

Chapter 9

Matched Sibling Donor Hematopoietic Stem Cell Transplantation

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Matched sibling donor (MSD) transplantation for Fanconi anemia is currently the best therapy available to cure the FA patient of marrow aplasia, to prevent progression to myelodysplasia or leukemia or cure the myelodysplasia or leukemia if they are already present.

Overview

In the early 1980s, the use of high-dose cyclophosphamide and radiation in preparative stem cell transplant regimens for FA patients from matched sibling donors often resulted in excessive organ toxicity and death in the early post-transplant period. Eliane Gluckman, MD, Hôpital St. Louis in Paris, showed that the extreme hypersensitivity of FA patients to high dose alkylator therapy or irradiation was an inherent aspect of the disease.¹ The use of low doses of cyclophosphamide (20-40 mg/kg) combined with 400-600 cGy of thoraco-abdominal or total body irradiation resulted in reduced toxicity, substantially improved the outcome for the FA patients transplanted from HLA-matched donors, and became the standard of care cytoreductive regimen for FA patients transplanted from matched sibling donors.

In the 20 years since, and through collaborations sponsored by the Fanconi Anemia Research Fund and the IBMTR/ABMTR,² physicians from a number of hospitals with expertise in FA transplants have been working

on developing protocols to reduce the toxic effects of standard chemotherapy and radiation preparative regimens, while enhancing engraftment and reducing graft-versus-host disease (GvHD). The collaborations are critical because of the small numbers of FA patients undergoing transplantation.

Results of Transplants from Matched Sibling Donors

Research into the most effective protocol for MSD transplants for FA patients is ongoing. Several centers around the world, including Hôpital St. Louis (France); IRCCS Gaslini and IRCCS Policlinico, San Pavia (Italy); University of Paraná (Brazil); Hadassah Hospital (Israel); Charité Hospital (Germany); Tokai University (Japan); and, in the U.S., the University of Minnesota; Cincinnati Children's Hospital Medical Center; Hackensack University; and Memorial Sloan-Kettering have been active in transplantation of patients with Fanconi anemia. Early results of transplants of FA patients from matched sibling donors are encouraging (Tables 1 and 2).

Outcomes for several large series of patients with FA who have received transplants from matched sibling donors have been published, comprising a total of approximately 250 patients. Results of earlier studies were associated with a disease-free survival rate of 64%. Recently, data from several centers reflect very encouraging outcomes of 81-93%. These results are similar to those obtained in non-FA patients with non-malignant hematologic disorders, such as idiopathic severe aplastic anemia or the hemoglobinopathies (thalassemia and sickle cell disease), for which hematopoietic stem cell transplants represent the standard of care therapeutic approach when HLA-matched sibling donors are identified.

Table 1: HSCT for Fanconi Anemia from Matched Related Donors – TBI-based Cytoreductive Regimens

Author(s); Year	Socie, Gluckman; France 2007	Ayas; Saudi Arabia 2001	Dufour; Italy 2001	Harris; Cincinnati 2007
N	50	19	27	35
Age	11 (4-26)	9 (3-15)	6 (2.4-13)	7.6 (3-23)
Diagnosis	AA 43 MDS 7	AA	AA 25 MDS 2	AA 30 MDS/ AML 5
Cytoreduction	CY 20-40 TAI 500 hATG 120	CY 20 TAI 400 hATG 160	22 pts w/ TBI/TAI 500 CY 20; 5 pts w/ CY 120	CY 20 TAI 400 hATG 120
GvHD Prophylaxis	CSA	CSA 13; CSA/MTX 6; hATG 120 19	CSA/MT X (26); MTX (1)	CSA/ Steroid ATG 120
Graft	BM 46 Cord 4	BM	BM 26 Cord 1	BM 32 Cord 3
Graft Failure	4/49	2/19 (late)	8%	2/35
Mortality	18: 1 Rejection; 7 GvHD; 4 Secondary malignancy; 6 Other	5: 1 Sepsis; 1 Bleeding; 2 CMV; 1 AML	18.5% (Overall and Treatment -related mortality (TRM))	11% 2 TRM; 1 Leukemia; 1 Secondary malignancy
Disease-Free Survival	64% 32/50	74% 14/19	81.5%	89% 29/35

Cytoreductive regimens used in these published studies have mainly included:

- Total lymphoid irradiation, Cyclophosphamide (CY) and ATG (France, Italy and Cincinnati);
- Fludarabine (Flu), Cyclophosphamide, and ATG (Israel, Japan, Italy and Minnesota);
- Cyclophosphamide alone (Brazil).

