Chapter 11: Hematopoietic Stem Cell Transplantation

Introduction

Good to Know

A complete list of definitions is provided at the end of this chapter. Here are a few terms you should know right now:

- **Stem cells:** Cells that can develop into one of many types of specialized cells in the body.
- **Allogeneic hematopoietic stem cell transplantation (HSCT):** A medical procedure that destroys the stem cells in a patient's bone marrow and replaces them with stem cells from a HLA-matched or partially matched related or unrelated donor's bone marrow.
- **Human leukocyte antigen (HLA):** A protein found on the surface of cells in the body; this protein helps the body determine what is "self" and what is "foreign." An HLA-matched donor increases the chances that the patient's body will accept the transplant cells and vice versa.

At the time of publication, allogeneic hematopoietic stem cell transplantation (HSCT) remains the only treatment that can correct the hematologic complications common to most patients with Fanconi anemia (FA). Transplants from human leukocyte antigen (HLA)-identical sibling donors are generally associated with excellent outcomes. Currently, survival rates exceed 85% for children younger than 10 years and 65% for children and adults combined [(1)]. In contrast to those with HLA-matched sibling donors, alternative donor (i.e., HLA-mismatched related or unrelated) transplants are more complex due to increased immunological risks. Over time, however, survival rates are increasingly similar between donor sources [(1)].

Because of the unique complications associated with HSCT and the late effects associated with FA itself, it is recommended that whenever possible, patients be cared for at selected centers with comprehensive care clinics specific to FA. Though only a few of these specialized centers exist worldwide, patients who travel to these centers help advance FA research as much as they themselves benefit from the centers' comprehensive care. The dramatic improvements in

transplantation for patients with FA over the past decades, for example, would not have been possible without research that benefited from the concentration of patients at a few centers. Treating patients at selected centers may also help clinicians and researchers improve the management of FA-associated conditions that develop later in life, particularly cancer.

This chapter will describe the current state of knowledge in this area and explore the following issues specific to HSCT in patients with FA:

- *Current expectations of patient survival after HSCT*
- *Exploring the possibility of transplant: Indications for HSCT, referral to a transplant center, initial assessments, and donor identification*
- *Addressing the potential risks of HSCT: Pre-transplant conditioning, GvHD immunosuppression, and infectious disease prophylaxis*
- *The transplant: Pre-transplant work-up, the transplant stay, and late effects of FA and HSCT*
- *Alternatives to HSCT*

Good to Know

Graft-versus-host disease (GvHD): This complication occurs when immune cells in the transplanted marrow consider the patient "foreign" and attack the patient's body.

Myelodysplastic syndrome (MDS): A group of conditions that develop when blood cells in the bone marrow begin to look abnormal (e.g., changes in the size and appearance of the nucleus and cytoplasm). Also known as "preleukemia."

Umbilical cord blood (UCB): Blood present in the placenta and umbilical cord of an infant after birth. This blood contains high numbers of stem cells that can be used in transplants.

Recent Developments in HSCT for FA

The general experience with HSCT for the treatment of FA has been detailed elsewhere [1-12]. From the institutional and registry studies performed to date, three important findings emerge:

1) Survival rates after HSCT continue to improve, particularly for patients undergoing alternate donor transplant.

2) The best outcomes of allogeneic HSCT occur in patients younger than 10 years, patients who test negative for cytomegalovirus (CMV), patients with

no or few blood product exposures, and patients treated with fludarabine in the conditioning regimen prior to HSCT.

3) The technologies of in vitro fertilization (IVF) and preimplantation genetic diagnosis (PGD) can be useful for providing a healthy HLA-matched donor. Successful use of these technologies reduces the need for higher dose therapy and exposure to the risks of alternate or HLA-mismatched donor HSCT.

Since the 2003 and 2008 editions of the *Guidelines* were published, survival outcomes have improved significantly for patients with FA, primarily due to refinements in the treatment plan, HLA-matching between the patient and donor, and earlier referral for HSCT prior to the onset of myelodysplastic syndrome (MDS), acute leukemia, and/or systemic infection. Several other observations about HSCT have been made since the previous edition of the *Guidelines* (Box 1).

Box 1. Recent observations related to HSCT in patients with FA.

- Patients who avoid transfusions and systemic infections tend to have superior outcomes after unrelated donor HSCT.
- Order of priority: For patients without a 7-8/8 matched related donor, 7-8/8 matched adult unrelated donor and 5-6/6 matched umbilical cord blood (UCB) are superior to a 4/6 matched UCB.
- In transplanted FA patients, the risk of cancer appears to be primarily associated with the development of significant graft-versus-host disease (GvHD) with no clear relationship to any particular conditioning regimen.

Current Expectations of Patient Survival

Sibling donor HSCT

In an analysis of 209 FA patients with an HLA-identical sibling donor who were transplanted between 1994 and 1999, the 3-year survival was 81% in patients younger than 10 years (109 patients) and 69 ± 10% in older patients (100 patients) [2]. Today, fewer patients with an HLA-identical sibling donor receive radiation, a treatment that can be associated with late effects such as low thyroid hormone levels. In the largest single-center study of a radiation-free regimen to date [5], 85 patients with FA (median age 9 years, ranging from 3 to 34 years) were treated between 1999 and 2011. Of these 85 patients, 82 were treated for aplastic anemia and 3 were treated for MDS. The treatment consisted of cyclophosphamide (CY) 15 mg/kg x 4 days (60 mg/kg total dose)

along with methotrexate (MTX) and cyclosporine (CSA) immunosuppression to prevent GvHD. At the time of the last report, approximately 85% of patients had survived 5 years, with a higher (96%) survival rate among patients who were younger than 10 years (48 patients) at the time of transplant. Notably, all patients with MDS relapsed after HSCT and died from progressive disease despite receiving a second transplant. Graft rejection occurred in approximately 7% of patients, with acute GvHD in 17 of 81 patients and chronic GvHD in 23 of 78 evaluable patients.

