Chapter 3

Treatment of Hematologic Abnormalities in Fanconi Anemia

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Hematologic Abnormalities in FA

Patients with FA generally develop some degree of marrow dysfunction, ranging from mild asymptomatic cytopenias in any lineage to severe aplastic anemia, myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). The absence of marrow failure, however, does not rule out the diagnosis of FA. Most patients with FA will have macrocytosis (high MCV for age) in infancy or childhood.

The time of onset of bone marrow failure is highly variable, even among siblings. Approximately 3/4 of FA patients develop evidence of marrow failure ranging from mild to severe within the first decade of life.[1] Rarely, marrow failure from FA can present in infants and adults. Despite the potentially misleading nomenclature, patients with FA can develop neutropenia and thrombocytopenia as well as anemia. Indeed, thrombocytopenia is commonly the presenting cytopenia.

Cytopenias in FA patients warrant a thorough hematologic work-up to rule out additional treatable causes of cytopenias other than primary bone marrow failure, acquired or inherited. Red cell folate, B12 levels, and urine methylmalonic acid levels should be assessed to rule out nutritional causes of megaloblastic anemias. Absence of red cell macrocytosis may be a manifestation of concurrent iron deficiency or thalassemia trait.

Red cell antibody testing to assess for autoimmune hemolytic anemia should be considered where clinically indicated.

Marrow suppression secondary to infection should be considered. Effects of potentially myelosuppressive medications (e.g., antibiotics such as Bactrim or macrolides or H2-blockers such as cimetidine) should be evaluated.

Marrow cellularity is best evaluated by bone marrow biopsy. Marrow cellularity must be interpreted in the context of the peripheral blood counts, since marrow cellularity may be patchy and subject to sampling variation. Following trends in marrow cellularity and peripheral blood counts over time is helpful. Therapeutic intervention should not be based on marrow cellularity alone in the absence of clinically significant peripheral cytopenias or evidence of a myelodysplastic or malignant process.

Patients with FA are at high risk of developing MDS and AML.[2] Patients with the *FANCD1/BRCA2* or *FANCN* subtypes are at particularly high risk of developing AML or solid tumors at a very young age and warrant close clinical monitoring (see Chapter 2). Many different AML subtypes have been described in FA patients. Acute lymphocytic leukemia (ALL) is rare in FA patients.

The bone marrow cellular morphology often appears dysplastic in FA patients. Marrow dysplastic features, such as nuclear/cytoplasmic dysynchrony, hypolobulated megakaryocytes, and binucleated erythroid cells, are often seen in patients with FA and must be distinguished from MDS syndrome. Baseline marrow dysplasia is commonly associated with the pediatric

marrow failure syndromes and is not necessarily a harbinger of impending AML. The distinction between marrows with dysplastic but stable features versus MDS associated with imminent progression to acute leukemia is often challenging in patients with marrow failure syndromes. Marrow dysplasia warrants careful evaluation by a hematopathologist with expertise in these rare syndromes.

Significance of Clonal Abnormalities

In FA patients, the relationship between clonal cytogenetic abnormalities and progression to leukemia is not always clear in a marrow without accompanying morphologic evidence of MDS.

Many isolated cytogenetic clones of unclear clinical significance have been observed to come and go without apparent progression to leukemia in many FA patients and have persisted without adverse consequences for more than a dozen years in some cases.[3] Nonetheless, findings of cytogenetic abnormalities commonly associated with MDS (e.g., monosomy 7) warrant careful evaluation and referral to a transplant center experienced in the treatment of FA patients. The most common cytogenetic abnormalities observed to date in FA patients involve chromosomes 1, 3, 4 or 7 (John Wagner, MD, University of Minnesota, personal communication).

