Bone Marrow Transplantation for Inherited Bone Marrow Failure Syndromes

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KEYWORDS

- Inherited bone marrow failure syndromes
- Bone marrow transplantation • Gene mutation
- Diagnostic tests

The inherited bone marrow failure (BMF) syndromes are characterized by impaired hematopoiesis and cancer predisposition. Most inherited BMF syndromes are also associated with a range of congenital anomalies. In the past, the diagnosis of these diseases relied on the recognition of characteristic clinical features. With the advent of laboratory and genetic tests for many of these disorders, the understanding of their clinical spectrum has broadened (**Table 1**).[1] Indeed, it is becoming increasingly apparent that patients lacking characteristic physical stigmata may still harbor an inherited BMF syndrome and develop marrow failure or malignancy. Clinical presentation is no longer confined to the pediatric population but may manifest in adults as well. Sensitive and specific diagnostic tests, including identification of mutations in specific genes, are available for many disorders (**Table 2**).[2]

FANCONI ANEMIA

Fanconi anemia (FA) is a genetic disorder characterized by congenital anomalies, progressive BMF, and predisposition to malignancies. Even though this disorder is

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Table 1
Characteristics of the inherited bone marrow failure syndromes compared with idiopathic aplastic anemia

	FA	DC	SDS	DBA	CAMT	AA
Inheritance pattern	AR, XLR	XLR, AR, AD	AR	AD	AR	?
Somatic abnormalities	Yes	Yes	Yes	Yes	Yes	?
Bone marrow failure	AA (>90%)	AA (~80%)	AA (20%)	RCA[a]	Meg[b]	AA
Short telomeres	Yes	Yes	Yes	Yes	?	Yes
Cancer	Yes	Yes	Yes	Yes	Yes	Yes
Chromosome instability	Yes	Yes	Yes	?	?	Yes
Genes identified	13	4	1	3	1	[c]

Abbreviations: AA, idiopathic aplastic anemia; AD, autosomal dominant; AR, autosomal recessive; CAMT, congenital amegakaryocytic thrombocytopenia; DBA, Diamond-Blackfan anemia; DC, dyskeratosis congenita; FA, Fanconi anemia; SDS, Shwachman-Diamond syndrome; XLR, X-linked recessive.

[a] RCA: red cell aplasia, although some patients can develop global bone marrow failure.

[b] Meg: low megakaryocytes, which can progress to global bone marrow failure.

[c] Heterozygous mutations in TERC and TERT are risk factors for some cases of idiopathic AA.

Data from Dokal I, Vulliamy T. Inherited aplastic anaemias/bone marrow failure syndromes. Blood Rev 2008;22:141–53.

rare, with an incidence of 1 per 100,000 live births, FA represents the most common inherited BMF syndrome. The clinical presentation of FA is highly heterogeneous. Approximately two-thirds of patients present with physical anomalies, which may vary greatly in number and severity. Common congenital abnormalities include short stature, skin pigment abnormalities (eg, café-au-lait spots), radial ray anomalies, genitourinary abnormalities, and microphthalmia.[3–5] It is important to recognize that disease manifestations and severity vary extensively and a subset of patients may lack the characteristic physical stigmata of FA. In addition, patients may first present in adulthood with BMF or malignancy as the primary clinical manifestation of FA. Hence, the possibility of an inherited basis for BMF must be considered for adults as well.

In patients with FA, the risk of developing BMF and hematologic and nonhematologic neoplasms increases with advancing age with a 90%, 33%, and 28% cumulative incidence, respectively, by 40 years of age.[6] The most common malignancies reported include acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and squamous cell carcinoma (SCC) of the head, neck, vulva and cervix.[6,7] BMF in FA typically presents between the ages of 5 and 10 years,[6,7] and the median age of patients who develop AML is 14 years.[8]

The cellular phenotype of FA is characterized by an abnormally high level of baseline chromosomal breakage along with an increased sensitivity to DNA cross-linking or alkylating agents that block DNA replication and RNA transcription.[9] FA is a complex genetic disorder with 13 complementation groups identified to date.[10] Multiple FA gene products form a nuclear complex believed to function in the DNA damage response and repair pathway.[11–15] Inheritance is mainly autosomal recessive, but is X-linked in a small number of children with biallelic mutations in the *FANCB* gene. Some genotype-phenotype correlation is known and has been reported to affect the transplant outcome.[16,17]

Current treatment of FA involves hematological support in the form of transfusions once advanced marrow failure occurs. Patients with FA do not respond to

Table 2
Genetic and laboratory tests for inherited bone marrow failure syndromes

Syndrome	Inheritance Pattern	Gene	Additional Laboratory Testing
Fanconi anemia	Autosomal recessive	FANCA FANCC FANCD1 FANCD2 FANCE FANCF FANCG FANCI FANCJ FANCL FANCM FANCN	Chromosome breakage
	X-linked recessive	FANCB	
Dyskeratosis congenita	X-linked recessive	DKC1	Telomere length
	Autosomal dominant	TERC TERT TINF2	
	Autosomal recessive	NHP2/NOLA2 NOP10/NOLA3	
Shwachman-Diamond syndrome	Autosomal recessive	SBDS	Serum trypsinogen, pancreatic isoamylase, fecal elastase, pancreatic imaging
Congenital amegakaryocytic thrombocytopenia	Autosomal recessive	C-MPL	
Diamond-Blackfan anemia	Autosomal dominant	RPS19 RPS17 RPS24 RPL35A RPL11	Erythrocyte adenosine deaminase (ADA)

Data from Shimamura A. Clinical approach to marrow failure. In: Gewirtz AM, Keating A, Thompson AA, editors. American Society of Hematology Education Program Book. Washington, DC: American Society of Hematology; 2009. p. 329–37.

antithymocyte globulin (ATG) or cyclosporine (typical treatments for acquired aplastic anemia), but 50% improve with androgen preparations,[16] with a median prolongation of life of 2 years in responders (age from 16 to 18 years at death), although relapses are inevitable.[18] Androgen therapy causes significant liver toxicity, virilization, and risk of hepatic adenoma and carcinoma. Androgens are reported to adversely affect the outcome of subsequent hematopoietic stem cell transplantation (HSCT) in some studies,[16] but not in others.[19] Ultimately, virtually all patients with FA will require treatment with allogeneic HSCT.