Because transplants can lead to acute and chronic GvHD, and are associated with cancers later in life, MacMillan et al. modified the transplant procedure to incorporate T-cell depletion of the bone marrow, even in sibling donors. This is known to be the best strategy for minimizing the risk of GvHD [1, 3]. At the University of Minnesota, patients were conditioned with CY 5 mg/kg x 4 days (20 mg/kg total dose), fludarabine (FLU) 35 mg/m^2 x 5 days (175 mg/m^2 total dose), and antithymocyte globulin (ATG) 30 mg/mg x 5 days (150 mg/kg total dose) followed by the infusion of T-cell-depleted marrow with CSA and either methylprednisolone or mycophenolate mofetil (MMF) to prevent GvHD. Of the 23 patients (median age 8.5 years; ranging from 3.2 to 43.3 years) included in the study, 92% survived at least 5 years. One recipient of cord blood developed acute GvHD and died; this was the only patient with acute GvHD. None of the patients developed graft failure/rejection or chronic GvHD.

In 2008, Pasquini et al. compared transplant outcomes in recipients conditioned with (77 patients) and without (71 patients) irradiation-containing treatment regimens prior to HLA-identical sibling donor transplantation, as reported to the Center for International Blood and Marrow Transplant Research (CIBMTR)[6]. With a median follow-up of more than 5 years for both groups, the overall survival rates were 78% and 81% at 5 years ($p = 0.61$), respectively, suggesting that there are no advantages to radiation. Future studies are needed to explore whether radiation helps prevent disease recurrence in patients with MDS or more advanced disease.

Unrelated donor HSCT

As the majority of FA patients do not have an HLA-identical unaffected sibling donor, alternative types of donors must be explored. The two most common donor types are adult volunteers registered with organizations like the National Marrow Donor Program (NMDP) and those who have banked or donated umbilical cord blood (UCB) obtained from the placenta after the birth of a baby.

At the University of Minnesota, 48 patients with FA (ranging from 1.7 to 34.3 years) who had aplastic anemia or MDS received FLU, CY, ATG, and low-dose total body irradiation (TBI) (300 cGy) followed by T-cell-depleted 7-8/8 HLA-matched bone marrow (32 patients) or by HLA-mismatched UCB (16 patients) if an unrelated donor was unavailable. All recipients of marrow engrafted at a median of 11 days (ranging from 9 to 23 days). In contrast, engraftment was only 88% at a median of 19 days (ranging from 10 to 40 days) in recipients of UCB. The incidence of acute and chronic GvHD was low (12% and 6%, respectively), with similar outcomes in patients transplanted with bone marrow and UCB. The overall survival for the entire cohort was 78% at a median of 2.9 years (ranging from 0.6 to 6.3 years). However, patients without a prior history of opportunistic infection or transfusions had a 92% (95% confidence interval is 54% to 99%) chance of survival at 5 years (1; MacMillan, unpublished data).

In a preliminary and multi-institutional study reported by Boulad et al. that explored the safety and efficacy of a new conditioning regimen for patients undergoing unrelated donor HSCT, 27 patients (median age 8.1 years, range 4.3 to 31.8 years), primarily with aplastic anemia and/or MDS, received FLU, CY, and ATG in combination with busulfan (BU) followed by transplantation of T-cell-depleted peripheral blood stem cells. All patients engrafted with 1 losing the graft at a later time point. Grade 2-4 GvHD occurred in only 1 patient. Moderate to severe toxicities included severe pulmonary hypertension and veno-occlusive disease of the liver in 1 patient each. The median follow-up time was 8 months (ranging from 0.5 to 37.8 months), and 19 of 23 patients were living at the time of the report [12].

Exploring the Possibility of Hematopoietic Stem Cell Transplant

Indications for HSCT

With improved outcomes, the indications for alternate donor HSCT are increasingly similar to the indications for sibling donor HSCT. Patients with an exceptional risk of transplant-related mortality (e.g., patients with severe organ dysfunction, those who are 35 years or older, and those with pre-existing malignancies or systemic infections) may prefer to explore alternative treatment options first, such as the use of hematopoietic growth factor therapy and androgens. These alternatives are discussed later in this chapter.

Box 2. Eligibility for sibling donor and alternative donor HSCT.
Aplastic anemia (Hgb < 8 g/dL or ANC < 500/μL or platelet count < 30,000/μL)
MDS or acute leukemia
Progressive complex cytogenetic abnormalities*
Absence of active infections
Available HSC donor Order of priority: • HLA 8/8 (followed by 7/8) allele-matched sibling • HLA 8/8 (followed by 7/8) allele-matched relative other than sibling • HLA 8/8 (followed by 7/8) allele-matched unrelated adult volunteer • HLA 5-6/6 antigen matched UCB • Other (4/6 UCB or haploidentical relative**)

*There is currently a lack of unanimity on this criterion.

