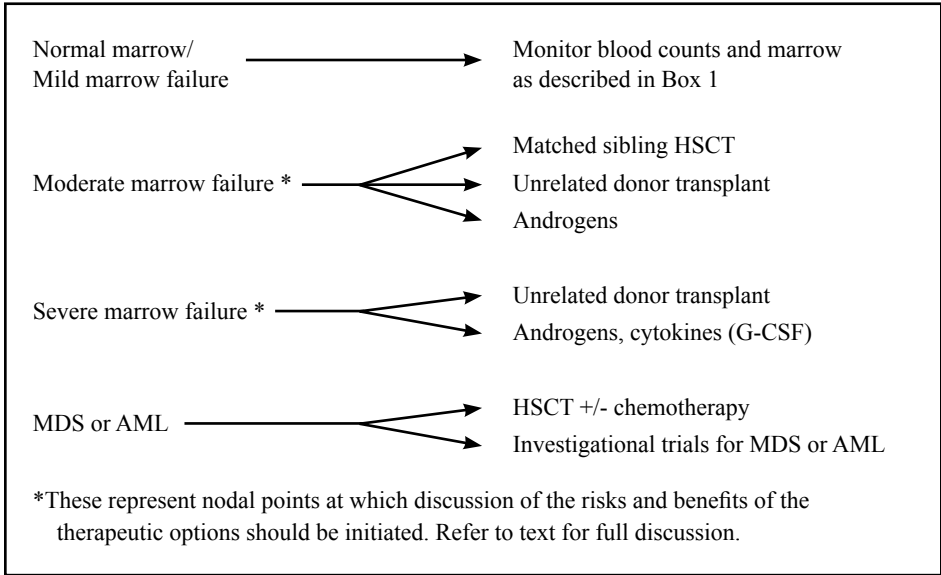
- Consider supportive management with transfusions and/or investigational protocols.

*Guidelines for patients with MDS or AML:*

- No standard therapy has been established for patients with FA who have MDS or AML. Treatment options include chemotherapy, hematopoietic stem cell transplant with or without prior induction chemotherapy, and Phase I/II trials for MDS or AML. Chemotherapy should be undertaken by centers experienced with FA. Because chemotherapy may cause severe, prolonged, or even irreversible myelosuppression in patients with FA, back-up plans for potential stem cell rescue should be considered. If patients have MDS/AML at the time of their diagnosis with FA, then low-intensity chemotherapy may be used to prepare the patients for transplantation. Published reports of chemotherapy regimens for AML in patients with FA are sparse and limited by the lack of longitudinal follow-

up. It remains unclear whether chemotherapy prior to transplant improves or worsens outcomes.

**Box 2. Marrow failure algorithm.**



## Supportive Care for Patients with Severe Marrow Failure

### Anemia

The onset of anemia in patients with FA is insidious. Hemoglobin levels should be monitored closely, as outlined above, so that treatment may be instituted before transfusion with packed red blood cells is required. Treatment of anemia should be considered when the patient's hemoglobin level consistently falls below 8 g/dL. The hemoglobin level at which treatment is started should be raised for patients who live at high altitude, which increases the normal range for hemoglobin levels. Patients with cardiorespiratory problems in addition to anemia also have elevated baseline hemoglobin levels and may require a higher threshold Hgb value for recognition of failing erythropoiesis and for treatment. When treatment is anticipated, it should be initiated under the care of a hematologist. Many patients with FA will require red blood cell transfusions. Transfusions should be scheduled regularly to help patients with bone marrow failure to maintain as normal a quality of life as possible. A patient should be transfused to maintain hemoglobin levels at a minimum of approximately 7-8

g/dL so that the patient will be asymptomatic for his or her activity level. A post-transfusion hemoglobin level of 10-12 g/dL is generally sufficient to allow for normal activity, growth, and development in children, with a 3- to 4-week interval between transfusions. Clinical adequacy of the transfusion regimen must be assessed continuously. As discussed above, other treatment options for anemia currently consist of bone marrow transplant or androgens.

All patients should receive red blood cells that have been depleted of leukocytes to reduce the risk of cytomegalovirus (CMV) infection. Some centers only use red blood cells that are CMV-negative, whereas most accept leukocyte-depletion as an equally effective alternative to CMV-negative products. Irradiated blood products should be used to avoid transfusion-associated graft-versus-host disease. A procedure known as extended antigen matching may be important for patients in certain racial groups for whom minor antigen mismatch is more commonly encountered. Directed donation for a specified recipient should be discouraged, especially from family members of the patient. Patients who receive blood transfusions from family members may develop an immune response towards substances in the donor blood (a process known as alloimmunization) that would increase the risk of graft rejection after related donor hematopoietic stem cell transplant. Blood from unrelated designated donors offers no increase in transfusion safety.