Hematopoietic Stem Cell Transplant in Patients with Fanconi Anemia

The definitive treatment for BMF, AML, and MDS associated with FA is allogeneic HSCT. Commonly agreed-upon indications for HSCT in these patients include evidence of severe marrow failure as manifested by an absolute neutrophil count

(ANC) less than 1000/ml[3] with or without granulocyte colony-stimulating factor (G-CSF) support, or hemoglobin less than 8 g/dL, or a platelet count less than 50,000/ml[3], or a requirement for blood product transfusions on a regular basis. In addition, HSCT is indicated for FA patients with evidence of progression to myelodysplasia, as diagnosed by marrow dysplasia or the presence of a cytogenetic clone together with dysplasia. Finally, allogeneic transplantation is indicated for FA patients with AML.

The earliest attempts at transplanting patients with FA in the 1970s and 1980s used the same preparative regimens designed for patients with idiopathic severe aplastic anemia (ie, 50 mg/kg of cyclophosphamide $\times$ 4 days). These transplantations had high mortality and morbidity.[20] In one report, only 1 of the 5 FA patients transplanted survived for more than 3 years. Four patients died of severe acute graft-versus-host disease (GVHD) soon after grafting. In addition, all had signs of severe cyclophosphamide toxicity. This study provided the first clinical evidence of a special sensitivity of FA cells to alkylating chemotherapy agents, indicating the need to modify the conditioning regimen in FA patients. Such hypersensitivity was also observed in vitro when FA cells were incubated with alkylating agents.

Gluckman and colleagues[21] were the first to investigate a markedly attenuated conditioning regimen for FA patients. These investigators successfully demonstrated that HSCT could be safely performed using low-dose cyclophosphamide, with long-term survival in 75% of patients with an human leukocyte antigen (HLA)-matched donor. The same group also tested the in vivo radiosensitivity and cell repair after skin contact radiotherapy to calculate the irradiation dose that could be tolerated by patients with FA. The results confirmed the suspected increased radiosensitivity in the majority of patients with FA. Following these results, 4 FA patients were conditioned with low-dose cyclophosphamide (20 mg/kg) in combination with 5 Gy thoracoabdominal irradiation. All engrafted without major complications from the conditioning regimen.[22]

In their long-term follow-up of 50 patients with FA transplanted using this conditioning regimen and a matched sibling donor, Socie and colleagues[23] documented survival estimates of 74.4% at 54 months and 58.5% at 100 months. Acute GVHD (grade II or more) developed in 55% of patients, and 69.9% were diagnosed with chronic GVHD. The survival of patients without chronic GVHD (n = 13) was 100%. In addition to chronic GVHD, 20 or more pretransplant transfusions were shown to have an adverse impact on survival by multivariate analysis (relative risk = 7.08, $P = .0003$).

Results from 151 matched sibling HSCTs for FA performed between 1978 and 1994 and reported to the International Bone Marrow Transplant Registry (IBMTR) were summarized by Gluckman and colleagues[24] in 1995. The 2-year probability of survival was 66%. The incidence of graft failure was 8%; grade II to IV acute GVHD occurred in 44% of patients, and chronic GVHD in 42%. Also, GVHD prophylaxis with cyclosporine and methotrexate resulted in a decreased incidence of GVHD compared with methotrexate alone. Gluckman and colleagues also noted that the adverse impact of increasing age and lower pretransplant platelet count on transplant outcome favors earlier intervention, especially when there was an HLA-identical sibling donor.

The addition of ATG to the Gluckman regimen was the next important milestone in HSCT of patients with FA. This addition further improved outcomes by decreasing the incidence of both acute and chronic GVHD.[23,25–27] The most recent of these reports[27] showed a 10-year actuarial survival of 89%, with a significant decrease in acute (23%) and chronic (12%) GVHD in 35 patients undergoing matched sibling donor HSCT using peritransplant ATG in combination with low doses of cyclophosphamide and radiation.

Over the last 3 decades, preparative regimens for FA have been modified significantly, with the goal of limiting toxicity while maintaining engraftment and improving outcomes by decreasing GVHD. For those patients with FA who have an HLA-identical related donor, HSCT when severe marrow failure develops is now the first-line treatment of choice, preferably before transfusion dependence develops, to limit the risk of graft failure.

Due to hypersensitivity of FA cells to DNA damage, one of the important goals during HSCT is to use conditioning regimens that minimize the development of treatment-induced secondary malignancies in these patients. A report of the joint Seattle and Paris experience with secondary cancers in patients with aplastic anemia and FA suggested that the risk of secondary cancers was mostly due to radiation. A total of 23 malignancies were reported among 700 patients transplanted for aplastic anemia or FA. At 20 years post transplant, the risk by Kaplan-Meier estimate was 14% for all patients and 42% for patients with FA. A diagnosis FA was an independent risk factor for development of secondary malignancy. Other risk factors included the development of chronic GVHD and the use of radiation in the preparative regimen. Five of the 79 patients with FA developed head and neck SCC.[28] More recent analyses point to the presence of acute or chronic GVHD as a major cause of development of SCC in this patient population.[23,29] Guardiola and colleagues[30] reported a 28% incidence of head and neck cancers 10 years post HSCT in FA patients with a history of acute GVHD versus 0% in those with no such history; this finding points to the importance of minimizing the risk of GVHD.

