

Chapter 10

Unrelated Donor Hematopoietic Stem Cell Transplantation

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Introduction

As of June 2008, allogeneic hematopoietic cell transplantation (HSCT) remains the only treatment that can correct the hematologic complications common to most patients with Fanconi anemia. HSCT from HLA-identical sibling donors is generally associated with an excellent outcome (i.e., survival rates in excess of 85% for children less than 10 years of age and 65% for children and adults together).^{1,2} HSCT from alternate (i.e., HLA-mismatched related or unrelated) donors, however, is relatively more complex and challenging. It is associated with a higher risk of complications, with survival rates lower than that observed with HLA-matched sibling donors, although significantly better than survival rates of five years ago. For these reasons, it is recommended that HSCT from alternate donors be performed at selected transplant centers experienced in the care of FA patients, in the use of alternate donor HSCT, and in clinical trials which are specifically designed to address the high risks of regimen-related toxicity and infection unique to this patient population.

Overview

The general experience with alternate donor transplantation for the treatment of FA has been detailed

elsewhere.¹⁻⁹ From these institutional and registry studies, four important findings emerge: 1) survival rates at three years after alternate donor HSCT range between 40-75%; 2) regimen-related toxicity and infection are the primary reasons for treatment failure; 3) risk factors for best outcome after alternative donor HSCT are: age <10 years; recipient cytomegalovirus (CMV) seronegativity; history of fewer than 20 blood product exposures; and use of fludarabine in the preparative regimen; and 4) results with HLA 5-6/6 matched unrelated donor umbilical cord blood are similar to that observed with bone marrow.

Compared to the 2003 edition of this handbook, survival outcomes are significantly better, due to 1) safer and more effective pre-transplant cytoreductive therapies; 2) improved supportive care measures; 3) better methods of HLA-matching between the patient and donor; and 4) earlier referral for HSCT prior to the onset of myelodysplastic syndrome (MDS), acute leukemia and/or systemic infection (Table 1).

Indications for Alternate Donor Hematopoietic Stem Cell Transplant

With improved outcomes, the indications for alternate donor HSCT are increasingly similar to those described for sibling donor HSCT (Chapters 3 and 9). For some patients considered to be at an exceptional risk of transplant-related mortality (e.g., those with severe organ dysfunction, age ≥ 35 years, pre-existing malignancy or systemic infection), alternative treatment options, such as use of hematopoietic growth factor therapy and androgens, may be appropriate.

If the patient develops persistent and severe cytopenia (i.e., hemoglobin [Hgb] <8 g/dL; absolute neutrophil count [ANC] <500/mm³; and/or platelets [PLT]

Table 1: Observations since the 2003 Edition

- Transplantation using HLA-mismatched related or HLA-matched/mismatched unrelated donors should be performed at transplant centers that specialize in Fanconi anemia transplants and perform five or more such transplants a year.
- Umbilical blood transplantation is an acceptable alternative, if HLA 8/8 matched marrow is not available.
- Transplantation should be considered prior to the administration of blood products. Data document reduced survival after transplant in recipients of ≥ 20 blood product exposures.
- Other risk factors adversely affecting survival after unrelated transplant potentially include HLA mismatch, prior exposure to androgens, and number of congenital malformations ≥ 3 .
- Fludarabine, in combination with cyclophosphamide and total body radiation, represents a new standard of care in the setting of unrelated HSCT. It is associated with an increased incidence of engraftment and survival in recipients of umbilical cord blood, peripheral blood stem cells or marrow and appears to reduce the deleterious effect of T-cell mosaicism.

$<20,000/\text{mm}^3$) or evidence of MDS or leukemia, the patient should be offered the option of alternate donor HSCT, provided the patient has adequate organ function and controlled infection (Table 2). Earlier transplantation may be considered for patients with specific mutations deemed to be particularly high risk for rapid progression to MDS or leukemia and markedly shortened survival (e.g., breast cancer [*BRCA*] gene mutations).^{10,11}

Table 2: Eligibility for Alternate Donor HSCT

- Severe cytopenia (Hgb <8 g/dL, ANC <500/mm³, PLT <20,000/mm³)
- MDS or leukemia
- High risk mutation (e.g., *BRCA2*)
- Absence of an HLA-A, B, DRB1-identical sibling donor

Referral to a transplant center

Transplant centers with valuable areas of expertise exist in many countries. Some centers might be limited to adult transplants or to the use of autologous (patient's own marrow) versus both autologous and allogeneic (another person's marrow). While most transplant centers are experienced in the treatment of leukemia, few have experience with FA.