**Haploidentical transplants are uncommon in the setting of FA, though there have been some reports of success. Haploidentical transplant should be considered in patients with no other alternative. Some treatment plans using haploidentical transplant incorporate significant doses of CY after transplant. This agent at appreciable dose is generally avoided, as patients with FA are inordinately sensitive to high dose CY and would be expected to be at risk of severe toxicity, although experience to date in the Curitiba program (Bonfim, personal communication) has been favorable.

Patients who develop persistent and severe cytopenia [i.e., hemoglobin (Hgb) < 8 grams/deciliter (normally 12-14); absolute neutrophil count (ANC) < 500/μL (normally 2,500-4,500); and/or platelets (PLT) < 20,000/μL (normally 150,000-450,000)] or evidence of MDS or leukemia, should be considered for allogeneic HSCT provided the patient is not too old, has adequate organ function, and controlled infection (Box 2). Earlier transplantation may be considered for patients with specific genetic mutations, who are deemed to be at particularly high risk for rapid progression to MDS or leukemia, and may face markedly shortened survival times [e.g., breast cancer (*BRCA*)-related genetic mutations [13]]. The predictive nature of specific mutations is an active area of clinical investigation.

Referral to a transplant center

Most transplant centers do not have experience with FA. Some centers might be limited to adult transplantation or to the use of autologous (the patient's own) marrow, versus both autologous and allogeneic (another person's) marrow. Even large centers experienced in treating children and adults with allogeneic marrow frequently have no or little experience caring for patients with FA and the short- and long-term complications unique to this patient population.

To best assess a potential transplant team's experience, specific questions should be asked at the time of the initial phone call or visit (Box 3). Additional information can be found on the NMDP website, available at: http://bethematch.org/Patient/Transplant_Planning/Choosing_a_Transplant_Center/U_S__Transplant_Centers.aspx. It should be noted, however, that information about the center's specific experience with FA is usually difficult to discern because FA is often lumped together with other diseases such as sickle cell disease and Diamond Blackfan anemia under the category "Inherited abnormalities of erythrocyte differentiation." In addition, these data do not describe the center's experience with the specific treatment regimen proposed for a given individual; for example, a patient with FA who has aplastic anemia versus a patient with FA who has MDS or leukemia.

Referring doctors and insurance companies may be associated with certain transplant centers, often based on their experiences with patients who have leukemia. Proximity to home may not be the deciding factor for a patient with FA if FA-specific expertise is not locally available. If the insurance company is associated with a bone marrow transplant (BMT) center that has limited or no expertise in FA, the insurance company will often give approval for the FA patient to travel to an experienced FA center once the insurance company understands the differences in the centers' experience and the importance of experience in patient survival. Insurance denials or less than complete coverage for transplant at a FA-experienced transplant center (because they are "out-of-network") can often be contested successfully.

Box 3. Questions to help assess a transplant center's experience with FA.
• What is the total number of transplants that the center has performed specifically in patients with FA?
• How many FA transplants have been performed each year for the past 5 years? How many of those patients are still alive?
• What treatment regimen do you propose? Please tell me the exact doses of each drug and the radiation dose (if applicable). How many patients have been treated with this regimen at this center? How many are still alive?
• What is the risk of acute and chronic GvHD in FA patients using this regimen? How do you plan to prevent GvHD?
• How long will you follow the patient (me/my child/my spouse)? Who will follow the patient (me/my child/my spouse) long term?

*** IMPORTANT NOTE! ***

The insurance company may indicate that a FA-experienced transplant center is not a "Center of Excellence". This does not necessarily reflect on the suitability or quality of the center. "Center of Excellence" is the designation made by the insurance company to indicate that a center has met criteria and operates under a negotiated contract with the specific insurance company.

As a rule, a family should not immediately accept a denial from an insurance carrier without asking the FA-experienced transplant center to directly negotiate with their insurer if such a center is desired.

First assessments

Before the first visit to a FA transplant center, the patient's physician will be asked to put together a packet of information to help the transplant physician provide the best recommendations specific to the patient, whether that patient is you, your child, or your spouse. This packet should include the information listed in Box 4.

Past medical history. The manifestations and complications associated with FA vary dramatically from one patient to the next. Because certain malformations and ongoing treatments could impact the proposed HSCT treatment plan, the physician must obtain a complete medical history, including an evaluation of the severity of the malformations (particularly those of the heart and kidney) and prior or ongoing treatments. All infectious disease complications, prior use of androgens, prior surgeries and cancers must be carefully detailed in the medical history, as these complications may affect the design of the transplant treatment plan. The medical history must detail all past surgeries (e.g., tracheoesophageal fistula, duodenal atresia, or ureteral reflux); medical treatments (e.g., metoclopramide and ranitidine for gastroesophageal reflux, or Bactrim prophylaxis for ureteral reflux); transfusion history (e.g., number of red blood cells and platelets); history of androgen use (e.g., type, dose, and duration), and general issues such as immunizations, allergies, and the patient's use of vitamins, iron supplements, or herbal remedies.

