



Published in final edited form as:

*Bone Marrow Transplant.* 2016 July ; 51(7): 938–944. doi:10.1038/bmt.2016.32.

## Late effects in patients with Fanconi anemia following allogeneic hematopoietic stem cell transplantation from alternative donors

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### Abstract

Hematopoietic stem cell transplantation (HSCT) is curative for hematological manifestations of Fanconi anemia (FA). We performed a retrospective analysis of 22 patients with FA and aplastic anemia, myelodysplastic syndrome or acute myelogenous leukemia who underwent a HSCT at Memorial Sloan Kettering Cancer Center and survived at least one year post-HSCT. Patients underwent either a total body irradiation (TBI) (N=18) or busulfan (N=4) based cytoreduction followed by T-cell depleted transplants from alternative donors. Twenty patients were alive at time of study with a 5 and 10 year overall survival of 100% and 84% and no evidence of chronic GVHD. Among the 18 patients receiving a TBI-based regimen, 11 (61%) had persistent hemochromatosis, four (22%) developed hypothyroidism, seven (39%) had insulin resistance and five (27%) developed hypertriglyceridemia after transplant. Eleven of 16 evaluable patients (68%), receiving TBI, developed gonadal dysfunction. Two patients who received a TBI-based regimen died of squamous cell carcinoma. One patient developed hemochromatosis, hypothyroidism, and gonadal dysfunction after Busulfan-based cytoreduction. TBI appears to be a risk factor for malignant and endocrine late effects in the FA host. Multidisciplinary follow-up of patients with FA (including cancer screening) is essential for early detection and management of late complications, and improving long-term outcomes.

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**Conflict of Interest:**

The authors declare no conflict of interest.

## Introduction

Fanconi anemia (FA) is an inherited bone marrow failure syndrome characterized by chromosome fragility, constitutional abnormalities, and cancer susceptibility. Bone marrow failure can lead to marrow aplasia with severe aplastic anemia (SAA), myelodysplastic syndrome (MDS) and/or acute myeloid leukemia (AML). Allogeneic hematopoietic stem cell transplantation (HSCT) is the only curative option for the hematological manifestations of this disease. In the past decade, cytoreductive regimens including fludarabine and T-cell depleted grafts have improved the overall survival in FA after allogeneic transplants from alternative donors.<sup>1,2</sup> Long term survival rates in this group now range from 50–70%.<sup>1,2</sup> Although HSCT can restore long term hematopoiesis and cure the hematologic complications of patients with FA, these patients do not always recover to complete health. The inherent defective DNA repair in somatic lineages predisposes them to cancers and an increased susceptibility to complications of HSCT, affecting their long-term survival. Indeed, in addition to long term complications of HSCT, patients with FA may have disease-specific complications such as endocrinopathies and increased risks for squamous cell carcinoma. In order to improve overall outcomes and further increase survival rates, it is necessary to better understand the long-term complications in patients with FA following HSCT.

Late effects after HSCT and recommendations for follow-up have been reported in pediatric patients.<sup>3</sup> However data for patients with FA post transplant has been limited.<sup>4</sup> Herein we report the late effects and long-term health among 22 patients with FA following HSCT at Memorial Sloan Kettering Cancer Center (MSK) with a median follow up of 7.45 years. This represents one of the largest reports of late effects in patients with FA undergoing HSCT.

## Patients and Methods

We performed a single-institutional, retrospective review of long-term outcomes of patients with FA who underwent HSCT at MSK from March 1999 to December 2012. Data collection was approved by the MSK Institutional Review Board / Privacy Board. Clinical and laboratory data were abstracted from the MSK medical records.

## Patient Characteristics

Thirty-eight patients with a diagnosis of FA, confirmed by diepoxybutane testing, received an allogeneic HSCT from alternative donors during this time period. Among these 38 patients, 22 patients who underwent first transplantation from an alternative donor and survived more than one year post-transplant were eligible for inclusion in this study. Patient characteristics are summarized in Table 1. Age at transplant ranged from 5.4 – 35.6 years (median: 12.1 years): 8 patients were younger than 10 years of age, 8 patients were between 10–17 years, and 6 patients were older than 18 years of age at time of transplant. Hematologic diagnoses at time of HSCT were SAA (N=11), MDS (N=6) and AML (N=5). All patients with MDS and AML were transplanted with active disease and without pre-transplant chemotherapy. Fifteen patients (68%) had received androgens and seven patients received >20 blood transfusions prior to transplantation.