One center reported a striking association between chromosome 3q26q29 amplifications (partial trisomies and tetrasomies) and rapid progression to MDS or AML.[4] This cytogenetic abnormality was detectable in marrow cells and, with lower sensitivity, in peripheral blood cells in 18 out of 53 FA patients studied. In 8 of the 18 patients with 3q26q29 amplification,

monosomy 7 was also noted in the 3q clone. Thirteen of the 18 patients with 3q amplifications developed MDS or AML. Clinical testing for chromosome 3q abnormalities is available using fluorescent *in situ* hybridization (FISH) probes for this chromosomal region. All reported cases of chromosome 3 amplifications were detectable as extraneous chromosomal material by G-banding. However, the identity of the duplicated chromosomal material was not always apparent by G-banding alone and required confirmation by FISH, spectral karyotyping (SKY), or comparative genomic hybridization (CGH). Given the poor prognosis of the patients with 3q amplifications in this study, it is recommended that patients with a 3q cytogenetic clone undergo evaluation for a possible hematopoietic stem cell transplant with close monitoring of the peripheral blood counts and bone marrow. Whether all FA patients with a 3q cytogenetic clone are at high risk for progression to AML is currently unclear. Therapeutic decisions must be made on an individualized basis in consultation with a physician experienced in the care of FA patients.

Definition of Bone Marrow Failure

Bone marrow failure is clinically manifested by blood counts that are below age-appropriate norms due to decreased effective marrow hematopoiesis. While many patients progress to frank aplastic anemia, others may remain at mildly abnormal levels indefinitely. Clinical surveillance and therapeutic management are guided by the severity of the cytopenias, the stability of the blood counts, the presence of morphologic and cytogenetic marrow abnormalities, and potentially high-risk genotypes such as *FANCC* IVS 4; *FANCD1/BRCA2* or *FANCN* mutations.

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

Table 1: Severity of Bone Marrow Failure

	Mild	**Moderate**	**Severe**
ANC	<1,500/mm³	<1,000/mm³	<500/mm³
Platelets	150,000-50,000/mm³	<50,000/mm³	<30,000/mm³
Hb	>8 g/dl*	<8 g/dl	<8 g/dl

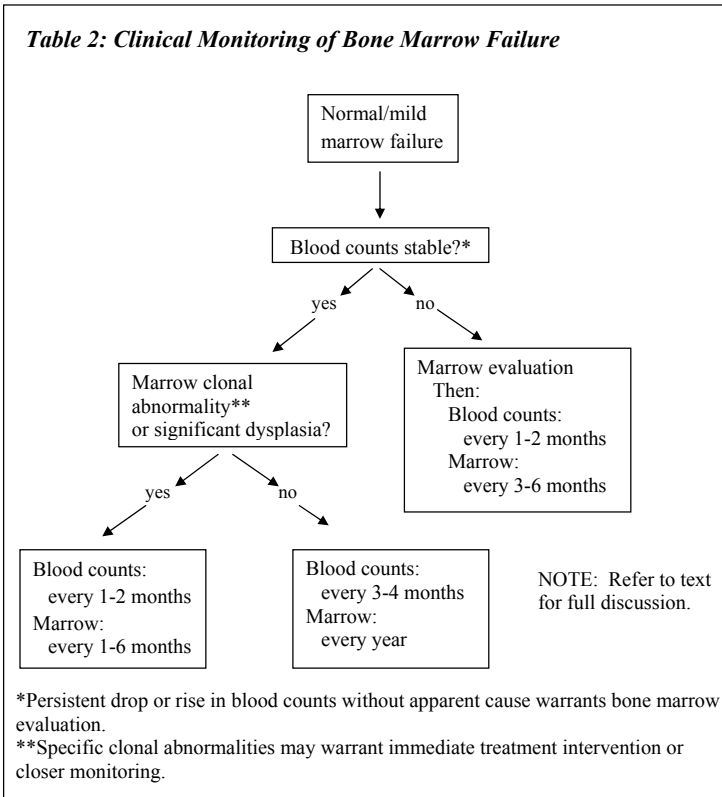*Less than norm for age but >8 g/dl

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Importantly, to meet these criteria for marrow failure, the cytopenias must be persistent and not secondary to another treatable cause, such as infection, medications, 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 cytology and cytoge-netics with G-banding and FISH (where available) for abnormalities associated with MDS. A bone marrow trephine biopsy provides valuable information regard-ing marrow architecture and cellularity. Periodic moni-toring 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 demand immediate intervention. Annual evaluation of the bone marrow 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 allows for more informed decisions about the significance of a clonal abnormality. Recommendations for clinical monitoring are summarized below (Table 2):

Table 2: Clinical Monitoring of Bone Marrow Failure

Normal/mild marrow failure
↓
Blood counts stable?*

yes → Marrow clonal abnormality** or significant dysplasia?

no → Marrow evaluation
Then:
  Blood counts:
    every 1-2 months
  Marrow:
    every 3-6 months

Marrow clonal abnormality** or significant dysplasia?
yes → Blood counts:
    every 1-2 months
  Marrow:
    every 1-6 months

no → Blood counts:
    every 3-4 months
  Marrow:
    every year

NOTE: Refer to text for full discussion.