Table 3: Transplant Center Interview Questions

1. How many allogeneic FA transplants has your center performed? How many in children? How many in adults? How many have survived beyond one year?
2. How many unrelated donor transplants on FA patients has your center performed in the prior calendar year?
3. What specific preparatory therapy does your center recommend? (Obtain the doses of each therapy.)
4. What is your center's long-term follow-up plan for transplanted patients with FA; e.g., growth and development late effects?

To determine the experience of a transplant center being considered, the physician or patient should ask the questions listed in Table 3.

Referring doctors and insurance companies may have associations with transplant centers, often based on experience with patients with leukemia. Proximity to home is a factor that may not be appropriate for the patient with FA, if specific FA expertise is not locally available.

Patients and families should note that they or their advocate can often negotiate with the insurance company concerning where a transplant is performed. A transplant center's experience in FA and the use of alternative donors can change an insurer's preference and allow the development of individual contracts, even when the transplant center is "out of network" or not considered one of the insurer's "Centers of Excellence." Note: "Center of Excellence" is the designation for a center with an existing negotiated contract and is not related to a center's expertise. As a rule, a family should not accept a denial from an insurance carrier without asking a transplant center expert in FA transplants to negotiate with the carrier.

Assessment

An evaluation at an FA transplant center will address the following elements (Table 4).

Past medical history

FA is a genetically and phenotypically heterogeneous disorder, often accompanied by multiple congenital malformations, growth failure, learning disabilities, etc. Congenital malformations may range from none to many and may involve any of the major organ systems.

Table 4: Required Elements of the History to be Prepared Prior to Going to the Transplant Center

- Reason for FA testing.
- Date of diagnosis.
- Results of DEB and MMC tests, including evidence of somatic mosaicism (i.e., presence of DEB/MMC-resistant cells).
- Results of complementation group or mutation analysis (including *BRCA2* testing for those with early onset of leukemia [age <6 years] or negative complementation group testing results).
- List of congenital malformations and treatments (e.g., kidneys, gut, liver, bladder, heart, lungs, limbs).
- Gynecological (females) and sexual history (males and females).
- Chronic pain and management.
- Nutritional assessment.
- Documentation of endocrine status. Consider the use of growth hormone therapy prior to the use of agents such as TBI and steroids that could interfere with later therapy.
- List of medications and responses to treatments (e.g., androgens, steroids, hematopoietic growth factors, chemotherapy, radiotherapy, hormonal replacement) and alternative therapies (complementary medicine).
- Transfusions (e.g., number of red cell or platelet exposures).
- Known alloimmunization.
- Details of prior infections (organism, antibiotic sensitivities, sites, response to treatment, history of prophylaxis).
- History of cancer (site, treatment).

Because certain malformations and treatments may interfere with HSCT, the physician must take a complete medical history, including evaluating these malformations and prior or ongoing treatments. All infectious disease complications, prior use of androgens, prior history of hepatic adenomata, and cancer must be carefully detailed, as these complications may affect the design of the treatment plan for transplantation. The history must detail any past surgeries (e.g., tracheoesophageal fistula, duodenal atresia, ureteral reflux); medical treatments (e.g., metoclopramide and ranitidine for gastroesophageal reflux, Bactrim prophylaxis for ureteral reflux); and general issues (immunizations, allergies, use of vitamins, iron supplements, and herbal remedies).

Family medical history

The family medical history is extremely important. Without exception, all siblings, regardless of phenotype and HLA match, 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 determine if there are full siblings who are no longer 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. Alcohol and smoking (cigarette and cannabis) exposure should be determined, because of cancer risk and risk of infection in the early transplant period. Additionally, the physician should inquire about the use of other drugs which potentially could interfere with liver function or metabolism rates of drugs used in the transplant setting.

Concurrent medications

Use of complementary medications should be assessed by the transplant team. Some agents, like echinacea, believed to help the immune system and prevent colds, flu and infections, may cause rashes and diarrhea (similar to symptoms of graft-versus-host disease). Others, like ginkgo, believed to treat asthma and bronchitis as well as improve memory, may cause bleeding problems. St. John's wort, 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 (precancerous lesions, infection, dental health); ears (hearing); nose and sinuses (infection); respiratory system (infection, reactive airway disease); and urogenital system (infection, bladder anomalies, 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 size, and scars from prior surgeries.