### **Secondary iron overload**

Each mL of packed red cells contains approximately 0.7 mg of iron. Because the human body lacks mechanisms to actively eliminate excess iron, patients who receive multiple red blood cell transfusions are at risk of accumulating toxic levels of iron (for reviews see<sup>40-43</sup>). The liver is a primary site of iron accumulation, and hepatic fibrosis and cirrhosis may result. Iron deposition in the myocardium (the muscular tissue of the heart) may cause irregular heartbeats and cardiac failure, which may be sudden and acute despite regular monitoring with electrocardiograms and measurements of cardiac function. Recent data from patients with thalassemia (a condition in which the body makes less hemoglobin and fewer red blood cells than normal) strongly suggest that magnetic resonance imaging (specifically, T2\* MRI) is the best technique to use to follow cardiac siderosis (the deposition of iron in the heart) and risk of cardiac disease in patients with significant iron overload<sup>(41,44)</sup>. Iron also targets endocrine organs such as the pituitary, pancreas, thyroid, and parathyroid.

The clinical complications of iron overload include the following:

- *Liver disease with fibrosis and cirrhosis*
- *Cardiac failure and arrhythmias*
- *Hypopituitarism, including central hypogonadism, growth hormone deficiency, and central hypothyroidism*
- *Poor growth*
- *Diabetes mellitus*
- *Primary hypothyroidism*
- *Primary hypogonadism*
- *Hypoparathyroidism*

While ferritin levels are often followed as a convenient marker for total body iron load, their interpretation is complicated by additional factors such as acute or chronic inflammation, infection, hepatitis, and androgen treatment. In addition, ferritin levels fail to correlate with iron stores in many patients. Ferritin levels may be useful to monitor trends in total body iron over time but quantitative measurement of hepatic and cardiac iron burden are essential. The measurement of total body iron by liver biopsy has been largely replaced, where available, by MRI techniques. However, a liver biopsy is the only technique that can determine the degree of hepatic fibrosis/cirrhosis. Liver iron concentrations of 3-7 mg/g dry weight indicates mild iron overload. Liver iron concentrations between 7-15 mg/g dry weight are associated with an elevated risk of iron toxicity. A liver iron concentration of greater than 15 mg/g dry weight is associated with a high risk of cardiac toxicity<sup>(45)</sup>. The possible complications of surgical, blind or image-directed biopsy procedures include bleeding or infection, which are of heightened concern in patients who are thrombocytopenic or neutropenic. Non-invasive MRI R2 and T2\* imaging techniques to measure hepatic and cardiac iron burden do not pose the risks associated with biopsy<sup>(44)</sup>. The use of MRI-based techniques is now widely accepted and they are the preferred way to measure hepatic and cardiac iron burden.

Little data on iron overload in FA is available. Guidelines for the institution of iron chelation therapy in patients with bone marrow failure as a general class are based on the guidelines established for patients with thalassemia, with the caveat that thalassemia patients, who have accelerated (albeit ineffective) production of red blood cells, often have concomitant increases

in iron absorption and are transfused to the point of suppressing endogenous hematopoiesis. The total volumes of red blood cells that are transfused into patients with FA must be carefully monitored, particularly in infants and small children. Total body iron status, as reflected in liver iron, cardiac iron, and ferritin levels, should also be monitored. Iron overload may be treated or—better yet—prevented with chelation therapy. As a general guide, chelation therapy should begin when the total volume of red cells transfused reaches 200 mL/kg (which roughly corresponds to a total of 12-18 red cell transfusions) or the liver iron concentration reaches 3-7 mg/g dry weight. Chronically transfused patients heading to a hematopoietic stem cell transplant may also benefit from total body iron measurements and chelation therapy to reduce the iron burden to safe levels. A serum ferritin level that is persistently greater than 1,000 µg/L without other apparent causes has been used as a surrogate, albeit imperfect, marker of elevated iron burden in situations where liver iron measurements are not clinically available.