*Persistent drop or rise in blood counts without apparent cause warrants bone marrow evaluation.
**Specific clonal abnormalities may warrant immediate treatment intervention or closer monitoring.

1. Blood counts stable in the normal to mild marrow failure range AND clonal cytogenetic abnormalities absent

For patients with normal blood counts and no cytogenetic clonal marrow abnormalities, the recommendation is a complete blood count with differential white blood cell count at least every 3-4 months and a bone marrow with cytogenetics at least yearly. A similar monitoring regimen is recommended for patients with mildly abnormal, but stable, blood counts without any associated clonal marrow abnormalities.

2. 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, increased frequency of surveillance blood counts and bone marrow exams 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 1-2 months and the bone marrow every 1-6 months initially to determine if the blood counts are stable or progressively changing. If the blood counts are stable, then the frequency of bone marrow exams may be decreased. Appropriate plans for stem cell transplantation should be in place, as adverse changes may evolve rapidly.

3. 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 evaluation with

a complete blood count and bone marrow exam with cytogenetics. Such patients warrant continued close monitoring with complete blood counts every 1-2 months and a marrow exam with cytogenetics every 1-6 months. Appropriate plans for intervention should be in place, as adverse changes may evolve rapidly.

Treatment Options for Bone Marrow Failure

Available treatments for marrow failure in FA patients 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."

Hematopoietic stem cell transplant
Hematopoietic stem cell transplant is the only current curative treatment for bone marrow failure, although it does not cure other non-hematopoietic complications of FA. FA patients, with their underlying defect in DNA repair, experience undue toxicity from the chemotherapy and radiation used in standard transplant conditioning regimens. Excellent results have been achieved using modified transplant regimens for matched sibling donor transplants. Currently available alternate donor regimens appear to have markedly improved results so far compared to past regimens, representing a new opportunity for patients. These regimens for alternate donor transplant will continue to evolve over the coming years and need to be discussed on an individualized basis with a physician experienced in transplants for FA patients.

Since 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 mortality and the unknown long-term side effects of transplant in FA patients. Since it is currently not possible to predict which patients will progress to severe marrow failure, 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. Potential long-term transplant-related risks such as increased risk of solid tumor development remain to be ascertained. For example, one study identified GvHD as a risk factor for oral squamous cell carcinoma in FA patients. An ongoing dialogue with an FA transplant specialist should be initiated early after the diagnosis of FA.

Androgens
Androgens have been widely used for the treatment of cytopenias in FA. The effects of androgens are most pronounced in the red cells and platelets, but neutrophil counts may also improve.[5,6] The mechanism(s) whereby androgens raise blood counts is currently unclear. The advantages of androgens include the low risk of therapy-related mortality and the long history of experience with their use; their side effects have been well documented. The major potential side effects associated with androgen therapy are listed in Table 3. About half of all patients treated will respond to androgen therapy, and a subset of those who initially respond may become refractory over time. An additional significant risk is that androgens do not prevent progression to AML that, once developed, creates a significantly higher transplant risk. For patients for whom hematopoietic stem cell transplant is indicated, delay in going to transplant may increase transplant-associated risks.

Table 3: Possible Side Effects of Androgens

• Virilization (including acne, facial hair growth/scalp hair loss, deepening of voice, pubic hair, enlargement of penis or clitoris)

• Growth spurt followed by premature closure of epiphyses and adult short stature

• Hyperactivity and behavioral changes

• Cholestatic jaundice or transaminitis

• Hepatic adenoma or hepatoma, hepatocellular carcinoma

• Peliosis hepatis

• Hypertension

The major effect of androgen therapy is to increase the hemoglobin, though it can also improve 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^3. Since there is no evidence that androgens can forestall bone marrow failure, treatment is initiated when cytopenias drop to clinically significant levels but before the marrow becomes completely devoid of hematopoietic stem cells for androgens to stimulate.