Donor Identification: HLA Typing and Donor Search Process

Principles of the donor search

Physicians should pursue an extended family and/or

unrelated donor search well before the development of severe marrow failure, transfusion dependence, MDS or AML, so that delays are minimized when HSCT is required. According to the National Marrow Donor Program (NMDP), the average time from search initiation to HSCT is approximately 3-4 months¹²; therefore, a search should be initiated well 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 peripheral blood stem cell collection date. After that time, the NMDP will request more specific information as to 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 on other patient searches so, although uncommon, it is possible that a patient with urgent need could request that donor, in which case the NMDP will work to seek an equitable solution. Note: A donor may not be reserved for years in the hope that the “perfect” donor will be available in the future. Also, it is not generally possible to collect marrow and store it for the future.

A search should be performed with urgency if the patient has advanced bone marrow failure, necessitating scheduled 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, urgency and lack of allele level HLA-matched

adult volunteer donors have resulted in a growing utilization of cord blood units for FA.

For alternate donors (any donor 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 performed elsewhere originally. HLA-typing results are typically available within 7-10 business days.

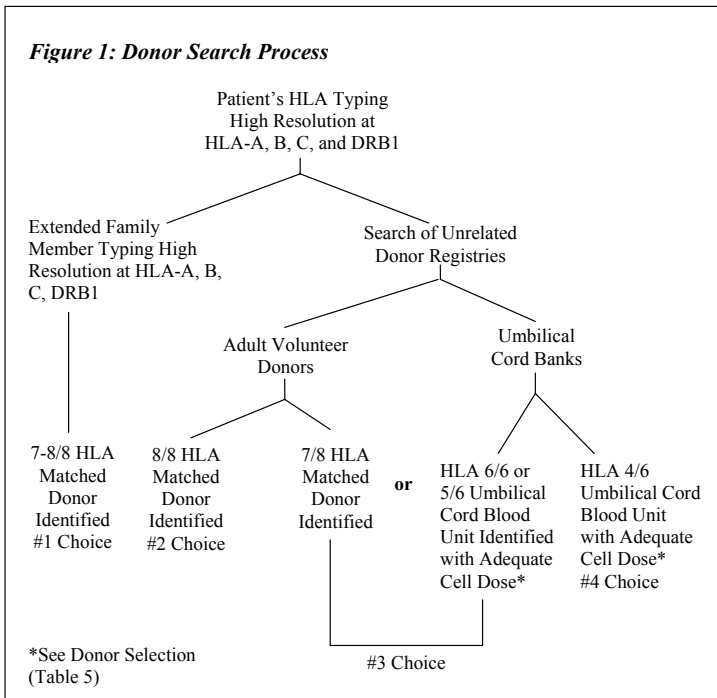
A search of the marrow and cord blood registries requires submission of the patient's HLA type and, in the case of umbilical cord blood (UCB), the patient's weight. A preliminary search can be performed by any physician at no cost. A formal search and the pursuit of a potential donor, however, must be performed by a transplant center with the consent of the patient (age ≥ 18 years) or parent/legal guardian (for patients < 18 years). A formal search will result in charges, 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.

Note: Even if a formal search has been initiated by a transplant center, the patient is not obligated to have a transplant at that center or have a transplant at all. Transfer of the search only requires notification of the National Marrow Donor Program or other coordinating center (varies on country) and a newly signed consent from the patient or family.

The search process is summarized in Figure 1.

Donor selection

For non-FA patients, we recommend that an antigen HLA-mismatched related donor be chosen over a



HLA-matched unrelated donor. Based on the general experience with non-FA patients, donor priority accepted by major FA transplant centers is shown in Table 5.

In some circumstances, greater degrees of HLA disparity might be considered acceptable. In the context of a transplant center phase I–II trial, related marrow donors mismatched at 2 or 3 antigens and unrelated umbilical cord blood donors mismatched at 3 antigens might also be used as a source of hematopoietic stem cells for transplantation.