Box 4. Preparing for a new transplant assessment appointment.
History of Present Illness • FA diagnosis (date and place of FA testing) • Presenting symptoms that ultimately led to FA testing • Complementation group/mutation testing results (if performed) • List of organs involved • Most recent blood counts • History of transfusions • History of infections
Past Medical History • Perinatal birth history (i.e., number of pregnancies and miscarriages prior to the patient's birth); complications during the pregnancy and delivery; APGAR scores; presence of birth defects • Growth records (height and weight charts) • Developmental history • Surgeries • Hospitalizations • Immunization record
Current Medications and Allergies • Include over-the-counter drugs so that the physician can determine which drugs might damage the bone marrow • List of current medications associated with reactions and severity of reactions
Family Medical History • Number of siblings; have they been tested for FA? • Medical histories for parents of the patient and for other first- and second-generation relatives, particularly noting cancers, anemias, and birth defects
Social History • Home environment, exposure to chemicals, types of pets • School experience (e.g., learning challenges)

Family medical history. The family medical history is extremely important. ***Without exception, all full siblings (i.e., siblings with the same mother and father), regardless of appearance, blood counts, HLA, or blood types, must be tested for FA***. It has been repeatedly shown that siblings who appear to be completely healthy and without any manifestation suggestive of FA may still have FA. Further, it is important to reveal if there are full siblings not living with the family or, because of donor compatibility issues, if the child with FA is adopted.

Social history. Behavioral, school, and work performance issues should be reviewed with the clinician. An open discussion of alcohol consumption and smoking history (cigarette and cannabis) is very important because of the risks of cancer and infection in the early transplant period. Additionally, the

physician should inquire about the use of other drugs that could potentially interfere with the patient's liver function or drug metabolism during and after the transplant.

Concurrent medications. The patient's use of complementary medications should be assessed by the transplant team. Some agents, like echinacea, which is believed to help the immune system and prevent colds, flu, and infections, may cause rashes or diarrhea that resemble the symptoms of GvHD. Other supplements, like ginkgo, which is believed to treat asthma and bronchitis as well as improve memory, may cause bleeding problems. St. John's wort, which is believed to treat anxiety and depression, may interfere with the metabolism of cyclosporine A, an important drug used in the early transplant period. A summary of published results of various complementary medications and potential side effects can be found at http://nccam.nih.gov.

Physical examination. Prior to HSCT, the physician will assess potential factors that may alter the risk or plan of transplant therapy. Careful attention will be paid to the oropharyngeal area (to check for precancerous lesions, infection, and dental health); ears (to check hearing); nose and sinuses (to check for infection); respiratory system (to check for infection or reactive airway disease); and urogenital system (to check for infection, bladder anomalies, or cervical/vulvar precancerous/cancerous lesions). The general examination should carefully document pre-existing cutaneous changes (e.g., *café au lait* spots, areas of hyper- or hypopigmentation, nail abnormalities, nevi, and lesions characteristic of squamous cell carcinoma or melanoma), heart sounds/murmurs, liver and spleen sizes, and scars from prior surgeries.

Donor identification: The search process and HLA typing

Physicians should embark on an extended family and/or unrelated donor search well before the patient develops severe bone marrow failure, MDS, or AML, so that delays are minimized once HSCT is required. According to the NMDP, the average time from search initiation to HSCT is approximately 3-4 months; therefore, a search should be initiated before the need for transfusions or development of leukemia. In general practice, the NMDP will allow the transplant center to "reserve" a donor for several months without having received a request for a marrow harvest or a peripheral blood stem cell collection date. After that time, the NMDP will request more specific information about the proposed timing of the transplant procedure. In some cases, the NMDP and medical director of the collection center will permit an exception and allow the donor to be kept on "reserve" without a specific

date. This is decided on a case-by-case basis. It is important to recognize that a donor on "reserve" may still appear in other patient searches. Though uncommon, it is possible that a patient with an urgent need could request that same donor, in which case the NMDP will work to seek an equitable solution. Some patients or parents ask if it is possible to collect and store bone marrow, either from a related or unrelated donor, for future use so that it is available at the time it is needed. This is generally not recommended and, in the case of unrelated donors, rarely permitted. In some cases, a donor may not be reserved for years in the hope that the "perfect" donor will be available in the future.

A search should be performed with urgency if the patient has advanced bone marrow failure that requires recurrent transfusions or hematopoietic growth factor therapy, or if the patient shows evidence of MDS or acute leukemia. The search should include both adult volunteer and cord blood donor registries. While use of adult volunteers has generally been the preferred source of transplants, urgency and lack of an HLA-matched adult volunteer donor have resulted in the growing use of cord blood for transplants in patients with FA.

For alternate donors (any donors other than an HLA-matched sibling), high-resolution typing at HLA-A, B, C, and DRB1 of the patient must be obtained. Most transplant centers will require confirmatory HLA typing at their institution if HLA typing was originally performed elsewhere. The results of HLA typing are typically available within 7-10 business days.

A search of the bone marrow and UCB registries requires submission of the patient's HLA type and, in the case of UCB, the patient's weight. A preliminary search can be performed by any physician at no cost. A formal search and the pursuit of a potential donor, however, must be performed by an approved transplant center with the consent of patients who are at least 18 years old or the patient's parent/legal guardian if the patient is younger than 18 years. A formal search will result in charges to your insurance plan, so the patient should obtain insurance approval prior to the initiation of the search. The cost will vary depending on the number of donors identified and evaluated.