Investigators from Brazil have returned to the original approach of cyclophosphamide alone as a conditioning regimen for matched sibling donor HSCT. These investigators have systematically reduced the cyclophosphamide dose and have shown an excellent outcome with 93% overall survival (OS), and probabilities of acute and chronic GVHD of 17% and 28.5%, respectively, using a conditioning regimen that uses only 60 mg/kg of cyclophosphamide.[31,32] Ayas and colleagues[33] similarly reported significantly greater OS in patients receiving nonradiation, low-dose cyclophosphamide and ATG regimens compared with those receiving preparative regimens with cyclophosphamide and additional thoracoabdominal radiation (96.9% vs 72.5%; $P = .013$).

In 1997, Kapelushnik and colleagues[34] from Israel published the first case report using a fludarabine-based conditioning regimen for a child with FA in leukemic transformation. This highly immunosuppressive nucleoside analogue is well tolerated by patients with FA and has allowed for the elimination of radiation, with good results.[35–39] Tan and colleagues[36] recently reported an actual OS of 82% in a cohort of 11 patients who underwent a conditioning regimen with low-dose cyclophosphamide, fludarabine, and ATG, followed by transplantation with T-cell–depleted bone marrow or umbilical cord blood stem cells. Transplant-related mortality (TRM) was 9%, and GVHD was minimal. Longer follow-up times are needed to fully evaluate whether this conditioning regimen can reduce the risk of later malignancy after matched related donor HSCT in the FA population.

A recent report by Pasquini and colleagues[40] compared outcomes after radiation and nonradiation regimens in 148 FA patients undergoing matched sibling donor transplant to identify risk factors impacting HSCT outcomes. Hematopoietic recovery, acute and chronic GVHD, and mortality were similar after radiation and nonradiation regimens. In both groups of recipients older than 10 years, prior use of androgens and cytomegalovirus (CMV) seropositivity in either the donor or recipient were associated with higher mortality. With a median follow-up greater than 5 years, the 5-year probability of OS, adjusted for factors impacting overall mortality, was 78% after

radiation and 81% after nonradiation regimens (P = .61). In view of the high risk of cancer and other radiation-related effects on growth and development, these results support the use of nonradiation conditioning regimens in this population. However, as the peak time for developing solid tumors after HSCT is 8 to 9 years, longer follow-up is required before definitive statements can be made regarding the impact of nonradiation regimens on cancer risk.

Matched Unrelated Donor Transplantation for Patients with Fanconi Anemia

The heritable nature of FA unfortunately reduces the chances of finding an unaffected HLA-matched family donor, which usually leaves matched unrelated donor (MUD) transplantation as the only alternative for most patients with FA who require HSCT. Outcomes of unrelated donor HSCT for FA using unrelated donor stem cells have been inferior to those reported with related donor stem cells. This result is primarily due to high risk of graft failure, acute GVHD, an increased risk of infections, and excessive regimen-related organ toxicity.

In 2000, the results of a retrospective multicenter study of 69 unrelated donor HSCTs for FA facilitated through the European Group for Blood and Marrow Transplantation (EBMT) and the European FA Registry were reported by Guardiola and colleagues.[16] The 3-year probability of survival was 33%. The causes of death were acute GVHD (n = 18), primary or secondary graft failure (n = 13), chronic GVHD (n = 4), infections (n = 7), and veno-occlusive disease of the liver (n = 1). In that study, the presence of 3 or more extramedullary congenital malformations, the use of androgens prior to HSCT, positive recipient CMV serology, and the use of a female donor were independent risk factors associated with poor survival. Because of the high risk of TRM from graft failure and GVHD, unrelated donor transplantation has generally not been recommended until failure of other treatment modalities, such as use of androgens and transfusions.

Graft rejection rates following unrelated donor transplantation has traditionally exceeded 20% in most reported series. This high frequency of graft failure in FA patients contrasts with a lower frequency of approximately 5% in other patient populations receiving unrelated donor HSCT,[16,21,24,41] and seems to be due to reduced doses of radiation and immunosuppressive alkylating chemotherapy agents generally used to reduce regimen-related toxicity associated with excessive sensitivity of FA cells, as discussed earlier. Reduced doses of these agents are typically used in FA patients to avoid excessive toxicity, and the consequence is a high frequency of graft failure due to inadequate peritransplant immune suppression. In an attempt to improve engraftment, MacMillan and colleagues[42] escalated the radiation dose to 600 cGy and added ATG; this decreased the incidence of acute GVHD and chronic GVHD, but did not improve OS. Thus, before the recent introduction of fludarabine in the FA-preparative regimen, OS for unrelated donor transplants was approximately 30%.[16,30]

The introduction of fludarabine-based preparative regimens has resulted in considerable improvements in outcome, with sustained engraftment without significant toxicity. Reported survival rates with fludarabine-containing preparative regimens range from 38% to 96%.[17,19,35,43–45] In a large retrospective study of 98 alternative donor transplantations for FA reported to the IBMTR, Wagner and colleagues[17] reported that fludarabine-containing regimens were associated with improved engraftment, decreased TRM (47% vs 81%), and improved 3-year OS (52% vs 13%, P<.001) compared with nonfludarabine regimens (**Fig. 1**).