Chelation must be adjusted over time to reduce or prevent iron accumulation while avoiding excessive amounts of chelator relative to total body iron levels. The risk of side effects increases as the dose of chelator exceeds body iron stores. The notion of a “safe” hepatic iron load is controversial. The target liver iron concentration level is typically between 3-7 mg iron/g dry weight but many experts prefer levels less than 3 mg iron/g dry weight. Two chelators are currently clinically available in the US: deferoxamine (Desferal) and deferasirox (Exjade). In the US, deferiprone (L1) is indicated only for iron chelation in patients with thalassemia, and may be associated with significant neutropenia. The features of each chelator are summarized in Table 3.

Deferoxamine therapy for transfusional iron overload has been used extensively and its efficacy in treating iron overload is well established. Although generally effective, its use is complicated by the need for subcutaneous or intravenous injection. Furthermore, deferoxamine must be administered over prolonged periods of time (8 to 24 hours) because only a small proportion of total body iron is available for chelation at any given moment and deferoxamine is eliminated from the body quickly. Subcutaneous infusions pose a risk of bleeding or infection in patients with thrombocytopenia or neutropenia. Side effects of deferoxamine include loss of hearing or peripheral vision, particularly when deferoxamine doses are high relative to iron burden, and risk of infection with iron-chelating organisms (known as siderophores) such as the bacterium *Yersinia enterocolitica*. Patients who develop a fever should immediately cease deferoxamine therapy and undergo medical evaluation. Continuous intravenous

infusion of deferoxamine over a period of weeks to months is a very effective way to rescue patients with severe iron overload.

**Table 3.** Iron chelation therapies.

Drug	Route	Toxicities	Advantages	Disadvantages	Monitoring
<i>Deferasirox (Exjade)</i>	PO	GI symptoms Rash Renal Transaminitis Neutropenia	Convenience (PO) Low toxicity No risk of cutaneous bleeding or infection	Relatively new Limited long-term experience	Creatinine monthly Creatinine clearance ALT monthly (and 2 weeks after initiation of the drug) Neutrophil count monthly Ferritin every 3 months Liver iron annually Cardiac iron and cardiac function annually (after age 10)
<i>Deferoxamine (Desferal)</i>	SQ, IV	Skin irritation Hearing impairment Decreased visual acuity, night blindness, color vision abnormality, retrobulbar optic neuropathy, and retinal pigment degeneration Skeletal abnormalities Infection risk ( <i>Yersinia</i> )	Well-defined efficacy and toxicity profile Efficacious Treatment of cardiac iron overload	In-convenience Poor compliance Infection and bleeding risks with SQ infusion if neutropenic or thrombocytopenic	Annual auditory and visual testing Ferritin every 3 months Liver iron annually Cardiac iron and cardiac function annually (after age 10)
<i>Deferiprone (Ferriprox)</i>	PO	Neutropenia Arthritis Hepatic fibrosis	Convenience (PO) May enhance cardiac iron chelation	Possible lower efficacy Risk of cytopenias Frequent laboratory monitoring Not approved in US for patients with FA	Regular CBC with differential ALT monthly Ferritin every 3 months Liver iron annually Cardiac iron and cardiac function annually (after age 10)

Abbreviations: *By mouth, PO; subcutaneous, SQ; intravenous, IV; gastrointestinal, GI; alanine aminotransferase, ALT; complete blood count, CBC*

Given the disadvantages of a parenterally administered drug, deferasirox offers an attractive alternative for iron chelation. Deferasirox is conveniently administered orally once a day as a slurry with a variety of palatable beverages, however more palatable preparations are forthcoming. Short- and long-term side effects of deferasirox include renal toxicity, gastrointestinal symptoms, skin rash, and elevated levels of the liver enzyme alanine aminotransferase (ALT), and are generally well tolerated. The optimal dose of deferasirox is between 20-40 mg/kg, which can maintain iron balance in most patients, but unlike deferoxamine, may not be sufficient to reduce iron overload. Therefore, patients who continue to have unacceptable iron levels on deferasirox despite maximal dose escalation should be switched back to deferoxamine (perhaps as a 24 hour/day intravenous infusion) until target iron levels have been achieved. A recent study from Turkey reported that average ferritin levels of 3377 ng/mL were decreased by one third in FA patients taking oral deferasirox therapy for 13 months, and 6 out of 39 patients demonstrated renal or hepatic toxicities <sup>(46)</sup>.