## Transplant Characteristics

Patients and donors were HLA typed for HLA-A, B, C, DRB1 and DQB1 using high resolution typing. Unrelated donors (N=14) were matched (N=9) or mismatched (N=5) at one antigen (N=1) or greater than 1 antigen (N=4; A,DQ – C,DQ – B,C – B-C). Related donors (N=8) were HLA mismatched at one antigen (N=2; A) or greater than one antigen (N=6; A,C – A,C – Dr,DQ – Dr,DQ – B,DR,DQ – B,C,DR,DQ). Source of hematopoietic stem cells included bone marrow (N=4) or peripheral blood (N=18). All patients received T-cell depleted grafts. T-cell depletion methods included soybean lectin agglutination with sheep RBC rosette depletion (N=4) or CD34+ positive selection using an ISOLEX 300i Magnetic Separator with sheep RBC rosette depletion (N=15) or positive CD34+ selection with use of Miltenyi system (CliniMaCS device) (N=3) as previously described.<sup>2,5</sup> Cytoablative regimens for transplantation included single dose total body irradiation (TBI) 450cGy, fludarabine (Flu) 30 mg/m<sup>2</sup> × 5 and cyclophosphamide (Cy) 10 mg/kg × 4 (N=18) or a busulfan (0.8–1.0 mg/Kg/dose q 12hrs × 4 doses), Cy 10 mg/Kg × 4 days and Flu 35 mg/m<sup>2</sup> × 4 (N=4). Rejection prophylaxis included anti-thymocyte globulin for all patients. Additional GVHD prophylaxis included tacrolimus or cyclosporine. G-CSF was started on Day +7 for all patients to promote engraftment. T-cell depletion, Single dose TBI, PBSC collection and supportive care methods were previously described.<sup>2</sup> Neutrophil engraftment, primary graft failure, chimerism, MDS, AML and GVHD were defined as previously described.<sup>2</sup>

## Long Term Follow-Up Care

All 22 patients were seen for comprehensive long-term follow-up in the MSK Pediatric Survivorship/Long-Term Follow-Up (LTFU) clinic, which follows patients who have survived at least one year after completion of therapy. Patients received risk-based, comprehensive care according to COG Long-term Follow-Up Guidelines<sup>6</sup> either annually or biannually. All FA patients also underwent annual head and neck cancer screening exams, and adult female patients underwent gynecologic evaluation. Female patients also received three doses of quadrivalent human papilloma virus vaccine (HPV) after immune reconstitution.

Patients were evaluated by physical exam and laboratory evaluation at each visit. All patients had a serum ferritin measurement drawn at the initial visit, before transplant, and periodically after transplant with at least one measurement at one year post transplant follow-up. Liver iron concentration (LIC) was measured using T2\*-MRI (Normal Range: 0.17–1.8 mg/g dry weight of liver) using a 1.5T MRI machine. MRI measurement of LIC was based on imaging of proton transverse relaxation rates (T2\*) within the liver. Thyroid function was evaluated using thyroid-stimulating hormone (TSH) and free T4 (FT4). Glucose homeostasis was measured using fasting or two-hour postprandial glucose and insulin levels. Blood glucose levels were classified according to American Diabetic Association recommendations.<sup>7</sup> Insulin resistance was defined by homeostasis model assessment-estimated insulin resistance (HOMA-IR) Index, where  $HOMA-IR = \frac{[\text{fasting insulin } (\mu\text{U/ml})] \times [\text{fasting glucose (mg/dL)}]}{405}$ ; with the denominator of 405 serving as a normalizing factor. HOMA-IR values above 2.6 (75<sup>th</sup> percentile) were considered diagnostic of insulin resistance.<sup>8</sup> Gonadal function was evaluated by levels of follicle stimulating

hormone (FSH) and luteinizing hormone (LH); early morning testosterone was measured in males to assess Leydig cell function and clinical information on menstrual regularity was abstracted on postpubertal females. Elevated FSH levels (> 15mIU/ml) were consistent with ovarian dysfunction or male germ cell dysfunction. Ovarian failure was defined as ovarian dysfunction requiring hormone replacement therapy, or elevated FSH levels (>15mIU/ml) with pubertal arrest or clinical amenorrhea. Leydig cell dysfunction was defined as elevated LH levels (> 15mIU/ml) with low morning testosterone levels (< 250 ng/dl) in a sexually mature male.