In the same report, an increased risk of graft failure was confirmed in transplant recipients with mosaicism who underwent transplantation using preparative regimens

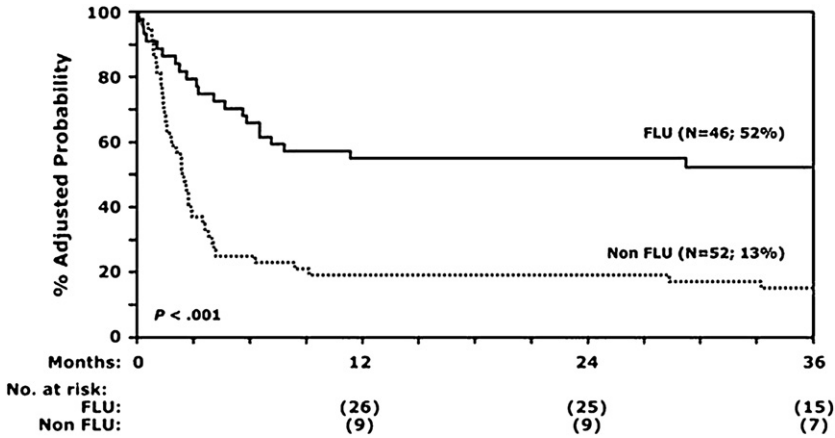

Fig. 1. Probability of overall survival with fludarabine and nonfludarabine regimens after adjusting for prior red blood cell transfusions and CMV serostatus. (*From* Wagner JE, Eapen M, MacMillan ML, et al. Unrelated donor bone marrow transplantation for the treatment of Fanconi anemia. Blood 2007;109(5):2256–62; with permission.)

without fludarabine compared with those using fludarabine-containing regimens. Further, for patients receiving nonfludarabine-containing regimens, the 100-day probability of developing grades 2 to 4 acute GVHD was 70% after the transplantation of non-T-cell–depleted bone marrow and 21% after transplantation with T-cell–depleted bone marrow. The probability of grades 2 to 4 acute GVHD was 16% in patients receiving a fludarabine-containing preparative regimen. Similarly, a reduced incidence of GVHD has been reported in other studies of FA patients using fludarabine, both in the matched related and unrelated donor HSCT settings.[32,36,44] It must be noted that in a study of Japanese patients who received non-T-cell–depleted grafts, the acute GVHD rate was even lower than that for patients who received a T-cell–depleted transplant.[43] Although the numbers of patients and ethnicities in the Japanese and Center for International Blood and Marrow Transplant Research studies are different, these data seem to suggest that, in the presence of fludarabine, T-cell depletion may not be absolutely crucial in abating acute GVHD.

Umbilical Cord Blood Transplantation for Patients with Fanconi Anemia

Umbilical cord blood (UCB) is an attractive source of hematopoietic stem cells for patients who lack an HLA-matched unrelated bone marrow donor. The low incidence of GVHD associated with unrelated UCB HSCT may be particularly advantageous for FA patients, given their increased risk of GVHD. Transplantation of acceptable cell doses can usually be accomplished with UCB HSCT because of the young age and small size of FA patients. The first reported use of UCB as a stem cell source was for a child with FA. Since this initial report, the use of cord blood as a stem cell source for transplanting patients with FA has been increasingly reported.[46,47]

Gluckman and colleagues[48] retrospectively analyzed results of UCB HSCT in 93 FA patients. In 57 patients (61%), the preparative regimen included fludarabine. GVHD prophylaxis consisted mostly of cyclosporine with prednisone. OS was 40% and the incidence of grade II to IV acute and chronic GVHD was 32% and 16%, respectively. As with unrelated bone marrow, patients who received a fludarabine-containing regimen had improved engraftment (72% vs 42%) as well as improved OS (50% vs

25%) compared with those who received other nonfludarabine-containing regimens. These outcomes are very similar to MUD transplants, suggesting that UCB HSCT is a viable stem cell option for patients with FA.

Transplantation for Patients with Fanconi Anemia and Myelodysplasia or Acute Myeloid Leukemia

Allogeneic HSCT can be curative for patients with FA presenting with progressive marrow failure, and excellent disease-free survival (DFS) rates have been documented in different reports. Data are scarce, however, on the ideal management of patients with FA who present with cytogenetic clones, MDS, or AML. FA patients with myelodysplasia or clonal abnormalities are a distinct group that may require more intensive conditioning before HSCT, as the presence of either abnormality may herald the development of AML and hence is considered a marker for an adverse outcome.[5,49] Although very early reports of intensive conditioning for these patients resulted in high TRM,[50] Socie and colleagues[23] reported 5 patients with FA and MDS on presentation who did well; they were prepared with thoracoabdominal irradiation plus cyclophosphamide 40 mg/kg, instead of the 20 mg/kg routinely used for FA patients without myelodysplasia. The study reported an 8-year survival of 75%.

Most recently, groups from Saudi Arabia and New York reported their experience with HSCT of these high-risk FA patients. Ayas and colleagues[51] transplanted a total of 11 patients, 10 patients with MDS and 1 with AML. Ten patients had matched sibling donors and 1 patient was transplanted using a one-antigen mismatched UCB unit. The conditioning regimen included CY (20 mg/kg), ATG (total dose 160 mg/kg of the equine product or 52 mg/kg of the rabbit product), and total body irradiation (TBI) at 450 cGy. Ten patients are currently alive with no evidence of disease, with a median follow-up of almost 4 years. Chaudhury and colleagues[44] similarly reported transplants in 18 high-risk FA patients, with high risk defined as progressive disease with MDS in 22% of patients, 33% with AML, 83% with multiple transfusions, 72% with prior androgen treatment, 77% with prior infections, and 4 patients older than 20 years. A mix of related and unrelated HLA-matched and mismatched donors were used. Cytoreduction included single dose TBI (450 cGy), fludarabine (150 mg/m^2), and CY (40 mg/kg). Immunosuppression included ATG and tacrolimus. Grafts were CD34-selected T-cell–depleted peripheral blood stem cells in 15 patients and T-cell–depleted marrows in 3. All 18 patients engrafted with 100% donor chimerism; only one patient developed GVHD. OS and DFS were 72.2% and 66.6%, respectively, at a median follow-up of 4.2 years, suggesting that this approach might be sufficient to control malignancy in FA.