Author(s); Year	Bonfim, Pasquini; Brazil 2007	Bitan, Slavin; Israel 2007	Yabe, M, Yabe, H; Japan 2008	Ebell; Germany; Personal Communication	Gillio; New Jersey; Personal Communication	Wagner, MacMillan; Minnesota 2006
N	43	5	5	2	3	11
Age	9 (5-29)	12 (9-31)	8 (6-17)	?	?	9.5 (4-22)
Diagnosis	AA	AA 3 AML 2	AA	AA	AA	AA 10 MDS 1
Cyto-reduction	CY 60	CY 10 Flu 180 fATG 40	CY 40 Flu 150 rATG 5	Bu 2 Flu 180 fATG 60	CY Flu ATG	CY 20 Flu 175 ATG 150
GvHD Prophylaxis	CSA/ MTX	ATG/ Campath CSA	CSA or CSA/ MTX	OKT3 CSA	CSA/ Steroid ATG	CSA/ Steroid
Graft	BM	BM 3 Cord 1 PBSC 1	BM	BM PBSC	BM	BM 8 Cord 3
T-cell Depletion	None	None	None	None	None	Yes: 8 of 11
Graft Failure	5/43	0	0	0	0	1/11
GvHD Acute >Grade 2 Chronic	Acute 17%; Chronic 28%	Acute 1; Chronic 1	None	?	None	Chronic 1
Mortality	6% 2 Rejection; 1 TRM	0%	0%	1/2	0%	2 of 11: 1 Leukemia; 1 GvHD
Disease-Free Survival	40/43	5/5	5/5	1/2	3/3	9/11

The combination of these cytoablative regimens, followed by unmodified marrow grafts used by most centers, was associated with a risk of primary or secondary graft failure of 5-10%. Graft-versus-host disease prophylaxis included mostly cyclosporine (CSA), either alone or with steroids. A few centers used other agents, including methotrexate (MTX), ATG, OKT3 or Campath. With such regimens in the largest series, the risk of acute GvHD varied from as low as 8% (using CSA/MTX) to as high as 55% (using CSA alone).

One center, the University of Minnesota, used the CY/Flu/ATG cytoreductive approach followed by T-cell depleted marrow grafts, resulting in minimal graft failure or GvHD.

Physicians who transplant FA patients continue to test research protocols to find more effective transplantation methods. The reader is urged to contact the FA specialists listed in the Appendix for their most current protocols.

The consensus of the physicians who participated in the development of these guidelines is as follows: if the local transplant center has performed fewer than five transplants for FA, strong consideration should be given for referral to a transplant center with greater experience in transplants for FA. FA patients often experience complications which are not routine in other transplants, such as a marked increased risk in organ toxicity (mucositis, GI toxicity, hemorrhagic cystitis), infections, graft failure, GvHD and the development of glucose intolerance requiring insulin therapy.

Proceeding to Transplant

Definitive diagnosis

An FA patient being considered for a matched sibling donor BMT must first have a definitive diagnosis of FA (see Chapter 2).

Patients with a proven diagnosis of FA who have a matched sibling donor are all potential candidates for transplant. The indication and timing of the transplant are sometimes controversial and depend on several factors including (1) the patient's hematologic status; (2) the patient's age and overall clinical condition; (3) the transplant center and experience, as well as the

transplant physician's recommendation; and (4) the parental or adult patient's decision.