### Statistical analysis

Patient demographic data are reported as range, mean and median values. Survival rates were calculated using Kaplan-Meier method, censoring at time of last contact using SPSS (IBM, Armonk, NY). For Student's *t* test, a p-value of less than 0.05 was considered significant. Disease free survival (DFS) was defined as survival with absence/resolution of hematologic disease (SAA, MDS or AML).

## Results

### Transplant Outcome

The median follow-up for the 22 patients included in this study was 7.45 years (range: 2.28 - 15.33 years). Twenty patients were alive at time of study with a 5 and 10 year overall survival (OS) of 100% and 84%, respectively (Fig 1). Eighteen of 20 evaluable patients achieved durable 100% donor chimerism, and two patients had >90% donor chimerism at last follow-up. Two of the 22 patients, died of metastatic squamous cell carcinoma (SCC). One 19 year old patient who underwent HSCT for MDS in refractory anemia with cytogenetic abnormalities including der(13), t(13;1;3) had a relapse of primary MDS three years after transplant. He underwent a second transplant from an unrelated donor elsewhere, and is alive disease-free.

### Graft versus Host Disease

None of the 21 patients who survived disease-free for more than one year post transplant had any evidence of chronic GVHD. One patient who relapsed with primary MDS and underwent a second unmodified HSCT from an unrelated donor elsewhere had cGVHD of the gut.

### Hematologic Outcome

All patients had full recovery of WBC and RBC counts. One patient with moderate thrombocytopenia, one year after primary HSCT received an uncytoreduced TCD peripheral blood stem cell boost and recovered his platelet count without GvHD. Two additional patients who were transplanted for MDS and AML, had evidence of polycythemia (Hb>17gm/dl), two years after transplant. At the time of polycythemia, both patients had elevated erythropoietin levels (64 mUnits/ml, 102 mUnits/ml), normal bone marrow M/E ratio, normal cytogenetics and >95% donor hematopoietic cells by chimerism studies with no evidence of JAK2 mutation. This resolved spontaneously in one patient while one patient continues with periodic phlebotomy.

## Secondary Malignancies

Two young adult female patients who received a TBI-based regimen developed metastatic SCC. One patient, who underwent HSCT at the age of 24 for AML, and who was sexually active had HPV positive cervical intraepithelial neoplasia Grade 1 (CIN-1) pre-HSCT and developed metastatic SCC 4 years after HSCT. She received chemotherapy, surgery and radiation, but died one year later of disease progression. Another female patient aged 21 developed metastatic SCC of the tongue, 7 years after HSCT for AML. She underwent partial glossectomy and radiotherapy, but died within one year of diagnosis from progressive disease.

## Hemochromatosis

Among 22 patients, nine patients (40%) had received <20 transfusions pre-transplant and had ferritin levels <500 ng/ml (Mean: 261 ng/ml; Range: 38–410 ng/ml); all nine patients are doing well with the persistence of low ferritin. Of the remaining 13 patients (60%) with ferritin levels >500 ng/ml (Mean: 2565ng/ml; Range: 613–6045ng/ml), six had received <20 transfusions pre-transplant and seven had received >20 transfusions. Twelve of these thirteen patients with a ferritin >500 ng/ml had persistence of a high ferritin (> 500 ng/ml) [Mean 1711 ng/ml; Range:641–3331 ng/ml) at one year post transplant. There was no association between high ferritin at one year post transplant with either overall survival (OS) (p=0.39) or disease free survival (DFS) (p=0.79). T2\*MRI was performed in only 4 of the 12 patients with high ferritin at one year post transplant, either due to availability or noncompliance. Six of the twelve patients with hemochromatosis at one year post transplant underwent phlebotomy, albeit with poor compliance. However, among those who underwent phlebotomy, there was a trend towards a decrease in ferritin levels.