Patients with FA who present with overt AML pose a further challenge. FA patients have excessive toxicity with chemotherapy regimens used in non-FA AML patients. Given the positive impact of pretransplant chemotherapy in AML on outcome, it is not clear how to best approach FA patients with AML prior to the initiation of the HSCT procedure. Mehta and colleagues[52] recently showed that FA patients can tolerate a reduced-intensity AML chemotherapy regimen as induction chemotherapy before initiation of the HSCT process, with clearance of AML blasts. However, HSCT still remains the only definitive therapy for these patients.

SHWACHMAN-DIAMOND SYNDROME

Shwachman-Diamond syndrome (SDS) is a rare autosomal recessive disorder characterized by exocrine pancreatic insufficiency, skeletal abnormalities in the form of metaphyseal dysostosis, and bone marrow dysfunction manifested as cytopenias.[53–58]

Additional clinical manifestations seen in some patients include short stature, variable immune dysfunction, delayed dentition, and structural and functional abnormalities of the liver.[55,59–61] Patients with SDS are at an increased risk of developing aplastic anemia, MDS, and AML.[55,59,62–66]

Although most patients with SDS have some hematologic abnormalities, most of them do not require HSCT. In the largest reported series, 20% of cases developed pancytopenia and 6% progressed to MDS.[56] Other investigators have reported varying incidences of MDS ranging from 10% to 15% to as high as 44% of cases.[55,59,63,67] The risk of leukemic transformation in SDS patients is significant and increases with age, varying from 5% in childhood to nearly 24% as patients approach adulthood.[67] Although infections and thoracic dystrophy are the leading causes of morbidity and mortality during infancy, the likelihood of long-term survival correlates most closely with the degree of bone marrow dysfunction. Survival is particularly reduced in patients who develop bone marrow aplasia, MDS, or acute leukemia, averaging 14 years in patients with aplastic anemia.[63] The development of acute leukemia portends a poor prognosis as SDS patients do not respond well to chemotherapeutic intervention.

HSCT is the only known curative treatment for bone marrow dysfunction associated with SDS. However, the timing of transplantation remains a subject of controversy, and the apparent lack of genotype-phenotype correlation makes selection of patients for early preemptive HSCT difficult at present. In addition, like FA patients, children with SDS tend to have increased toxicity with intensive conditioning regimens. Tsai and colleagues[61] reported a case of fatal congestive heart failure following a cyclophosphamide-containing conditioning regimen in a patient with SDS. Other investigators have described neurologic complications,[66] pulmonary complications, and multiorgan failure with typical ablative regimens.[68,69]

Overall, the available literature on HSCT in SDS patients is limited and consists mainly of case reports.[70–80] Vibhakar and colleagues[81] recently reviewed the published experience with HSCT in SDS patients and reported a total of 28 patients, including their own. All but 4 patients received myeloablative conditioning regimens containing cyclophosphamide with or without TBI/total lymphoid irradiation (TLI). Most patients received unrelated bone marrow as a source of stem cells, although they reported 3 cases in which UCB was used successfully as a source of stem cells. At the time of reporting, 17 of these patients were alive, although mortality approached 40%. More than 50% of the patients who died succumbed to cardiopulmonary complications in the early posttransplant phase. Similarly, in a recent review of the European experience with HSCT in 26 SDS patients, Cesaro and colleagues[68] reported an overall TRM of 35.5% at 1 year. Interestingly (and reminiscent of the experience in FA), they found a significantly higher mortality rate in patients receiving a TBI-conditioning regimen (67% for TBI vs 20% for non-TBI containing regimen, $P = .03$).

Although the number of patients is very small, the patients who have undergone transplantation for aplasia have been noted to have better outcomes than those who have undergone transplantation for MDS or leukemia.[74] Also, despite the biologic mechanism being unclear, patients with SDS seem to have a predilection for increased cardiac toxicity with cyclophosphamide-containing conditioning regimens.[61,74,79] Savilahti and Rapola[82] reported significant cardiac dysfunction in patients with SDS even without exposure to cyclophosphamide. In their series of 16 Finnish patients, 8 had cardiac abnormalities on necropsy, including cardiac fibrosis and areas of necrosis.

Clinical reports also suggest that patients with SDS are more susceptible to transplant-related toxicity than patients with other disorders like Kostmann syndrome and

juvenile myelomonocytic leukemia.[83,84] Dror and Freedman[85] demonstrated that the bone marrow mononuclear cells from patients with SDS show an increased propensity for apoptosis mediated by hyperactivation of the Fas-signaling pathway. The same investigators also reported decreased telomere length in the marrow-derived mononuclear cells from patients with SDS.[86] It is possible, although currently unexplored, that similar mechanisms are important in the increased susceptibility to organ toxicity with intensive conditioning regimens seen in patients with SDS.