The decision-making process in the timing of transplantation is difficult and must include multiple factors:

- The vast majority of patients will progress to aplastic anemia and/or MDS/AML without transplant.
- Transplants for FA using matched sibling donors have a very good chance of success, at 85-90% in FA-specialized transplant centers;
- However, transplants are associated with a risk of peritransplant mortality of 10-15% and a risk of chronic GvHD for a "minimum" of 12% (with unmodified transplants);
- In general, results of transplants are better for patients with aplastic anemia than with MDS/AML;
- Results of transplants are generally better for patients who are younger, partly due to a lower risk of GvHD; and
- The patient's overall vital organ status, such as renal or hepatic function, influences the transplant outcome.

In addition to these factors, the following are relative and absolute indications for transplantation of FA patients from matched sibling donors based on patients' hematologic status and age:

Absolute indications

- Severe aplastic anemia and transfusion dependence. In this case, no trial of androgens prior to proceeding to BMT.

- High-risk myelodysplastic syndrome; i.e., refractory anemia with high-risk chromosomal abnormalities (involving chromosomes 3 or 7) or marrow blast count >5%.
- Acute myelogenous leukemia.

Relative indications

- Moderate isolated cytopenias or moderate aplastic anemia with evidence of progression towards transfusion dependence.
- Low-risk myelodysplastic syndrome; i.e., refractory anemia with no chromosomal abnormalities or low-risk chromosomal abnormalities.

Definitions of the Transplant Indications

Significant cytopenia

Platelet count <50,000, or hemoglobin <8 gm/dl, or transfusion dependence, or an ANC <1000 represent significant cytopenias. Any single cytopenia is reason enough to proceed to transplant in a patient with FA who has a matched sibling donor available. A patient with an ANC >1000 who has frequent severe infections is also eligible for early transplant.

Age over ten years

Univariate statistical data show that the outcome of transplant in general and for FA in particular is worse for those patients over age ten. However, the more important factors are probably the degree of cytopenia, the intercurrent development of serious infections, the number of prior transfusions, the prior use of androgens, and the presence of clones or dysplasia, all of which increase with age and are probably responsible for much of this increased risk. Thus, age over ten is not an absolute indication for immediate MSD BMT, but

should be considered in the final equation. If the patient has acceptable counts and is generally healthy on no medications, including androgens, transplant can probably be safely delayed.

Evidence of a clone, MDS or leukemia

Patients with FA may develop cytogenetic clones. These clones may disappear or be replaced by some other clone on a subsequent bone marrow test done just a few months later. The danger signs which should lead to transplantation include a clone which is steadily increasing in percentage, or a clone involving chromosome 7 or showing a gain in the 3q26q29 segment. Data suggest that such patients have a higher risk of progression to MDS or AML.

Myelodysplasia is a hard call in aplastic-appearing marrows of FA patients. Mild dysplasia is often seen, but significant multilineage dysplasia should prompt consideration for transplant. It is advisable to have bone marrow smears reviewed by physicians at a center with extensive experience in FA patients. Patients with FA who have developed advanced MDS or leukemia clearly need immediate referral for transplant. The goal is to proceed to transplant before definite advanced MDS or leukemia develops.

Occasionally, patients do progress quickly into advanced MDS or leukemia, making it necessary to transplant them at once. This is a very difficult situation which is best left in the hands of a center with extensive experience in FA. Some centers use an induction protocol prior to transplant, with a regimen specifically modified for FA patients. Patients are first administered a mild course of chemotherapy to get them into remission. Two to three weeks later, patients begin preparative therapy for a bone marrow transplant. Other centers

proceed directly to transplant using a total body irradiation or busulfan based regimen.

Organ Function Parameters

Patients should have adequate renal function (GFR >50 ml/min/1.73 m²), cardiac function (shortening fraction $>27\%$), and liver function (bilirubin <2 mg/dl, SGOT/ SGPT <5 x normal). If pulmonary function testing can be performed, those patients with a DLCO $<50\%$ normal or an FEV1 $<60\%$ of normal may be at increased risk of pulmonary failure post-transplant. These guidelines assume that the patient will be treated with a low-intensity preparative regimen.