## Immune Reconstitution

All 22 patients recovered CD3+, CD4+ and CD8+ counts to normal levels after transplant and nineteen of them had normal T-cell function measured by proliferation with PHA and three others had PHA proliferation levels >90%. Eighteen of these patients had normal IgG levels, three patients had borderline IgG levels at last follow-up, while one patient has persistent B cell dysfunction and hypogammaglobinemia and continues with monthly replacement with immunoglobulin, twelve years after transplant. This patient had developed Epstein Barr virus lymphoproliferative disease (EBV-LPD) post HSCT and was treated with rituximab. He also received a TCD peripheral blood stem cell boost to correct his immunodeficiency, without success.

## Endocrinopathies

**Primary Hypothyroidism**—Thyroid function was evaluated in all patients both prior to transplant and during long-term follow-up visits starting at one year after transplant. Among 22 patients, five patients had pre-existing primary hypothyroidism before transplant, with two patients receiving levothyroxine replacement therapy. Post-transplant, five additional patients developed primary hypothyroidism after receiving TBI-based cytoreductive regimens (N=4) or a busulfan based cytoreductive regimen (N=1). At last follow-up, nine of the ten patients with hypothyroidism required levothyroxine replacement therapy. One

additional patient had laboratory evidence of subclinical primary hypothyroidism (mildly elevated TSH) but was lost to follow-up prior to repeating laboratory values.

### Disorders of glucose and insulin homeostasis

Prior to transplant, one female patient, aged 9 years, had insulin-dependent diabetes mellitus (IDDM). Another male patient aged 17 years had hyperglycemia and insulin resistance (HOMA-IR =13.54) and was treated with metformin. All patients had at least one fasting lipid panel and fasting glucose level performed during long-term follow-up. After transplant, ten of eighteen patients who received a TBI-based regimen had evidence of hyperglycemia with insulin resistance noted in seven of them. (HOMA-IR Range: 3.52–25.29) Five of the 7 patients with insulin resistance were also noted to have hypertriglyceridemia. One female patient developed diabetes mellitus one year after a TBI-based regimen and required treatment with insulin. None of the patients treated with Busulfan-based cytoreduction had documented glucose intolerance or insulin resistance.

**Gonadal Dysfunction**—Among 17 evaluable patients, 12 (70.6%) had documented gonadal dysfunction. Twelve of 14 male patients were postpubertal with evaluable FSH, LH, and testosterone levels at the time of last follow-up. Among these 12 patients, eight had evidence of germ cell dysfunction, including one patient who also exhibited Leydig cell dysfunction (with elevated LH and low testosterone levels) and required testosterone supplementation. Seven of the 8 males had received a TBI-based regimen and one patient – with Leydig cell dysfunction - had received a busulfan-based regimen for cytoreduction.

Five of the 8 female patients were evaluable for treatment-related ovarian dysfunction at the time of last follow-up. Four patients had ovarian failure and required treatment with hormone replacement therapy due to elevated FSH levels with clinical amenorrhea. One patient on hormone replacement therapy achieved successful spontaneous pregnancy after presumed return of ovarian function. One patient had normal gonadotropins at the time of last follow-up, and had achieved menarche spontaneously. Three patients were inevaluable: one patient had surgical menopause due to hysterectomy performed four years prior to transplant for endometriosis, one patient was on oral contraceptives continuously from the time of transplant until the time of her death, and the third patient was pre-pubertal at the time of last follow-up. All female patients with documented ovarian dysfunction had received a TBI-based regimen.

### Psychological outcome

Twelve of the 22 long term survivors (54%) had psychologic issues pre-transplant requiring a psychiatric consultation or intervention. Pre-transplant psychiatric diagnoses included adjustment disorders (N=8), mood disorders (N=6), delirium (N=3), anxiety disorders (N=3), impulse control disorders (N=3), ADD, reactive attachment disorder, Asperger disorder (autistic spectrum disorder), and personality disorder. (N=1, each) Of these 12 patients, ten patients (45%) had clinically significant symptoms persisting beyond 12 months post-transplant and at last follow-up. In four patients, there was resolution of all reported symptoms after transplant. In the post transplant period, one female patient developed bipolar disorder five years after transplant, and another male patient developed behavioral



and mood issues in the context of a custody change. A third male patient who received a TBI based regimen had persistent learning and academic issues post-transplant. Ten patients were treated with one or more psychotropic medications including benzodiazepines (N=3), atypical antipsychotics (N=6), antidepressants (N=7) and stimulants (N=3), while five patients were treated with supportive psychotherapy alone. Of note, 10 of these 12 patients with psychological issues had pre-transplant exposure to androgen therapy, and although sample size was not adequate to show significant correlation with psychiatric symptoms, this may be an added risk factor for mood or behavioral problems in at-risk children.