Due to significant regimen-related toxicity observed during HSCT for SDS, recent efforts have focused on reduced-intensity preparative regimens that might ameliorate cardiac and pulmonary toxicities. Sauer and colleagues[87] reported 3 patients with SDS and BMF transplanted using a regimen consisting of fludarabine, treosulfan, and melphalan. All 3 patients engrafted rapidly with 100% donor chimerism. Although 2 of the patients tolerated the regimen with minimal toxicity, 1 patient died on day 98 secondary to idiopathic pneumonitis syndrome. The first 2 patients had the common 183-184 TA to CT mutation in the SBDS gene, whereas the third patient who died carried a c.297-300delAAGA deletion, leading the investigators to speculate on whether genotype is predictive of treatment-related toxicity. Attempts have been made to predict the clinical phenotype from the genetic mutation, but no correlation has been found thus far between the hematologic or skeletal manifestations and the genotype in the small numbers of patients that were studied.[88–90]

A recent report from Bhatla and colleagues[91] described the use of a reduced-intensity preparative regimen in 7 patients with SDS associated with aplasia or MDS/AML. The preparative regimen consisted of Campath-1H, fludarabine, and melphalan. Four patients received matched related marrow and 3 received unrelated donor stem cells (2 peripheral blood stem cells [PBSCs] and 1 marrow). All but one donor was 8 of 8 allele-level, HLA matched. All patients established 100% donor-derived hematopoiesis. No patient in this cohort developed grades III to IV GVHD. One patient had grade II acute skin GVHD that responded to systemic corticosteroids and one had grade I acute skin GVHD, treated with topical corticosteroids. Two out of 7 patients developed bacterial infections in the early posttransplant period. Viral infections were seen in 4 of 7 patients and were successfully treated with appropriate antiviral therapy. All 7 patients were alive at the time of the study report, with a median follow-up of 548 days (range, 93–920 days). These preliminary data indicate that HSCT with reduced-intensity conditioning is feasible in patients with SDS and is associated with excellent donor cell engraftment and modest morbidity.

DYSKERATOSIS CONGENITA

Dyskeratosis congenita (DC) is an inherited disorder that usually presents with the clinical triad of abnormal skin pigmentation, nail dystrophy, and mucosal leukoplakia.[92–95] There are also noncutaneous manifestations, including gastrointestinal disorders and pulmonary complications like progressive pulmonary fibrosis. DC is genetically heterogeneous with X-linked, autosomal dominant, and autosomal recessive subtypes recognized. Patients have very short germline telomeres, and at least one-half of patients have mutations in known telomere biology genes. Disease pathology is thought to be a consequence of chromosome instability related to telomerase deficiency due to mutations in *DKC1*, *TERC*, and *TERT*. In patients with *DKC1* mutations, defects in ribosomal RNA modification, ribosome biogenesis, translation control, or mRNA splicing may also contribute to disease pathogenesis. The involvement of telomerase complex components in X-linked and autosomal dominant forms and the

presence of short telomeres suggest that DC is primarily a disease of defective telomere maintenance.[96]

BMF is the leading cause of early mortality in these patients, with approximately 80% to 90% of patients developing hematopoietic abnormalities by age 30 years.[97,98] Patients with DC are also at increased risk for MDS/AML and solid tumors, especially SCC.[97,99,100] Transient responses to therapy with androgens, prednisone, splenectomy, and hematopoietic growth factors have all been reported.[101–104]

Allogeneic HSCT remains the only curative approach for marrow failure in patients with DC; however, outcomes have been poor due to early and late complications.[105] Langstone and colleagues[106] transplanted 8 patients with marrow failure associated with DC. Six patients received allogeneic marrow grafts from HLA-identical siblings and 2 from HLA-MUDs. Patients who received marrow from HLA-identical siblings were conditioned with CY (140–200 mg/kg), with or without ATG. Patients who received MUD were conditioned with CY (120 mg/kg) and TBI (1200 cGy). Six out of 8 patients who survived for longer than 2 weeks following transplant had hematological evidence of engraftment, and all 3 patients who survived for at least a year following transplant recovered normal hematological function. Three patients died with respiratory failure and pulmonary fibrosis at 70 days, 8 years, and 20 years post transplant. Three patients died of invasive fungal infections during the neutropenic period, one patient died of refractory acute GVHD on day 44, and one patient was alive at 463 days following transplant. The surviving patient underwent surgical resection of a rectal carcinoma diagnosed 14 months post HSCT. Other reports using myeloablative conditioning showed similar results.[105,107–113]

The presence of pulmonary disease in a significant proportion of DC patients prior to HSCT may explain the high incidence of fatal pulmonary complications in the setting of HSCT. More recent studies have used reduced-intensity regimens with encouraging results for successful engraftment with fewer complications, for both related and unrelated allografts.[114–119] However, long-term follow-up data are not available and it remains to be seen how these patients ultimately fare. Regardless of the potential reduction in toxicity associated with these regimens, preexisting conditions characteristic of DC (eg, pulmonary disease) may ultimately limit the effectiveness of HSCT in these patients.[116,120]

CONGENITAL AMEGAKARYOCYTIC THROMBOCYTOPENIA

Congenital amegakaryocytic thrombocytopenia (CAMT) is a rare autosomal recessive disorder characterized by isolated thrombocytopenia at birth due to ineffective megakaryocytopoiesis, and progression to pancytopenia in later childhood. CAMT is usually caused by defective c-mpl expression due to mutations in the thrombopoietin receptor *c-MPL*.[121] In a recent retrospective review of 20 patients with CAMT, approximately 70% patients developed marrow aplasia and one developed MDS that progressed to acute leukemia.[122] Several therapeutic modalities have been attempted in the treatment of CAMT. Steroids, cyclosporine, and cytokines and hematopoietic growth factors including interleukin-3, interleukin-11, and G-CSF have all been shown to produce only transient responses.[123,124]

HSCT remains the only known curative treatment for CAMT. However, due to the rareness of this disorder, there are only a few reports in the literature describing the role of HSCT in the management of CAMT. Lackner and colleagues[125] reported their experience in 8 patients with CAMT; 5 underwent HSCT from related donors, 2 from unrelated donors, and 1 from a haploidentical mother (T-cell–depleted peripheral stem cells). The preparative regimen was busulfan, cyclophosphamide, and ATG in