Transplants in patients with relatively poor organ function can be successful, but should be performed in a specialized center with extensive experience in FA transplants.

Androgen and Cytokine Therapy Prior to Transplant

FA patients are sometimes treated with androgens (see Chapter 3). This treatment is known to affect liver function adversely and is associated with other significant side effects. Experts generally recommend that an FA patient not receive androgens if the patient has a matched sibling donor available.

Before starting androgen therapy in an FA patient, the physician should first obtain family HLA typing to see if a matched sibling donor is available. Subsequently, the physician should speak to a transplant center experienced in FA transplants about the current recommendations relative to androgens and their later adverse effects on transplant outcomes.

Use of cytokines such as G-CSF is discussed elsewhere in this publication (see Chapter 3). There is no evidence that prior use of cytokines increases the risk of a later transplant. Thus, the use of cytokines, especially G-CSF for a low ANC, provided the marrow has been tested and shows no evidence of a clone or dysplasia, is acceptable. However, if the patient does not respond to the cytokine, the patient should proceed to transplant. Currently there is no generally available platelet-stimulating cytokine available with acceptable toxicity levels for children with FA.

The Transplant

Definition of matched sibling donor

Only those FA patients with a full genotypic sibling match are, in general, eligible for the low-dose regimens utilized for matched sibling BMT. Thus, patients with relatives who are full 6/6, 8/8 or 10/10 matches, but not genotypic matches, should not be treated on a matched sibling protocol, but should rather be treated on a regimen suited for an unrelated donor. This recommendation is based on the higher risk of GvHD and graft rejection in these phenotypically matched but not genotypically matched donor-recipient pairs.

To ensure that the donor does not have FA, DEB or MMC testing of the donor's peripheral blood lymphocytes must be performed. Some physicians recommend that the donors undergo mutation testing or have DEB or MMC testing done on skin fibroblasts to be certain that the donor does not have FA. Such FA-undiagnosed donors may have negative DEB or MMC testing due to high levels of mosaicism in peripheral blood lymphocytes, meaning that a large percentage of peripheral blood lymphocytes may have undergone reversion by

reciprocal recombination and may not show alkylator sensitivity above normal. Most of these undiagnosed patients will still have an elevated MCV on the CBC, the earliest sign of marrow dysfunction in FA. Thus, many physicians consider that a donor who is clearly DEB or MMC normal and has a normal MCV on the CBC is an acceptable donor for a sibling matched by HLA typing. If a potential donor is shown to be an FA carrier by mutation analysis, (i.e., has one abnormal copy of the FA gene and one normal copy), that person is acceptable as a donor for a MSD transplant. There is currently no evidence that a carrier has any increased risk of marrow failure, leukemia or other cancers, although studies at the NIH and The Rockefeller University are investigating this question.

Pre-transplant Evaluation

Patient

The pre-transplant evaluation should confirm the HLA typing by high-resolution Class I and Class II testing in both the donor and recipient at the lab utilized by the center to perform the transplant.

The patient should undergo a pre-transplant bone marrow evaluation including an aspirate and biopsy, cytogenetics, FISH for 7 and for 3q27 (or by comparative genomic hybridization [CGH] to rule out a 3q26q29 gain), and an evaluation to rule out MDS or leukemia, including flow cytometry if necessary.

Blood studies should include a CBC and differential, and a comprehensive metabolic panel. A ferritin level should be obtained and, if elevated (especially if >2000), consideration should be given to a quantitative evaluation for hemosiderosis (MRI liver or liver biopsy). Patients with elevated ferritin levels should

possibly be treated with iron chelation therapy for a period of time to reduce the iron deposition in the liver prior to transplant.

Patients should be closely evaluated to look for evidence of active infection. Standard testing would include serology for CMV, EBV, HSV, VZV and the hepatitis viruses. Most centers perform PCR testing on blood for CMV or EBV if the serologies are positive. Some centers perform CT scanning of the head, sinuses, chest, abdomen, and pelvis to look for occult fungal infections, since aspergillosis is one of the more common causes of death in FA BMT recipients.