Because of proven effect on transplant outcome, other factors are considered in the selection of an alternate donor, such as age of donor, CMV serostatus, female parity (i.e., number of pregnancies), and sex match

Table 5: Donor Selection: Prioritization of HSC Alternate Donors

Marrow or Peripheral Blood Stem Cells

- Relative (other than sibling) matched at 8 of 8 HLA-A, B, C and DRB1 alleles
- Relative (including sibling) matched at 7 of 8 HLA-A, B, C and DRB1 alleles
- Unrelated adult volunteer donor matched at 8 of 8 HLA-A, B, C and DRB1 alleles
- Unrelated umbilical cord blood unit matched at 6 of 6 HLA-A and B (antigen level) and DRB1 (allele level), cell dose $\geq 2.5 \times 10^7$ nucleated cells/kg recipient body weight

Umbilical Cord Blood or Unrelated Adult Volunteer

- Unrelated umbilical cord blood unit matched at 5 of 6 HLA-A and B (antigen level) and DRB1 (allele level), cell dose $\geq 3.0 \times 10^7$ nucleated cells/kg recipient body weight or unrelated adult volunteer donor matched at 7 of 8 HLA-A, B, C and DRB1 alleles

Unrelated Cord Blood or Haploidentical Relative

- Unrelated umbilical cord blood unit matched at 4 of 6 HLA-A and B (antigen level) and DRB1 (allele level), cell dose $\geq 4.0 \times 10^7$ nucleated cells/kg recipient body weight or 4-6/8 haploidentical donor or co-infusion of two partially HLA-matched cord blood units

between the donor and patient. Effect of donor age on transplant outcome is under investigation, with new data suggesting lack of effect. Factors included in choice of the cord blood unit may include cord blood bank track record and ability to confirm unit identity.

No data exist to indicate whether one stem cell source (8/8 marrow versus 8/8 peripheral blood versus 6/6 or 5/6 umbilical cord blood) is better or worse than another. Data in other patient populations (e.g.,

leukemia) suggest that when compared to bone marrow, there is greater risk of graft failure and slower recovery with cord blood and greater risk of chronic GvHD with unmodified peripheral blood. Recent data suggest that 6/6 or 5/6 HLA-matched cord blood results are similar to those with 8/8 HLA-matched marrow. Currently, the vast majority of FA patients have received marrow. There is relatively less experience using cord blood and peripheral blood to draw conclusions about the best stem cell source.

While UCB clearly extends the availability of HSCT to those lacking an 8/8 HLA-matched adult volunteer donor, it is not yet known whether a 6/6 matched cord blood is superior. Data thus far suggest a better outcome with 6/6 matched cord blood but larger patient numbers are required before a recommendation can be made.

Exclusion criteria

Alternate donor HSCT is not the appropriate treatment for all patients. While exclusion criteria may differ among transplant centers, usually patients will be considered ineligible for transplant if the transplant evaluation indicates that the patient has:

- Active uncontrolled infection
- HIV seropositivity
- Active extramedullary leukemia
- History of epithelial malignant solid tumors within two years of HSCT
- Severe end-organ dysfunction (variable)
- Karnofsky performance status <70% or Lansky status <50%.
- Pregnancy

Table 6: Laboratory Evaluations to Determine Eligibility for Alternate Donor HSCT

Diagnosis

- Confirmatory diepoxybutane (DEB) or mitomycin C (MMC) chromosome fragility test (if mosaic, test skin fibroblasts)

Complementation Group and Genotype

- Determination of complementation group and genotype (desirable but not required)

Hematologic

- Complete blood count and differential
- Bone marrow aspiration and biopsy with cytogenetic evaluation

Hepatic

- Liver enzymes, total bilirubin
- Ultrasound (to determine presence of adenomata, liver size)
- Abdominal CT (as indicated)

Renal / Bladder

- Serum electrolytes and creatinine
- 24-hour creatinine clearance or glomerular filtration rate (GFR)
- Ultrasound (to determine presence of renal dysplasia, hydronephrosis, abnormal bladder)

Cardiac

- Electrocardiogram (EKG)
- Echocardiogram with left ventricular ejection fraction (heart function)

Infectious Disease

- Chest radiograph
- Chest CT with high resolution inspiratory/expiratory films to rule out occult infection is performed at some centers.
- Sinus CT to rule out infection
- Panorex to rule out major dental problems

Cancer Evaluation (patients with biallelic *BRCA2* mutations)

- Abdominal CT (to rule out kidney cancer)
- MRI of the head (to rule out brain cancer)

Transplant Therapy

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 upon the hematopoietic stem cell source (marrow versus peripheral blood versus cord blood), degree of donor and patient HLA mismatch, age of patient, presence of specific end-organ dysfunction, the stage of the disease (aplastic anemia versus MDS versus acute leukemia), institutional preferences, and other personal factors (school, employment, etc).