The standard recommended androgen is oxymetholone, with a starting dose of 2-5 mg/kg/day rounded to the nearest 1/4 tablet (50 mg tablets are available in the United States, while 10 mg tablets are available in many countries in Europe). If the patient responds to the initial dose with a stabilization of or increase in the hemoglobin level, the daily dose may be tapered in 1/2 tablet decrements after 3 months. Thereafter, a reasonable taper schedule might involve gradually decreasing the androgen dose at 2-4 month intervals.

If, in the absence of other causes of cytopenias (such as viral or bacterial infection), no response is seen after 3-4 months, oxymetholone should be discontinued, although there are anecdotal reports of patients responding after 6 or more months. Studies of the optimal initial dosing of oxymetholone are lacking. Improvements in hemoglobin are seen earlier than platelet responses to androgens. The family should be counseled about the possible side effects of androgen therapy and the child, especially teenagers, should be forewarned about them. Every effort should be made to minimize the side effects by tapering the dose whenever possible. Aggressive acne treatment with topical benzoyl peroxide and topical antibiotics (clindamycin or erythromycin) may make the treatment more tolerable. Androgens should not be withheld from female patients.

Since the masculinizing side effects of oxymetholone are particularly troublesome in girls and women, some female patients have been treated with a different androgen, danazol, which is hypothesized to produce fewer of these side effects. The comparative efficacy of danazol versus oxymetholone to treat marrow failure in FA patients is unknown. It has not been established whether, dose for dose, danazol is as effective and, at the same time, less masculinizing than oxymetholone. A clinical trial using another androgen, oxandrolone, in FA patients has been ongoing. Clinical trials comparing efficacy and side effects of different androgens are currently being developed.

The use of low dose (5-10 mg every other day) prednisone in an attempt to attenuate the premature epiphyseal closure by androgens has been advocated by some physicians. There are no data to support any sparing of androgen toxicity with the use of low dose prednisone. Furthermore, prednisone therapy carries a risk of

additional bone toxicities, such as avascular necrosis or osteoporosis.

Monitoring for liver tumors and liver function test (LFT) abnormalities should be performed regularly while a patient is taking androgens. Blood tests for LFTs are recommended every 3-6 months, and a liver ultrasound is recommended every 6-12 months. Unfortunately, transaminases do not always correlate with the degree of liver inflammation on liver biopsy. If liver transaminases increase to 3-5 times above normal, the androgen dose can be tapered until the blood tests improve. Androgen-associated liver adenomas can resolve after androgens are discontinued, but some may persist even years after androgens are stopped. If screening tests raise a concern for adenocarcinoma, a liver biopsy (generally performed as an open procedure to minimize bleeding risk) should be considered.

Cytokines

Studies have demonstrated that G-CSF[7] or GM-CSF[8] can improve the neutrophil counts in FA patients. Treatment with G-CSF or GM-CSF should be considered if the neutropenia is associated with recurrent or serious infections, particularly if the neutrophil counts persistently fall below 500/mm³ or fail to rise in response to infection. A few patients have also shown improvements in hemoglobin or platelet counts while on G-CSF or GM-CSF therapy. No comparative trials of G-versus GM-CSF are available in FA patients.

G-CSF is typically started at a dose of 5 μg/kg/day. In one published study on G-CSF,[7] no FA patient required a higher dose to maintain an ANC >1,000/mm³. Patients have been maintained on lower doses given less frequently (e.g., every other day or 2-3 times per week),

and the dose should be tapered to the lowest effective dose. The recommended starting dose of GM-CSF is 250 $\mu g/m^2$/day. Patient responses to doses as low as 5 $\mu g/m^2$/day have been seen. Treatment should generally be discontinued if the neutrophil count fails to improve after eight weeks of G-CSF or GM-CSF therapy. Recently, long-acting preparations of G-CSF have become available. These formulations offer the advantage of decreased injection frequency (a particularly appealing prospect for thrombocytopenic patients). However, there is no experience with their use in FA patients.

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

Investigational protocols
For those patients who fail to respond to androgens or cytokines and have no acceptable transplant donor or pose an unacceptably high transplant risk, investigational protocols for new therapies may be considered (see Chapter 12).

Management Guidelines for Bone Marrow Failure

Since 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 available treatment options need to be discussed with hematologists experienced with FA. A suggested **treatment algorithm** is presented below.