Donor

Prior to proceeding to transplant, all matched sibling donors should be evaluated for FA. This should include a medical history, physical examination including height percentiles, skin examination, and detailed examination of the extremities. Blood work should include a CBC for evaluation of counts and MCV. Testing for Fanconi anemia should be performed as discussed above (see Chapter 2).

Stem Cell Grafts

The usual accepted stem cell source for a sibling donor transplant is bone marrow, as most of the available data published in the medical literature have been obtained using marrow grafts.

Cord blood from a full sibling is equally effective, although the number of sibling donor cord blood transplants reported in the registries is low. The engraftment rate, the incidence of GvHD, and the overall survival are favorable in these patients.

Peripheral blood stem cells (PBSC) are generally not

used in MSD FA transplants for two reasons: first, most donors are children and apheresis of a young donor is difficult and more risky, often requiring placement of an apheresis catheter; and second, when centers do not use T-cell depletion, there appears to be a higher risk of chronic GvHD in the PBSC transplants. Depending on the donor's age and whether there will be T-cell depletion of the graft, the PBSC collection and transplant could be a valid alternative as a stem cell source. However, this undertaking should be part of a clinical trial.

Cytoreduction

Low doses of cyclophosphamide (20-40 mg/kg) combined with 400-600 cGy of thoraco-abdominal or total body irradiation were the standard of care cytoreductive regimen for FA patients transplanted from matched sibling donors, as pioneered by Dr. Eliane Gluckman. Results of transplants using this approach represent almost half of the transplanted FA patients by three of the major transplant groups published in the literature. The Paris group, the Italian AIEOP/GITMO group, and the Cincinnati group used a cytoreduction that included TAI or TBI (400 or 500 cGy) and cyclophosphamide (20 mg/kg for aplastic anemia or 40 g/kg for MDS/AML). All three groups used unmodified grafts. Overall, risks of graft rejection and acute toxicity were within acceptable range.

However, recently, a number of investigators have eliminated the use of radiation in the preparative regimen in FA patients because of a fear of the later development of secondary cancers, especially squamous cell carcinomas (SCC) of the head and neck or the genitourinary tract. FA patients are at a much higher risk of developing SCC, at a higher frequency and at an earlier age than patients without FA. Radiation may further

increase or accelerate this risk. Additionally, radiation can be associated with other late effects such as endocrine dysfunction with delayed growth, hypothyroidism, and gonadal dysfunction.

Three non-TBI regimens have been used for transplantation of FA patients from matched sibling donors. For several years, the Curitiba (Brazil) group has pioneered a cyclophosphamide-only protocol, and established a dose de-escalation trial. The most recent results (2007) report on 43 patients who received cyclophosphamide at 15 mg/kg/day x 4 to a total of 60 mg/kg followed by unmodified marrow grafts. Here as well, risks of graft rejection and acute toxicity were within acceptable range.

Several other FA transplants groups used a cyclophosphamide/fludarabine/ATG approach, followed by unmodified marrow grafts, with one alternative cytoreduction including busulfan/fludarabine/ATG. Although these represent a smaller patient series (15 pts/5 centers), there appear to be acceptable risks of graft rejection and toxicity. Finally, the Minnesota group has been pioneering the cyclophosphamide/fludarabine/ATG cytoreductive regimen BUT followed by T-cell depleted grafts with very promising results.

Recently, one transplant group from Tunisia used a low-dose busulfan/cyclophosphamide approach with ATG, and a CSA/MTX GvHD prophylaxis approach. This regimen was associated with an 18% risk of graft rejection and, therefore, should not be a recommended approach for cytoreduction of FA patients.