Preparative therapy

The pre-transplant (or preparative) therapy most often used in 2008 in the United States consists of fludarabine (FLU), cyclophosphamide (CY), and total body irradiation (TBI). The purpose of the preparative therapy is to destroy the diseased marrow and to suppress the patient's immune system so that the hematopoietic stem cells from the donor have less chance of being rejected. Pre-transplant therapy in FA patients is significantly reduced compared to transplant patients without FA, due to the unique hypersensitivity to alkylating agents and irradiation of FA patients. While lower dose therapy in FA recipients of sibling donor HSCT has been successful, such therapy is not sufficient in recipients of alternate donor HSCT due to high risk of graft rejection. The side effects of FLU, CY, and TBI are outlined in Table 7.

Graft-versus-host disease (GvHD) prophylaxis

GvHD results when the immune system of the donor recognizes the patient as "foreign" and tries to reject the foreign tissues. GvHD occurs after HSCT because the donor immune system is transplanted along with the hematopoietic stem cells responsible for marrow

Table 7: Preparative Therapy Side Effects

Total Body Irradiation

- Sterility
- Fluid retention
- Temporary painful swelling of the parotid gland (located in the jaw area), as in mumps
- Lung scarring
- Hair loss
- Sores in the mouth
- Nausea, vomiting, and diarrhea
- Fever
- Dry skin and darkening of the skin
- Cataracts
- Hormone deficiencies (such as low thyroid hormone levels)
- Cancer

Cyclophosphamide

- Hemorrhagic cystitis (bleeding from the urinary bladder), which sometimes can be prevented by intravenous fluid and with the drug Mesna.
- Heart muscle injury
- Nausea, vomiting, and diarrhea
- Fluid retention
- Sores in the mouth
- Hair loss
- Skin rash
- Sterility

Fludarabine

- Infection
- Nausea, vomiting, and diarrhea
- Confusion, coma, rapidly progressive brain injury
- Kidney insufficiency and failure
- Mouth Sores

recovery and reconstitution of the blood cells. While GvHD can occur in all patients undergoing an

allogeneic HSCT, it is particularly common and severe after alternate donor HSCT because of the greater degree of HLA disparity. The signs and symptoms of acute and chronic GvHD are described in Table 8.

Table 8: Manifestations of GvHD

Acute GvHD

- Skin (maculopapular rash to generalized erythroderma to desquamation and bullae)
- Liver (hyperbilirubinemia)
- Gastrointestinal system (secretory diarrhea, abdominal pain, ileus, hemorrhage, nausea/vomiting)
- Pancytopenia
- Ocular (photophobia, hemorrhagic conjunctivitis, pseudomembrane formation, and lagophthalmos)
- Fever

Chronic GvHD

- Skin (lichen planus, scleroderma, maculopapular rash, hyperkeratosis, hair and nail loss)
- Liver (cholestasis, absent bile duct syndrome, cirrhosis, portal hypertension, hepatic failure)
- Gastrointestinal system (dysphagia, failure to thrive, aperistalsis, malabsorption syndrome)
- Obliterative bronchiolitis (restrictive/obstructive airway disease)
- Sicca Syndrome (keratoconjunctivitis sicca with burning, photophobia, irritation, pain; oral dryness, pain, lichenoid lesions, gingival atrophy, dental caries)
- Vaginitis, vaginal dryness/strictures
- Pancytopenia; eosinophilia
- Serositis (pleural, pericardial, joint effusions)
- Myofasciitis

Just as novel pre-transplant therapies are being evaluated in FA patients undergoing alternate donor HSCT, so are novel GvHD prophylactic regimens. Today, it is clear that T-cell depletion reduces the risk of acute

and chronic GvHD after alternate donor HSCT, and it appears to have improved disease-free survival in patients with FA.

Regardless of the source of hematopoietic cells, most patients receive cyclosporine A or tacrolimus for 6–12 months after HSCT to reduce the risk of GvHD. The side effects of GvHD prevention strategies are shown in Table 9.