Deferiprone is currently not licensed for clinical use in the US for patients with FA. Studies in populations of patients without FA suggest that deferiprone may be more efficient than deferoxamine at removing cardiac iron. However, the utility of deferiprone is limited by its side effects, which include neutropenia and fatal agranulocytosis, a particular concern in individuals with bone marrow failure, and arthralgias and arthritis. There is only one published case report of deferiprone use in a patient with FA <sup>(47)</sup>.

Continuous high dose (e.g. 50 mg/kg/day) intravenous infusion of deferoxamine has been shown to reduce dysrhythmias and to improve left ventricular function in patients with severe iron overload or with cardiac functional compromise (arrhythmias or failing left ventricular function) <sup>(48)</sup>. A small pilot study found that deferoxamine in combination with deferasirox was efficacious in individuals with severe iron overload. Cases of iron overload that are significant enough to warrant such aggressive treatments should be discussed with an expert who is familiar with combination therapy.

There is no demonstrated role for the use of erythropoietin (a hormone produced by the kidneys that stimulates red blood cell production) to treat anemia in patients with FA in the absence of erythropoietin deficiency (e.g., in association with renal failure).



### **Thrombocytopenia**

Bone marrow transplant should be discussed/considered when the platelet counts fall below 50,000/mm<sup>3</sup>. If transplant is not pursued, then thrombocytopenia should be treated with androgens as the platelet count declines toward 30,000/mm<sup>3</sup>. As noted above, a long trial of oxymetholone or danazol (up to 6 months) is required before treatment is considered unsuccessful due to the lack of a platelet response or unacceptable side effects.

Platelet transfusion is indicated in patients with severe bruising or bleeding, or who are undergoing invasive procedures. The strict use of a numeric trigger for transfusion is probably not necessary. However, platelets under 10,000/mm<sup>3</sup> are more often treated with transfusion of platelets. Platelets from a single donor should be provided in an effort to decrease the risk that the patient will develop an immune response to the transfusion. Transfused platelets should be depleted of leukocytes and irradiated.

The drugs epsilon aminocaproic acid (Amicar) or tranexamic acid may be used as an adjunct to platelet transfusion in a patient with mucosal bleeding. The drug Amicar is given at a dose of 50-100 mg/kg every six hours, with a maximum dose of around 12 g/day. A loading dose of 200 mg/kg may be considered. Amicar is usually administered for several days until the clot is stabilized. Amicar is generally contraindicated in patients with hematuria.

Additional factors that increase bleeding risk should be minimized. Drugs that inhibit platelet function, such as aspirin, non-steroidal anti-inflammatory drugs (e.g., ibuprofen), and some antihistamines, should be avoided. Supplements and foods such as omega 3s, flax seed and green tea are associated with increased bleeding and should be avoided in thrombocytopenic individuals and in anyone anticipating surgery. A soft toothbrush should be used. Stool softeners should be administered if constipation poses a risk of GI mucosal trauma. Activities carrying a high risk of significant trauma (particularly to the head or trunk) should be avoided. To date there are no data supporting the use of thrombopoietin-mimetic drugs.

### **Neutropenia**

Patients with mild neutropenia are often asymptomatic. Treatment with G-CSF as described above may be considered if the patient is having neutropenia-related infectious complications with neutrophil counts <500/mm<sup>3</sup>. G-CSF may also be considered for patients with a history of recurrent or severe infections. Patients with fever and neutropenia should have a thorough examination,

have samples of their blood cultured in a lab, and should receive broad-spectrum antibiotics until the blood cultures test negative for infection and the fevers resolve. There is no demonstrated role or/special need for the use of prophylactic antibiotics or antifungals in patients with FA, except as indicated for any patient (for prophylaxis of certain dental procedures for example). Such practices may lead to increased risks of fungal infections and antibiotic resistance. Recently, non-systemic antibiotics or ethanol lock therapy in concert with scrupulous line hygiene have been employed successfully to reduce infections associated with vascular access devices.

### **Sedation and analgesia for invasive procedures**

Given the need for frequent evaluation of the bone marrow, adequate sedation and analgesia should be offered to every patient undergoing bone marrow examination. The use of local anesthetic alone may be insufficient to alleviate the anxiety and pain that is associated with frequent, repeated bone marrow procedures. The use of propofol, an intravenous anesthetic, or a locally preferred regimen used in accordance with the guidelines established by the American Academy of Pediatrics is strongly recommended. Such regimens may make it easier for families and patients to accept a yearly bone marrow examination as a routine part of the care for FA.

## **Chapter Committee**

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