GvHD and Graft Rejection Prophylaxis and Treatment

FA patients who have received a BMT may be at increased risk of SCC, compared to those FA patients who have not received a BMT. One factor associated with this increased risk is the development of acute and/or chronic GvHD, especially in the younger patients. The use of radiation appears to be a secondary cause of cancer. Thus, the primary emphasis today should be on the prevention of acute and chronic GvHD.

The initial standard approach used by the Paris group included the sole use of cyclosporine (CSA) with unmodified marrow grafts. Other approaches to prevention of acute and chronic GvHD have included the use of different combinations of cyclosporine and methotrexate (MTX), cyclosporine and steroids with or without the addition of ATG in the preparative therapy, also using unmodified transplants. With such regimens, in the largest series the risk of acute GvHD was 55% (CSA alone); 36% (CSA or CSA/MTX); 23% (CSA/steroids/ATG); 17% (CSA/MTX); and 8% (CSA/MTX). Thus, more aggressive GvHD prophylaxis using the standard cyclosporine/methotrexate combination appears to be associated with a decreased/acceptable rate of acute GvHD. However, there are pros and cons for the different combinations. The addition of methotrexate may result in a slower rate of engraftment, increased risk of mucositis, and possibly liver dysfunction. It should not be used for cord blood transplants. The addition of ATG and/or steroids, on the other hand, may result in increased risks of infections.

Using these approaches, the risk of chronic GvHD varied from 12% to 70% in the different series. However,

in the case of chronic GvHD, there did not appear to be a suppression combination regimen that produced superior outcomes.

The use of T-cell depletion of the donor stem cell source has become more and more the standard approach for the transplant of FA patients from unrelated donors, and has been associated with low risks of GvHD. This approach, in general, is associated with the lowest risks of GvHD in transplants of non-FA patients. Therefore, to eliminate the risks of GvHD and the subsequent increased risk of secondary malignancies, the use of T-cell depletion in transplants of HLA-matched siblings should continue to be studied as part of a trial at a BMT center of excellence for the treatment of FA.

Post-transplant Evaluation

Transplant Complications

Early complications

Early post-transplant complications include (1) graft rejection, (2) graft-versus-host disease, (3) organ toxicity, and (4) infections. FA patients appear to be more at risk for these complications, compared to non-FA patients. The physician must follow FA patients post-transplant carefully and aggressively, including close follow-up of (1) clinical status (rashes, diarrhea, liver enzymes); (2) blood counts; (3) aggressive monitoring of infections with PCR or antigenemia testing for viruses (CMV, EBV, adenovirus) or fungi (galactomanann and b-D-Glucan), and appropriate monitoring of anti-microbial levels (voriconazole, ganciclovir, etc.).

Late complications

Physicians must provide follow-up of patients with FA by monitoring their blood counts for secondary

leukemia and screening for oral and urogenital cancers. Additionally, patients must be monitored for chronic GvHD and for other post-transplant late effects such as organ toxicity (cardiac, pulmonary, renal) or endocrinopathies (diabetes, hypothyroidism, gonadal dysfunction).

Finally, the previously transfused patient must be monitored for hemochromatosis by measures of ferritin and by T2-MRI or SQUID testing for more accurate iron quantitation. Patients with iron overload will need to be treated accordingly. The preferred approach remains the use of periodic phlebotomy for a usual period of one year.

Mixed chimerism status

The physician must follow the chimerism status of patients post-transplant. Rarely, mixed chimerism may exist with the presence of a certain percentage of host cells. Often, mixed chimerism is associated with the absence of any other issues. Rarely, it can be associated with a decrease in blood counts and need more careful attention. Regardless of blood counts, the presence of mixed chimerism could be associated with an increased risk of host-derived leukemia and MDS.

PGD and IVF

Preimplantation genetic diagnosis (PGD) coupled with *in vitro* fertilization (IVF) is an option for families who have a child with FA without a matched sibling donor. If the mother is fertile, the family may consider PGD/IVF to select a fertilized egg which is both FA-negative and an HLA match for their FA-affected child. At the time of delivery, the cord blood can be collected and utilized for the matched sibling donor transplant. More details can be found in the Genetic Counseling chapter.

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