*** IMPORTANT NOTE! ***

Even if a formal search has been initiated by a transplant center, the patient is not obligated to have the transplant performed at that center—or even to have a transplant at all.

Transfer of the donor search only requires notification of the National Marrow Donor Program or other coordinating center (policies vary by country) and a newly signed consent from the patient or family.

Other potential considerations in the donor selection process are the age of the donor, CMV serostatus, female parity (i.e., number of pregnancies), and sex match between the donor and patient. Additional factors that are sometimes included in the choice of a specific UCB unit may include the quality of the cord blood bank, the presence in the recipient of anti-HLA antibodies directed against the UCB unit, and the ability to confirm unit identity.

Addressing the Potential Risks of HSCT

Once the patient and donor meet the transplant center's eligibility criteria, the patient will be scheduled for the transplant admission. The exact timing and therapeutic plan may vary depending on the source of the HSC (i.e., from bone marrow, peripheral blood, or UCB), the degree of donor and patient HLA match, the patient's age, the presence of specific end-organ dysfunction, the stage of disease (e.g., aplastic anemia, MDS, or acute leukemia), institutional preferences, and other personal factors (e.g., school, employment).

Pre-transplant conditioning

The pre-transplant conditioning regimen works to destroy the diseased FA marrow and to suppress the patient's immune system so that the healthy HSCs from the donor are less likely to be rejected. Pre-transplant conditioning therapy in FA patients is significantly reduced in dose compared to that used in patients who do not have FA. This is because of their unique hypersensitivity to alkylating agents and irradiation, as a result of the DNA repair defect present in nearly all individuals with FA (the notable exception may be the patient with *BRCA2* genetic mutations). The generic side effects of the most commonly used pre-transplant conditioning agents are detailed in Table 1.

Table 1. Side effects of the most common pre-transplant conditioning agents.

Busulfan		
Common	Less Common	Rare
• Hair loss or thinning, including face and body hair (usually grows back after treatment) • Long- or short-term infertility (inability to have children) in men and women	• Tiredness (fatigue) • Sores in mouth or on lips • Fever • Nausea • Vomiting • Rash • Loss of appetite • Diarrhea • Liver damage/veno-occlusive disease	• Allergic reaction with hives, itching, headache, coughing, shortness of breath, or swelling of the face, tongue, or throat • Scarring of lung tissue, with cough, difficulty breathing, and shortness of breath that may occur after prolonged use, or even months or years after stopping the drug • Leukemia (several years after treatment) • Darkened skin • Heart problems with high-dose treatment, most often in people with thalassemia • Problems with the hormone system that cause weakness, tiredness, poor appetite, weight loss, and darker skin • Death due to lung or liver damage, or other causes

Cyclophosphamide		
Common	Less Common	Rare
• Hair loss or thinning, including face and body hair (usually grows back after treatment) • Nausea • Vomiting • Loss of appetite • Sores in mouth or on lips • Bleeding from bladder, with blood in urine • Diarrhea • Long-term or short-term infertility in women and men	• Darkening of nail beds • Acne • Tiredness • Infection	• Heart problems with high doses, with chest pain, shortness of breath, or swollen feet • Severe allergic reactions • Skin rash • Scarring of bladder • Kidney damage (renal tubular necrosis) which can lead to kidney failure • Heart damage with trouble getting your breath, swelling of feet, rapid weight gain • Scarring of lung tissue, with cough and shortness of breath • Second cancer, which can happen years after taking this drug • Death from infection, bleeding, heart failure, allergic reaction, or other causes

Figure 1 continued on next page.

Fludarabine		
Common	Less Common	Rare
• Tiredness (fatigue) • Nausea • Vomiting • Fever and chills • Infection	• Pneumonia • Diarrhea • Loss of appetite • Pain	• Numbness and tingling in hands and/or feet related to irritation of nerves • Changes in vision • Agitation • Confusion • Clumsiness • Seizures • Coma • Cough • Trouble breathing • Intestinal bleeding • Weakness • Death due to effects on the brain, infection, bleeding, severe anemia, skin blistering, or other causes

Total Body Irradiation		
Common	Less Common	Rare
• Nausea and vomiting • Diarrhea • Cataracts • Sterility • Endocrinopathies • Growth failure • Intestinal cramps • Mucositis	• Parotitis (inflammation of major salivary glands) • Interstitial pneumonitis • Generalized mild erythema • Veno-occlusive disease	• Dysphagia (difficulty swallowing) • Vertebral deformities • Nephropathy • Death from infection, lung injury, or other causes

GvHD immunosuppression

GvHD results when the transplanted immune system of the donor recognizes the patient as "foreign" and tries to reject the foreign tissues. This disease sometimes occurs after HSCT because the donor's immune system is transplanted along with the donor's HSCs, which are responsible for marrow recovery and reconstitution of the blood cells. While GvHD can occur in any patient undergoing an allogeneic HSCT, the disease tends to be more common and severe in mismatched donor recipients. The signs and symptoms of the two types of GvHD (acute and chronic) are detailed in Table 2A. The side effects of the most commonly used drugs to prevent and treat GvHD are shown in Table 2B.

Table 2A. Signs and symptoms of acute and chronic GvHD.