Table 9: GvHD Prevention Therapy Side Effects

T-Cell Depletion

- Graft failure
- Slow immune recovery and infection

Cyclosporine A/Tacrolimus

- Poor kidney function or failure (dialysis)
- Blood chemistry imbalances (low potassium and magnesium)
- Swelling of gums
- Excess body hair growth
- High blood pressure
- Bleeding problems
- Neurological side effects (seizures, coma, confusion, tingling/burning sensations, involuntary shaking of extremities)
- Infection

Methylprednisolone

- Infection
- Mood swings
- High blood sugar (requiring insulin)
- High blood pressure
- Avascular necrosis of long bones (damage to hip, knees, and shoulder bones most commonly)

Regardless of the prophylactic approach used, GvHD can still occur. The more severe the GvHD (e.g., grade 3-4 disease), the higher the risk of death, mostly due to opportunistic infection. If GvHD occurs, the mainstay

of treatment is methylprednisolone. Other agents successfully used in the management of acute and chronic GvHD include antithymocyte globulin (ATG), mycophenolate mofetil (MMF), thalidomide, and psoralens with ultraviolet light (PUVA). PUVA is **not** recommended, however, as it may be particularly toxic in FA patients.

Infectious Disease Prophylaxis

Infectious complications after alternate donor HSCT are a major problem for FA as well as non-FA patients, but may be a greater risk in FA patients due to: 1) the unique sensitivity of FA patients to chemoradiotherapy; 2) the resultant breakdown of mucosal barriers after treatment; 3) the extensive period of neutropenia; and 4) considerable transfusion exposure prior to HSCT and the resultant exposure to infectious agents.

For these reasons, strategies are needed to prevent infection in the early period after alternate donor HSCT and to hasten immune recovery. Prophylactic antibiotic regimens commonly used after HSCT are outlined in Table 10.

Table 10: Common Infection Prevention Strategies

Yeast/Fungal Infections

- Fluconazole (systemic yeast)
- Nystatin (oral yeast)
- Voriconazole (yeast and filamentous fungus)
- Amphotericin-based agents (yeast and filamentous fungus)

Viral Infections

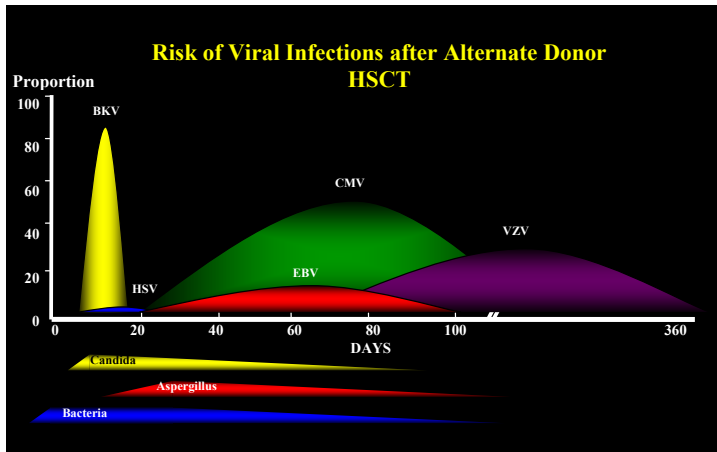
- Acyclovir (herpes simplex)
- Ganciclovir (cytomegalovirus)

Protozoal Infections

- Bactrim/Septa (pneumocystis)

The length of infection prophylaxis therapy depends upon the degree of immunosuppression, absolute CD4 T-cell level, development of acute or chronic GvHD, and development of infectious complications. In Figure 2, the timing of common viral, bacterial and fungal infections (if they occur) are shown:

Figure 2: Risk of Viral Infections after Alternate Donor HSCT



BKV: BK virus EBV: Epstein-Barr virus VZV: Varicella zoster virus
 HSV: Herpes simplex virus CMV: Cytomegalovirus

Late Effects

All recipients of chemoradiotherapy and allogeneic HSCT are subject to late effects that are not necessarily peculiar to patients with FA. These include late graft failure, recurrent acute and chronic GvHD, and the effects of prolonged steroid therapy, such as hypertension, hyperglycemia, and aseptic necrosis of bone. Other late effects such as short stature and sterility have not been formally evaluated 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