At the time of diagnosis of Fanconi anemia:
- Refer to a hematologist with expertise in FA for medical monitoring and management.

- Patients with any degree of bone marrow failure should be referred to a transplant center with expertise in FA to initiate a discussion of available treatment options and to assess available potential transplant options. Early discussion with a transplant expert is recommended to allow families the option of initiating the procedure at an optimal time for the patient. If the patient has no hematologic abnormalities at the time of diagnosis, it is reasonable to defer referral to a transplant center. Early high resolution HLA typing of the patient and immediate family members is recommended to assess the availability of potential bone marrow donors.

- Some families wishing to have additional children may be interested in pursuing prenatal screening or preimplantation genetic diagnosis (PGD) (see Chapters 9, 10, and 15). Such families should be referred for appropriate medical counseling.

Normal blood counts or mild marrow failure:

- Monitor blood counts and bone marrow as described earlier under "Clinical Monitoring of Bone Marrow Failure" until further therapeutic intervention is warranted. Since transplant risk is lowest in young patients prior to the development of complications from marrow failure, a few physicians have proposed that transplants might be offered to young FA patients with normal blood counts prior to the potential development of marrow failure. This suggestion for "preemptive transplantation" is highly controversial since some patients who might never progress to significant marrow failure would be unnecessarily subjected to both early and late mortality risk and potential morbidity associated with transplant. Research is ongoing to elucidate risk factors that identify a subset of FA patients who might benefit from very early transplant. A careful discussion with a hematologist and transplant physician is warranted for families interested in this investigational approach.

Moderate marrow failure:

- For eligible candidates with an HLA-identical sibling, consider allogeneic stem cell transplant; otherwise, continue monitoring if the patient is asymptomatic.

- For patients lacking an HLA-identical sibling, consultation with a transplant center to plan for a possible future unrelated donor transplant (see "Severe marrow failure" below) is recommended. Management would include high-resolution HLA typing and a preliminary *World Book* search through the National Marrow

Donor Program for a free, preliminary screen of potential HLA-matched donors. Selection of a donor requires additional confirmatory testing as well as determination of donor availability. This stage accrues a substantial charge and is not undertaken until active plans for transplant are underway. Information regarding the number of potential donors available is helpful in estimating the time likely required to complete a full donor search if the marrow failure progresses.

- For patients who do not wish to proceed to transplant or who have risk factors conferring a high transplant risk, androgens are indicated if the Hb falls below 8g/dl.

Severe marrow failure:
- Consider unrelated donor hematopoietic stem cell transplant for eligible candidates.

- Consider androgens/cytokines for patients with risk factors conferring a high transplant risk or who do not wish to proceed to transplant.

Severe marrow failure unresponsive to androgens/ cytokines and high transplant risks:
- Consider investigational protocols.

MDS or AML: No standard effective therapy has been established for FA patients with MDS or AML. Treatment options include:
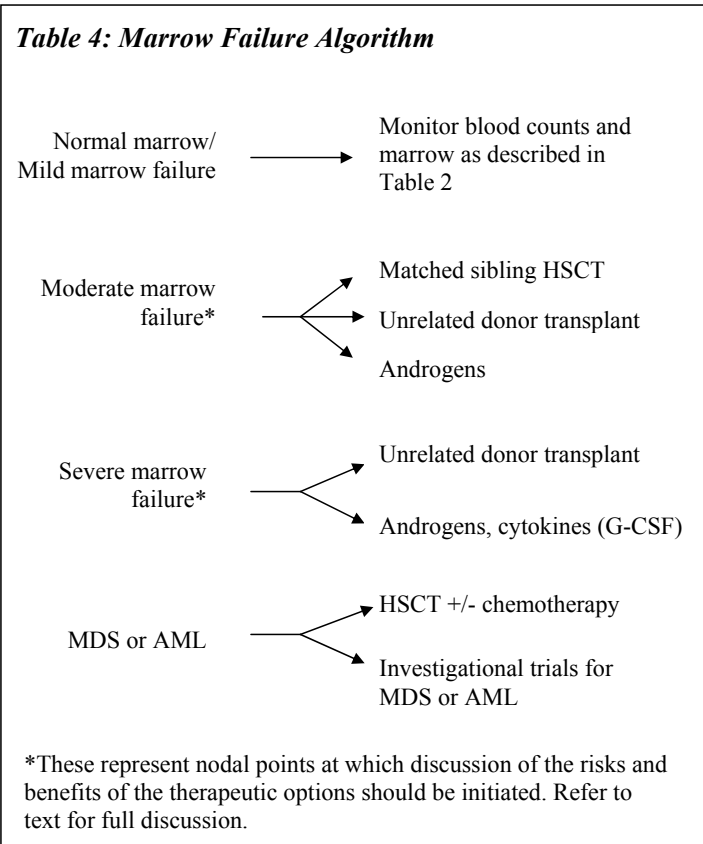- Chemotherapy: This treatment should be undertaken by centers experienced with FA. Since myelosuppression by chemotherapy may be severe, prolonged or even irreversible in FA patients, back-up plans for potential stem cell rescue should be considered