Graft-versus-Host Disease	
Acute GvHD	Chronic GvHD
• Skin rash (blistering with more severe disease) • Diarrhea • Jaundice (high bilirubin) • Marked predisposition to infections	• Skin rash/discoloration • Hair loss • Dry mouth/tooth decay • Dry eyes • Sores in the mouth/thrush • Steatorrhea (diarrhea that is oily) • Ridged/fragile nails • Shortness of breath/exercise intolerance • Marked predisposition to bacterial infections

Table 2B. Side effects of common GvHD immunosuppression regimens.

Cyclosporine A and Tacrolimus	
Common	Rare but possibly serious
• Headache • Diarrhea • Heartburn • Gas • Increased hair growth on the face, arms, or back • Excessive growth of gum tissue • Acne • Flushing • Uncontrollable shaking of a part of the body • Burning or tingling in the hands, arms, feet, or legs • Muscle or joint pain • Cramps • Pain or pressure in the face • Ear problems • Breast enlargement in men • Depression • Difficulty falling asleep or staying asleep	• Unusual bleeding or bruising • Pale skin • Yellowing of the skin or eyes • Seizures • Loss of consciousness • Changes in behavior or mood • Difficulty controlling body movements • Changes in vision • Confusion • Rash • Purple blotches on the skin • Swelling of the hands, arms, feet, ankles, or lower legs

Figure 2B continued on next page.

Mycophenolate Mofetil	
Common	Rare but possibly serious
• Constipation • Stomach pain or swelling • Nausea • Vomiting • Difficulty falling asleep or staying asleep • Pain, especially in the back, muscles, or joints • Uncontrollable shaking of a part of the body • Headache • Rash	• Diarrhea • Swelling of the hands, arms, feet, ankles, or lower legs • Difficulty breathing • Chest pain • Fast heartbeat • Dizziness • Fainting • Lack of energy • Pale skin • Black and tarry stools • Red blood in stools • Bloody vomit • Vomit that looks like coffee grounds • Yellowing of the skin or eyes

Prednisone/Methylprednisolone		
Common	Less Common	Rare
• Increased appetite • Trouble sleeping • Upset stomach • Excess fluid or swelling in the face, hands, or feet • Weight gain • Slowed wound healing • Increased blood glucose levels	• Headache • Feeling dizzy • Mood swings (shifts between euphoria, anxiety, depression, and others) • Low blood potassium level • Muscle weakness • High blood pressure • Feeling restless • Feeling depressed or anxious • Skin rash • Nausea/vomiting • Hot flashes • Menstrual changes • Sweating • Bone or muscle pain • Increased risk of infection due to suppressed immune system • Fewer and milder symptoms of infection • Skin thinning or bruising easily (with long-term use) • Cataracts (with long-term use) • Glaucoma (with long-term use) • Thinning of bones (osteoporosis) (with long-term use) • Aseptic necrosis of the major joints (hips > knees > shoulders)	• Bleeding or ulcers in the digestive tract • Vision changes • Confusion, losing touch with reality • Change in heart rhythm • Congestive heart failure (can cause shortness of breath or swelling in hands or feet) • Acne (with long-term use) • Thinning hair growth (with long-term use) • Bone fractures (with long-term use)

GvHD can occur regardless of the prophylactic approach used. The more severe the GvHD (e.g., grade 3-4 disease), the higher the risk of death, mostly due to infection. If GvHD occurs, the mainstay of treatment is methylprednisolone. Other agents successfully used in the management of acute and chronic GvHD include ATG, MMF, and psoralen with ultraviolet light (PUVA). PUVA is ***not*** recommended for patients with FA, however, as it may be more toxic in this population.

Infectious disease prophylaxis

Infectious complications after alternate-donor HSCT are a major problem for all transplant patients, regardless of FA status, but may pose a greater risk to FA patients due to 1) the unique sensitivity of FA patients to chemoradiotherapy with the resultant breakdown of mucosal barriers after treatment; 2) the extensive prior period of neutropenia; and 3) considerable transfusion exposure prior to HSCT and the resultant exposure to infectious agents.

Prophylactic antibiotic regimens are commonly used after HSCT to reduce the risk of infection. Most patients will be on trimethoprim/sulfamethoxazole (Bactrim or Septra) for 1 year after transplant and other antibacterial and antifungal drugs through day 100, or longer if they develop GvHD.

Good to Know

Neutropenia: A condition characterized by abnormally low levels of neutrophils in the blood. Neutrophils are immune cells that fight off bacterial and yeast infections. Therefore, neutropenia can lead to more frequent or severe infections.

Prophylactic therapy: Therapy given before symptoms are present, to reduce the patient's risk of developing a certain complication, such as infection or GvHD.

The length of prophylactic therapy to prevent infection depends upon the degree of immunosuppression, the patient's absolute CD4 T-cell level, the development of acute or chronic GvHD, and the patient's prior history of infectious complications.

The Transplant

The pre-transplant work-up
If a patient with FA appears to be a good candidate for transplant, based on history and physical examination, a number of routine tests should be performed immediately prior to transplant to verify eligibility for transplant and to determine if any adjustments are needed in the treatment. For example, poor kidney function could result in important drug dose adjustments or an anomaly on chest CT might result in additional evaluations, antibiotics, or delay in transplant until resolved. A list of the types of tests performed at most transplant centers is shown in Box 5.