6 patients, busulfan and cyclophosphamide in 1 patient, and busulfan and cyclophosphamide with thiotepa in another patient. Both patients receiving MUD transplants died. The remaining 6 patients had normal platelet counts 3 to 27 months post HSCT. Causes of death included bronchiolitis obliterans in one patient and engraftment failure followed by aspergillosis in a second. Recently, King and colleagues[122] reported HSCT outcomes in 15 CAMT patients. Median age at the time of HSCT was 38 months (range 7–89 months). Outcome was good for those who underwent transplantation from HLA-identical family donors (n = 11); in contrast, all of the patients who received HSCT from an unrelated donor (n = 4) died of complications. Similarly, other reports have described mixed results in terms of outcomes following HSCT in CAMT.[126,127]

Steele and colleagues[128] reported on successful unrelated donor HSCT using a reduced-intensity conditioning regimen in a CAMT patient with monosomy 7. The patient underwent a matched unrelated bone marrow transplant at 7.25 years of age. The conditioning regimen consisted of fludarabine (30 mg/m^2/d) from day −10 to day −5, CY (60 mg/kg/d) on day −6 and day −5, and equine ATG (ATGAM, 40 mg/kg/d) from day −4 to day −1. The patient received an 8/8 molecularly matched non-T-cell–depleted bone marrow allograft from a male unrelated donor. GVHD prophylaxis consisted of cyclosporine and steroids. The patient had rapid and durable engraftment with minimal complications, and was alive 24 months post transplantation at the time of the report. Based on this single case report, the possibility exists that reduced-intensity conditioning might be a feasible approach to HSCT in patients with CAMT who do not have a related donor and who are at known increased risk of toxicity from standard conditioning regimens. However, longer follow-up and additional patients are required to completely evaluate the long-term risks and benefits of a reduced-intensity preparative regimen in comparison with myeloablative conditioning.

DIAMOND-BLACKFAN ANEMIA

Diamond-Blackfan anemia (DBA) is a pure red blood cell aplasia of childhood, characterized by normocytic or macrocytic anemia, reticulocytopenia, paucity of bone marrow erythroid precursors and, in more than one-third of patients, somatic abnormalities. Patients also have elevated fetal hemoglobin and erythrocyte adenosine deaminase activity.[129,130] The other hematologic lineages are not generally involved, although slightly abnormal low leukocyte and high platelet counts have been reported at diagnosis.[131,132] Short stature and congenital abnormalities, mainly involving the head, upper limbs, heart, and urogenital system, occur in more than one-third of DBA patients.[133] Information with regard to cancer risk in patients with DBA has been limited primarily to case reports: 29 cases (as well as 3 with MDS who did not develop AML) have been reported among the more than 700 DBA patients in the literature.[3,134]

Recent data show that approximately 40% to 45% of DBA cases are familial with an autosomal dominant inheritance,[135] the remainder being sporadic or familial with seemingly different patterns of inheritance. The genetic basis of DBA is heterogeneous, and approximately 50% of patients are heterozygous for ribosomal protein genes *RPS17*, *RPS19*, *RPS24*, *RPL5*, *RPL11*, or *RPL35A*. All the mutations to date have been found in one allele, resulting in severe loss of function or protein haploinsufficiency. The most common mutation has been found in *RPS19*. A recent review[136] described more than 60 different *RPS19* mutations associated with DBA.[135–143] Overall, DBA is now considered a disorder of ribosome biogenesis or function. There is no

clear correlation between the type of *RPS19* mutation and the degree of hematological disease.

Corticosteroids remain the mainstay of treatment for patients with DBA. Approximately 80% of DBA patients respond to an initial course of steroids. Many patients require long-term high-dose steroids, or develop resistance to therapy and require long-term transfusions.[144–146] Although androgens,[147] growth factors (eg, interleukin-3, erythropoietin),[148,149] and cyclosporine[150,151] have been used with temporary success, the main therapeutic options in steroid-resistant patients are chronic red cell transfusions or allogeneic HSCT.

Allogeneic HSCT is a potentially curative treatment option for DBA. However, this approach remains controversial, as most of these patients can achieve long-term survival with supportive therapy alone. However, patients with DBA who are unresponsive to or intolerant of corticosteroids, experience treatment failure with other treatments, develop additional cytopenias or clonal disease, or opt for curative therapy can indeed be treated with allogeneic HSCT. Since the first report in 1976, several investigators have reported successful transplantation for selected patients with DBA.[152–159]

In the largest reported series, Roy and colleagues[160] studied the transplant outcomes of 61 DBA patients whose data were reported to the IBMTR between 1984 and 2000. Forty-one patients (67%) received transplants from an HLA-identical sibling donor, 8 (13%) from a nonsibling family donor, and 12 (20%) from a MUD. All patients but one received conventional, cyclophosphamide-based conditioning regimens. Only 18% of patients received TBI. Cyclosporine and methotrexate were the most frequently used agents for GVHD prophylaxis. Patients who received an alternative donor transplant were more likely to be older (9 vs 5 years; $P = .03$), to have had a longer median time from diagnosis to transplantation (110 vs 58 months; $P = .02$), and to have received TBI as part of the conditioning regimen (45% vs 5%; $P<.001$). The 3-year probability of OS was 64% (range, 50%–74%). Five patients did not achieve neutrophil engraftment. The 100-day mortality was 18% (95% confidence interval [CI], 10%–29%). Grade II to IV acute GVHD occurred in 28% (range, 17%–39%) and chronic GVHD was reported in 26% (range, 15%–39%). In general, more favorable outcomes were seen in patients with a better performance status at the time of transplantation and in recipients of matched sibling donor transplants. The 1- and 3-year probability of OS of patients with a good performance status who received allografts from HLA-identical sibling donors (n = 29) was 83% (95% CI, 67%–94%). Recipients of alternative donor transplants had worse survival compared with HLA-identical sibling donor transplant recipients (76% vs 39%; $P = .005$).