- Hematopoietic stem cell transplant with or without prior induction chemotherapy.

- Phase I/II trials for MDS or AML.

Published reports of chemotherapy regimens for AML in FA patients are sparse and limited by the lack of longitudinal follow-up. It remains unclear whether pre-transplant chemotherapy improves or worsens outcomes.

These recommendations are summarized in Table 4.

Table 4: Marrow Failure Algorithm

Normal marrow/ Mild marrow failure → Monitor blood counts and marrow as described in Table 2

Moderate marrow failure* →
- Matched sibling HSCT
- Unrelated donor transplant
- Androgens

Severe marrow failure* →
- Unrelated donor transplant
- Androgens, cytokines (G-CSF)

MDS or AML →
- HSCT +/- chemotherapy
- Investigational trials for MDS or AML

*These represent nodal points at which discussion of the risks and benefits of the therapeutic options should be initiated. Refer to text for full discussion.

Supportive Care

Anemia

The onset of anemia in patients with FA is insidious. Close monitoring of the hemoglobin is necessary, as outlined above, so that treatment may be instituted before transfusion with packed red blood cells is required. Treatment for anemia should be considered when the patient's hemoglobin consistently falls below 8g/dl. The hemoglobin level at which treatment is started should be modified upward for patients who live at high altitude, where the normal range for hemoglobin levels is higher. When treatment is anticipated, it should be initiated under the care of a hematologist. As discussed above, treatment options for anemia consist of bone marrow transplant or androgens. Many FA patients will require red blood cell transfusions. The standard of care for patients with FA is to transfuse patients only when they are clearly symptomatic with tachypnea, tachycardia or a decreased activity level. *High transfusion burden may adversely affect transplant outcomes, so timely consideration of transplant is recommended.*

Some physicians advocate a more aggressive and regularly scheduled transfusion program to maintain as normal a quality of life as possible for patients with bone marrow failure. These physicians reason that the patient should maximize the benefit of transfusion therapy. Using the latter approach, a patient would be transfused to maintain a minimal trough hemoglobin of 7-8 g/dl. A post-transfusion hemoglobin level of 10-12 g/dl is generally sufficient to allow for normal activity, growth, and development in children. Clinical adequacy of the transfusion regimen must be continuously assessed. In the end, the program which best contributes to the patient's quality of life—infrequent visits to the doctor,

but a lower hematocrit trough, or more frequent visits to maintain a higher hemoglobin—is a decision to be made by the patient, the patient's family, and the treating hematologist.

All patients should receive red blood cells that have been leuko-depleted. The most widely used and effective method is to use a leuko-depletion filter. Irradiated blood products should be used to avoid transfusion-associated graft-versus-host disease. Some centers use only CMV-negative red blood cells, while others accept leuko-depletion as an alternative to CMV-negative products. Extended antigen matching may be important for patients in certain racial groups, where minor antigen mismatch is more commonly encountered. Directed donation is not encouraged, especially for family members. *The use of family members as directed donors may cause alloimmunization to an antigen that would increase the risk of graft rejection after sibling donor hematopoietic stem cell transplant.*

Secondary iron overload
Each mL of transfused packed red cells contains approximately 0.7 mg of iron. Since the human body lacks mechanisms to actively eliminate excess iron, patients who receive multiple red blood cell transfusions are at risk for accumulating toxic levels of iron overload. The liver is a primary site of iron accumulation, and hepatic fibrosis and cirrhosis may result. Iron deposition in the myocardium may cause dysrhythmias and cardiac failure. Cardiac decompensation may be sudden and acute despite regular monitoring with electrocardiograms and measurements of cardiac function. Recent data in the thalassemia population suggests that T2* MRI may be a better modality to follow cardiac function and cardiac siderosis in patients with

significant iron overload. Iron also targets endocrine organs such as the pituitary, pancreas, thyroid, and para-thyroid (Table 5).