The transplant stay
Most transplant centers will expect the patient to remain near the facility for a minimum of 100 days. While major complications can occur after this period, the first 100 days are considered the highest risk period for the development of immunologic complications (i.e., graft rejection, GvHD, and opportunistic infection) associated with HSCT. During the initial hospitalization for the transplant procedure, all patients are kept in a single occupancy room equipped with a high-efficiency air filtration system to reduce exposure to infectious agents. Once the marrow has recovered sufficiently, patients are allowed out of their hospital rooms unless intervening problems prevent this. After discharge, patients are expected to avoid crowded enclosed spaces and often encouraged to wear masks in an attempt to reduce exposure to viral, bacterial, and fungal pathogens. Specific restrictions and suggestions will vary modestly between different centers.

Patients treated with HLA-matched sibling donor marrow or UCB may be discharged earlier in some cases. Factors that influence the time of discharge include the number of transplant complications such as GvHD and infections, access to a BMT facility closer to the patient's home, the comfort of the referring physician, and evidence of immune recovery. These factors should be discussed on a case-by-case basis.

Box 5. Pre-transplant laboratory tests.
• Confirmatory diagnostic testing for FA (DEB or MMC most commonly)
• Confirmatory HLA typing
• Bone marrow aspirate and biopsy with cytogenetic evaluation

• Infectious disease assessments
  • Prior exposures (cytomegalovirus; hepatitis A, B and C; HIV; HTLV1/2; EBV; syphilis)
  • Presence of active infections (CT scan of sinuses, chest, and abdomen; dental evaluation)

• Organ function assessments
  • Lung (pulmonary function tests, oxygen saturation)
  • Heart (EKG, echocardiogram)
  • Liver (liver enzymes, ultrasound)
  • Kidney (chemistries, nuclear medicine studies such as glomerular filtration rate or GFR, ultrasound)

Late effects of FA and BMT

All recipients of chemoradiotherapy and allogeneic HSCT are subject to health complications that develop long after the transplant. These are known as "late effects" and they are not necessarily unique to patients with FA (see *Chapter 11*). These effects include late graft failure, recurrent acute and chronic GvHD, and the effects of prolonged steroid therapy such as hypertension (high blood pressure), hyperglycemia (high blood sugar), and aseptic necrosis of bone (loss of bone primarily in the hip, knee, and shoulder joints). Other late effects such as short stature and sterility have not been formally evaluated with respect to the effect of HSCT in patients with FA since these are pre-existing problems in most FA patients. As survival improves for FA patients after HSCT, greater research is now being focused on reducing the risk of late effects, such as malignancy, sterility, or endocrinopathies (hormonal deficiencies), to improve quality of life.

Patients with FA have a high incidence of squamous cell carcinoma (SCC; see *Chapter 14*) [14, 15]. Some studies suggest that the risk of SCC may be higher after HSCT, although the factors responsible for this relationship remain a topic of debate. Studies suggest that the development of acute or chronic GvHD or the therapy to control GVHD may be the primary risk factor for the subsequent development of SCC, rather than the conditioning therapy or the transplant itself. Because of this association between cancer and GvHD, the use of T-cell depletion of the marrow or peripheral blood, which is recognized as the best approach for reducing GvHD risk, has been incorporated into many protocols. Although there is no proven method of cancer prevention in patients with FA,

recognition of the patient's risk and close monitoring of the head and neck region in particular, via frequent dental and ENT evaluations for example, are important strategies for reducing the morbidity and mortality associated with this late effect (see *Chapters 10* and *14*). The relationship of head and neck cancer with the HPV observed in non-FA adults has inspired the general recommendation that both males and females with FA should receive the HPV vaccine (Gardasil® or Cervarix®).

Alternatives to HSCT

Recent cloning of the FA genes has provided new insights into the molecular basis of FA, and has unveiled new opportunities to improve the care of FA patients. For example, knowledge of a patient's complementation group or genetic mutation not only allows the physician to predict the course of the patient's disease in some cases [(1)], but it may also allow for the potential use of gene therapy. Numerous research teams are currently working on the possibility of gene therapy using the patient's own HSC. Thus far, gene therapy has not cured a patient with FA; however, the techniques are being continually optimized and there is hope that this therapy may prove effective in the future (see *Chapter 13*). Most gene therapy protocols would exclude patients who have MDS, leukemia, or those with a high expectation of survival, such as a patient with a 7-8/8 HLA-matched sibling or unrelated donor based on today's outcomes.

Other alternatives are the use of hematopoietic growth factor, such as G-CSF (Neupogen), androgens, or chronic transfusions with iron chelation therapy for patients who receive red blood cells. While transplant is generally recommended as first-line therapy for bone marrow failure, MDS, or leukemia in patients with FA, patients who are considered to be too "high risk" to undergo transplant therapy may be good candidates for an alternative treatment plan. For example, patients with SCC or organ failure might be considered poor candidates for transplant but potential candidates for alternative treatments.

Notably, there has been resurgence in the use of androgens as first-line therapy for FA. In the late 1990s and 2000s, this practice was nearly eliminated because of its side effects and negative impact on transplant outcome in patients with FA. However, some clinicians are considering it as a means to delay or prevent the use of transplant on an investigational basis. The patient and family should discuss the risks and benefits of this approach with the hematologists at a FA comprehensive care center for updates as those studies progress. Additional

approaches that take advantage of new knowledge in FA, such as the effect of aldehydes or the role of various modulators of metabolism or oxidative stress, are also in development. Some are moving into trials now and others may become therapeutic alternatives in the not so distant future.