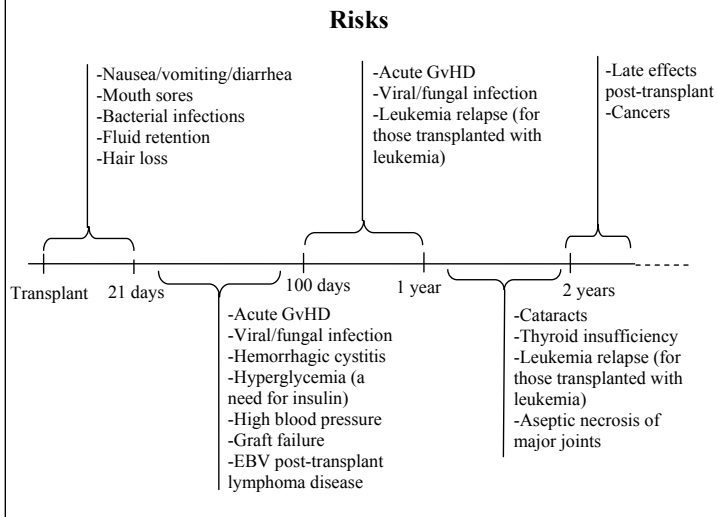
late effects, such as malignancy, sterility or endocrinopathies, to improve quality of life.

FA patients have an extremely high incidence of squamous cell carcinoma (SCC).¹³⁻¹⁷ Some studies support a conclusion that the SCC risk may be higher after HSCT (sibling or unrelated donor), although the factors responsible for this (if verified) are unclear. Studies suggest that development of chronic GvHD or its therapy (e.g., azathioprine) may be the relevant risk factor. Because of this association between cancer and GvHD, use of T-cell depletion (the best approach for reducing GvHD risk) has been incorporated into most protocols. Furthermore, as irradiation is a known risk factor for cancer in general, strategies to eliminate or reduce the dose of radiation are being explored. Although there is no proven method of cancer prevention in FA, recognition of the problem and close monitoring of the head and neck region in particular (such as with frequent dental and ENT evaluations) are important strategies toward reducing the morbidity and mortality associated with this late effect. Linkage of head and neck cancer to the HPV virus has led to a general recommendation that both males and females with FA receive the HPV vaccine (Gardasil). The timing of infections after alternate donor HSCT is summarized in Figure 3.

Other Issues

Collection of autologous stem cells

Although not uniformly performed, the collection of autologous hematopoietic stem cells prior to transplant has been recommended for patients at high risk of graft failure after unrelated donor HSCT. In many instances, patients with FA have very poor marrow cellularity, preventing this option. However, earlier consultation with patients (when their marrow has greater cellularity)

Figure 3: Timing of Infections after Alternate Donor HSCT

regarding the future need for transplantation has led to renewed consideration of this option. It is unknown whether the infusion of autologous hematopoietic stem cells collected at an earlier time would benefit patients as a method of rescue after graft rejection or as a source of hematopoietic stem cells for future gene therapy or multipotent adult stem cells for treatment of organs other than the bone marrow. The transplant team should consider the need for collecting autologous hematopoietic cells.

Exposure to infection post-HSCT

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 the immunologic complications (i.e., graft rejection, GvHD, and opportunistic infection) associated with alternate donor 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 intercurrent problems prevent this. After discharge, patients are expected to avoid crowded enclosed spaces and to wear masks in an attempt to reduce exposure to viral, bacterial, and fungal pathogens.

Alternatives to Unrelated Donor HSCT

Recent cloning of the FA genes has provided new insights into the molecular basis of FA and has made new opportunities available for better care of FA patients. For example, knowledge of the complementation group or mutation not only allows the physician to predict the course of the disease in some cases,¹ it permits the potential use of gene therapy and preimplantation genetic diagnosis (PGD). While gene correction of stem cells is not yet a clinical reality, PGD in combination with *in vitro* fertilization allows couples at high risk of having children with FA to have additional children free of the disease. In addition, PGD can be used to select those embryos that are HLA-matched with the child affected with the disease.¹⁸⁻²⁰ While there are ethical issues regarding the use of PGD and embryo selection, it is nonetheless a strategy that is being considered by many couples.

Remaining Challenges

Substantial improvement has been made in the survival of FA patients undergoing alternate donor HSCT, but challenges and questions remain. These include: 1) the optimal timing of alternate donor HSCT; 2) the impact

of androgens on survival after HSCT; 3) the selection of stem cell source (marrow versus peripheral blood versus umbilical cord blood); 4) the optimal pre-transplant and GvHD therapies; 5) the effect of the mosaic phenotype on the natural history of the disease; and 6) the role of radiation and chronic GvHD on the risk of malignancy later in life.

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