Table 5: Clinical Complications of Iron Overload

Liver disease with fibrosis and cirrhosis
Cardiac failure, arrhythmias
Hypopituitarism: central hypogonadism
　　　　　　　　growth hormone deficiency
　　　　　　　　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 and infection or hepatitis. In addition, ferritin fails to correlate with iron stores in some patients. Ferritin levels may be useful to monitor trends in total body iron over time. The gold standard for the measurement of total body iron has been a liver biopsy; however, hepatic iron distribution may be uneven, particularly with cirrhosis and, thus, liver biopsies may be limited by sampling error. Elevated liver iron >15mg/g dry weight is associated with a high risk of cardiac toxicity.[9] Liver iron levels between 7-15 mg/g dry weight are associated with an elevated risk of iron toxicity. Bleeding or infection as possible complications of the surgical biopsy procedure are of heightened concern in patients who are thrombocyto-penic or neutropenic. Magnetic susceptometry using a

superconducting quantum interference device (SQUID) offers a non-invasive measurement of liver iron, but availability is limited (two centers in the US and two centers in Europe). Recently, MRI R2 and T2* imaging parameters of the liver and heart have been used to measure iron load.[10] Since the correlation between liver iron and cardiac toxicity is not perfect, the ability to measure directly cardiac iron together with the left ventricular ejection fraction has generated considerable clinical interest, and experience with this modality to measure cardiac iron is growing.

Guidelines for the institution of iron chelation therapy in bone marrow failure patients are based on those established for thalassemia patients, with the caveat that thalassemia patients who undergo accelerated, albeit ineffective, erythropoiesis, often have concomitant increases in iron absorption and are transfused to the point of suppressing endogenous hematopoiesis. Total red cell volumes transfused, particularly for infants and small children, as well as total body iron status as reflected in liver iron, cardiac iron, and ferritin levels must be carefully monitored. Iron overload may be prevented or treated with chelation therapy. The optimal time to initiate chelation therapy has not been clearly determined. As a general guide, chelation is considered when the total red cell volume transfused reaches 200mL/kg (roughly corresponds to a total of 12-18 red cell transfusions) or the liver iron reaches 7mg/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 iron levels. In situations where liver iron measurements are not clinically available, a serum ferritin persistently greater than 1,500 without other apparent etiologies has been used as a surrogate, albeit imperfect (see prior discussion), marker.

Chelation must be titrated to reduce or prevent iron accumulation while avoiding excessive dosing of chelator relative to total body iron levels. The risk of side effects increases as the dose of chelator exceeds body iron stores. The goal liver iron level is typically between 3-7 mg iron/g dry weight. Two chelators are currently clinically available in the U.S.: deferoxamine (Desferal) and deferasirox (ICL670 or Exjade). Deferi-prone (L1) is not licensed for clinical use in the U.S. Features of each chelator are summarized in Table 6.

Table 6: Iron Chelation Therapies					
Drug	**Route**	**Toxicities**	**Advantages**	**Disadvantages**	**Monitoring**
Deferasirox (ICL670, Exjade)	PO	GI Rash Renal Transaminitis Neutropenia	Convenience (PO) Low toxicity to date	Relatively new Limited long-term experience	Creatinine (monthly) Creatinine clearance ALT monthly Liver iron annually Cardiac iron and cardiac function annually (after age 10)
Deferoxamine (Desferal)	SQ, IV	Skin irritation Hearing impairment Decreased vision Skeletal abnormalities Infection risk (Yersinia)	Well-defined toxicity profile Efficacy Treatment of cardiac iron overload	Inconvenience Poor compliance Infection and bleeding risks with SQ infusions if neutropenic or thrombocytopenic	Annual auditory and visual testing Liver iron annually Cardiac iron and cardiac function annually (after age 10)
Deferiprone (L1)	PO	Neutropenia Arthritis Hepatic fibrosis	Convenience (PO) May enhance cardiac iron chelation	Possible lower efficacy Toxicity profile Not approved in U.S.	Regular CBC with differential ALT (monthly) Liver iron annually Cardiac iron and cardiac function annually (after age 10)