Abbreviations and Important Terms

AA: *Aplastic anemia*. A condition that occurs when the bone marrow fails to produce the proper amount and type of blood cells. Patients with Fanconi anemia can develop aplastic anemia, but this disorder can occur in other settings as well.

ANC: *Absolute neutrophil count.* The number of neutrophils in one microliter of blood. Neutrophils are immune cells that fight off certain infections.

Antibodies: Proteins produced by the immune system to attack foreign material—such as bacteria, viruses, or transplants—that the body does not recognize as part of its self.

Aseptic Necrosis of Bone: Loss of bone primarily in the hip, knee, and shoulder joints.

ATG: *Antithymocyte globulin*. Animal-derived antibodies that attack a patient's immune cells. Treatment with ATG helps prevent the patient's immune system from rejecting the transplanted blood-forming stem cells. ATG is also used as a therapy for aplastic anemia (not Fanconi anemia).

BMT: *Bone marrow transplant*. A medical procedure in which a patient's bone marrow is replaced with healthy bone marrow from a suitable donor. In most cases, a patient's bone marrow will be destroyed by medication or radiation therapy before the transplant is performed.

BU: *Busulfan*. A drug used to destroy the patient's diseased marrow and treat some forms of leukemia.

CIBMTR: *Center for International Blood and Marrow Transplant Research*. An organization that supports research to discover, apply, and improve therapies for bone marrow failure. Read more at http://www.cibmtr.org.

CMV: *Cytomegalovirus*. A relatively common virus in the herpes family that causes mild symptoms in healthy people, but can pose a serious health risk to immune-compromised individuals.

CSA: *Cyclosporine*. A drug that suppresses the immune system after transplant and is used to prevent transplant rejection.

CY: *Cyclophosphamide*. A drug used to suppress the immune system before the transplant to prevent rejection of the new blood-forming stem cells, and is also used to treat certain cancers.

FA: *Fanconi anemia*. An inherited disease that affects the bone marrow's ability to produce blood cells.

FLU: *Fludarabine*. A drug capable of suppressing the immune system before transplant to prevent rejection of the new blood-forming stem cells, and is also used to treat some cancers.

GvHD: *Graft-versus-host disease*. This is a relatively common complication that occurs when immune cells in the transplanted material identify the patient as "foreign" and attack the patient's body. It most often involves the skin, gastrointestinal tract, and liver.

HgB: *Hemoglobin.* A red blood cell protein that is responsible for transporting oxygen to various parts of the body through the bloodstream.

HSCT: *Allogeneic hematopoietic stem cell transplantation*. A medical procedure that destroys the patient's blood and marrow followed by the infusion of bone marrow (as in bone marrow transplant), mobilized peripheral blood stem cells, or umbilical cord blood. All three are sources of hematopoietic (or blood-forming) stem cells.

HLA: *Human leukocyte antigen*. A protein found on the surface of all nucleated cells in the body that helps the body determine what is "self" and what is "foreign." An HLA-matched donor increases the chances that the patient's body will accept the transplant.

IVF: *In vitro fertilization*. A treatment for infertility, in which an egg is removed from a woman's ovary and fertilized by one sperm in a laboratory setting. The resultant embryo is then implanted into the woman's uterus.

"Late Effects": Health conditions that manifest more than 100 days after the transplant day.

MDS: *Myelodysplastic syndrome*. This is a disease that is diagnosed when the cells of the marrow have an abnormal appearance. Chromosomal abnormalities

are frequently present when this occurs and are often a prelude to full-blown leukemia. This syndrome is commonly thought of as a "preleukemia."

MMF: *Mycophenolate mofetil*. A drug used to suppress the immune system in patients after transplant as a way to prevent graft-versus-host disease.

MTX: *Methotrexate*. A drug used to suppress the immune system in patients after transplant as a way to prevent graft-versus-host disease. It can also be used to treat some forms of leukemia and other types of cancer.

Neutropenia: A health condition characterized by abnormally low levels of neutrophils in the blood. Neutrophils are immune cells that fight off infections. Therefore, neutropenia can lead to more frequent or severe infections.

Neutrophils: A type of white cells that fight off bacterial and yeast infections.

NMDP: *National Marrow Donor Program*. This US-based program operates the Be the Match Registry® of volunteer bone marrow, hematopoietic cell, and umbilical cord blood donors.

Opportunistic Infection: This type of infection is common in immune-compromised patients who are unable to fight off microbes that do not normally cause disease in humans.

PGD: *Preimplantation genetic diagnosis.* A technology for examining the genes of in vitro-derived embryos before they are implanted in a woman's uterus.

PLT: *Platelets*. Disc-like fragments of cells that circulate in the bloodstream and help promote clotting at the site of a cut or injury.

TBI: *Total body irradiation.* Treatment delivered in a controlled way to destroy the patient's immune system and diseased marrow prior to transplantation. It can also be used to treat leukemia and lymphoma that is resistant to chemotherapy.

T-Cells: White blood cells that play a key role in the immune response by searching out and destroying material that is considered "foreign." These cells are also responsible for protecting the patient from viruses and fungal infections.

UCB: *Umbilical cord blood or cord blood.* Blood present in the placenta and umbilical cord of an infant after birth. This blood contains high numbers of blood-forming stem cells that can be used in transplants.

Chapter Committee

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