The number of transfusions before transplantation was significantly correlated with the speed of neutrophil and platelet recovery. Patients who received less than 50 transfusions before transplantation were more likely to have neutrophil recovery by day 28 and platelet recovery by day 60 than patients who received 50 transfusions or more. However, this did not affect survival. Of the 38 surviving patients with a median follow-up of 11 years (range, 1–14 years), 37 were reported to have a normal white blood cell count. Of these 38 patients, 25 were known to be red blood cell transfusion independent, while transfusion data were not available for the remaining 13 patients.

Previous studies have reported similar OS rates (66%–87%),[157,158,161] and similar inferior results after alternative donor transplantations compared with matched sibling donor transplants (87% vs 14%).[158] The DBA registry of North America recently reported 36 patients who underwent HSCT, 21 using matched sibling donors and 15 with alternative donors. The majority of HLA-matched sibling transplants were done using a nonirradiation-containing conditioning regimen. The majority of

alternative donor transplants was performed using TBI. Sixteen of the 21 matched sibling donor transplants were alive and red cell transfusion independent. Of the 15 alternative donor HSCT, 4 were alive at the time of report. Of note, of the 16 deaths, 15 were related to infection, GVHD, or veno-occlusive disease of the liver, with only 1 death, in the alternative donor group, occurring as a consequence of graft failure. The survival for allogeneic sibling versus alternative donor transplant was 72.7% $\pm$ 10.7% versus 19.1% $\pm$ 11.9% at greater than 5 years from HSCT ($P = .01$) (excluding a patient with osteogenic sarcoma diagnosed after SCT) or 17.1% $\pm$ 10.8% (including the osteogenic sarcoma patient, $P = .012$).[162]

Mugishima and colleagues[156] reported their experience with HSCT in 19 Japanese patients with DBA. Stem cell source was bone marrow in 13 (6 HLA-matched siblings, and 6 HLA-matched and 1 HLA-MUDs), UCB in 5 (2 HLA-matched siblings and 3 HLA-mismatched unrelated donors), and peripheral blood from a haploidentical mother in the remaining patient. With regard to the preparative regimen, 13 patients (68%) received cyclophosphamide (60–200 mg/kg) with TBI (3.5–12 Gy)-based conditioning, and 6 patients (32%) received cyclophosphamide without radiation-based conditioning. GVHD prophylaxis included cyclosporine with or without methotrexate and tacrolimus with or without methotrexate. One patient experienced early death from pulmonary bleeding and sepsis on day 10 after a CD34+ cell-selected, peripheral blood stem cell graft from a haploidentical mother. Sixteen of the 18 evaluable patients (88.9%) achieved successful engraftment. Median observation time after transplantation was 89.5 months. Of the 3 patients who received UCB from HLA-MUDs, 1 had complete engraftment but developed grade II acute GVHD and died of EBV-associated lymphoproliferative disease 4 months after UCB HSCT.[163] The other 2 patients experienced graft rejection and returned to being transfusion-dependent. One patient subsequently underwent HSCT from an HLA-one-locus-mismatched father 2 months after the first transplantation. The other patient received bone marrow from an unrelated HLA-matched donor 11 months after the first transplantation. Both patients were reported to be alive 80 months and 63 months after successful second HSCT, respectively. Overall, 15 of 19 DBA patients (79%) survived with successful engraftment after the first HSCT, and 2 patients who initially received an unsuccessful unrelated-donor UCB transplant then received a successful second HSCT as described earlier. The failure-free survival rate of the patients 5 years after HSCT was higher than that after UCB HSCT (100% vs 40%, $P = .0019$). The OS rate after HSCT (100%) was higher than that after the other types of HSCT (60%, $P = .0293$) and after unrelated UCB HSCT (67%, $P = .0374$).

Long-term follow-up of DBA patients has suggested an increased risk of malignancies, including osteosarcoma.[162,164] In this context, reduced doses of radiation or other reduced-intensity preparative regimens are now of interest. Ostronoff and colleagues[165] reported that a 19-month-old patient underwent successful matched sibling donor HSCT following a nonmyeloablative conditioning regimen (2 Gy TBI plus 90 mg/m^2 fludarabine). GVHD prophylaxis included cyclosporine (6 mg/kg/d) and methotrexate on days 1, 3, 6, and 11. The posttransplant course was uneventful. With a follow-up of 10 months, no signs of toxicity or GVHD were observed. The patient had full donor chimerism and was transfusion independent, with a performance status of 100%. In contrast to this successful case report, a matched sibling peripheral blood stem cell transplant after a non-TBI reduced-intensity conditioning regimen led to graft failure in a 4-year-old DBA patient, and to mixed chimerism and chronic GVHD in a 5-year-old with DBA.[166] Thus, although these case reports of successful nonmyeloablative transplantations in DBA are encouraging, further studies with larger patient numbers are needed to critically evaluate its role.

SUMMARY AND FUTURE DIRECTIONS

Progress in improving the outcomes for children with inherited BMF syndromes has been limited by the rarity of these disorders, as well as disease-specific genetic, molecular, cellular, and clinical characteristics that increase the risks of complications associated with HSCT. As a result, the ability to develop innovative transplant approaches to circumvent these problems has been limited. However, recent progress has been made, as best evidenced by the addition of fludarabine to the preparative regimen for children undergoing unrelated donor HSCT for FA. The highly immunosuppressive nature of fludarabine now allows for a high degree of donor engraftment without overlapping toxicities and tissue injury, with further reduction in GVHD. The improvement in outcome with fludarabine has been evident in smaller studies, despite a lack of traditional, large, multicenter clinical trials; this is likely a rare circumstance. The rarity of these diseases coupled with the far more likely incremental improvements that will result from ongoing research will require prospective international clinical trials to improve the outcome for these children.

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