Experience with deferoxamine therapy is extensive and its efficacy in treating iron overload is well established. Although generally effective, its use is complicated by the need for parenteral infusion (subcutaneously or intravenously). Furthermore, deferoxamine must be administered over prolonged periods of time since only a small proportion of total body iron is available for chelation at any given moment and the half-life of deferoxamine is short. Subcutaneous infusions pose risks of bleeding or infection in patients with thrombocytopenia or neutropenia. Side effects of deferoxamine include loss of hearing or vision, particularly when desferoxamine doses are high relative to iron stores. Immediate cessation of deferoxamine and medical evaluation is warranted if such symptoms arise. Deferoxamine therapy is associated with an increased risk of *Yersinia enterocolitica* infection, and the drug should be stopped for unexplained fevers pending the results of blood cultures and infection work-up. Side effects and monitoring guidelines are summarized in Table 6.

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 on an empty stomach. Clinical experience with deferasirox is limited, but short- and long-term side effects reported to date are generally mild. Renal toxicity, gastrointestinal symptoms, skin rash, and elevated ALT have been reported. Optimal dosing of deferasirox is still under investigation. Patients who continue to have unacceptable iron levels on deferasirox despite dose escalation may benefit from switching back to deferoxamine until goal iron levels have been achieved.

Deferiprone (L1) is currently not licensed for clinical use in the U.S. Studies suggest that deferiprone may be more efficient than deferoxamine at removing cardiac iron. Its utility is limited by its side effects, which include agranulocytosis, arthritis, and hepatic fibrosis.

For patients with severe iron overload or with cardiac functional compromise (arrhythmias or failing left ventricular function), continuous high dose (e.g., 50 mg/kg/day) intravenous deferoxamine infusion has been shown to reduce dysrhythmias and to improve left ventricular function.[11]

There is no demonstrated role for the use of erythropoietin to treat anemia in FA patients in the absence of erythropoietin deficiency (e.g., in association with renal failure).

Thrombocytopenia
Bone marrow transplant should be considered when the platelet counts fall below 50,000/mm^3. If transplant is not pursued, then thrombocytopenia should be treated with androgens as the platelet count declines to 30,000/mm^3. As noted above, a longer trial of oxymetholone, up to six months, is required before treatment is discontinued for lack of a platelet response.

Platelet transfusion is indicated in patients with severe bruising, bleeding or undergoing invasive procedures. The strict use of a numeric trigger for transfusion is probably not necessary. Single donor apheresis platelets should be provided in an effort to decrease the risk of alloimmunization and to decrease the risk of infection from exposure to multiple donors. Studies of the use of leukocyte depletion filters to decrease the risk of infection with CMV and alloimmunization may result in the return to the use of random donor platelets in the future.

Transfused platelets should be leuko-depleted and irradiated.

Amicar (epsilon aminocaproic acid) may be used as an adjunct to platelet transfusion in the patient with mucosal bleeding. The drug is given at a dose of 50-100 mg/kg every six hours, with a maximum dose of around 12 grams/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 or non-steroidal anti-inflammatory drugs (e.g., ibuprofen), should be avoided. 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.

Neutropenia
Patients with mild neutropenia are often asymptomatic. Treatment with G-CSF or GM-CSF as described earlier may be considered if the patient is having neutropenia-related infectious complications with neutrophil counts <1,000/mm³. 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 and cultures, and should receive broad spectrum antibiotics until the cultures are found to be negative and the fever resolves. Precautions to minimize the risk of infections from endogenous bacterial flora should be instituted according to local guidelines. There is no demonstrated role for the general use of prophylactic antibiotics in FA patients, and

such practices may lead to increased risks of fungal infections and antibiotic resistance.

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 aspiration and biopsy. The use of local anesthetic alone may not be sufficient to alleviate the anxiety and pain that is associated with frequent, repeated bone marrow aspirations. The use of intravenous propofol, fentanyl and midazolam, or similar regimens 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.

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