### Others

All 22 patients had pre-transplant echocardiograms, which were all within normal limits. All patients had normal repeat echocardiograms post-transplant. Twenty of 22 patients, who were greater than 7 years at time of transplant had pulmonary function testing (PFT) performed before transplant and at least once after transplant. Two survivors of HSCT had gastrointestinal issues including chronic issues of early satiety, poor oral intake and poor weight gain. None of these patients had any GI tract abnormalities preceding HSCT. No significant changes were noted in PFTs measured after transplant. Among eighteen patients who received TBI based regimens, four patients developed cataracts, while five developed conductive hearing loss.

### Discussion

Survival of patients with FA receiving transplants from alternative donors has improved with OS up to 70% after fludarabine-based cytoreductive regimens and T-cell depleted grafts.<sup>1,2,9</sup> The complications of HSCT such as graft failure and acute GVHD, which earlier resulted in high peri-transplant mortality, have decreased significantly contributing to this improvement in outcome. The overall survival in our cohort of patients surviving more than a year post transplant is 100% at 5 years and 84% at 10 years. However, the late complications and life expectancies of patients with FA following allogeneic HSCT are not similar to age matched controls. Patients with FA are still at risk for long term complications either from transplant-related factors or secondary to FA related issues unrelated to transplantation, including complications of congenital anomalies, endocrinopathies and increased cancer susceptibility.<sup>10,11</sup> Further improvement in survival may result from a better understanding of complications of transplant affecting long-term outcomes

Patients with FA are at particularly high risk for GVHD after HSCT probably due to their impaired DNA repair mechanism and increased susceptibility to apoptosis.<sup>12</sup> Previous studies have indicated that the rate of chronic GVHD in patients with FA undergoing transplant from alternative donors could be as high as 60%.<sup>9</sup> It is a significant cause of delayed morbidity and mortality in patients undergoing HSCT due to associated immune deficiency, infectious complications, organ insufficiency or secondary malignancies.<sup>4, 13</sup> In an international cohort of 24,000 transplant recipients the severity, duration and treatment of cGVHD was a major risk factor for development of SCC after HSCT.<sup>14</sup> T-cell depletion has been proven to be the most effective method for the prevention of GVHD, both in FA and non-FA patients undergoing transplant from HLA disparate or alternative donors.<sup>5,15</sup> In our

cohort of 22 patients who underwent a TCD transplant, all patients engrafted and no patient who survived disease-free for more than one-year post transplant had any evidence of cGVHD. In addition to the absence of graft failure and GvHD, only one of 11 patients with MDS or AML relapsed post transplant, despite the absence of pre-transplant induction chemotherapy. In our experience, aggressive TCD radically reduces the risk of cGVHD without an increased risk of graft failure or of relapse of myeloid malignancies.

Patients with FA have inherent cancer susceptibility due to their defective DNA repair mechanism. They have a 785 fold higher risk of leukemia<sup>11</sup> and 500 fold higher risk of squamous cell carcinoma as compared to the general population.<sup>16</sup> Patients with FA undergoing transplant have a 4.4 fold higher risk of developing SCC - particularly of anogenital and head & neck areas - than those patients with FA who do not undergo HSCT.<sup>17</sup> SCC which occurs in patients with FA is aggressive, occurs at a relatively younger age than the general population (median onset 31 vs. 45 years old) and carries 2 year survival rates below 50%.<sup>18, 19</sup> In our study, two patients (9%), developed aggressive metastatic SCC at a very young age and died soon after diagnosis. In unrelated donor transplants, there is now evidence that cGVHD induces a chronic inflammatory state leading to microsatellite instability and frequent genomic alterations in epithelial tissues, predisposing to development of cancers.<sup>20, 21</sup> Among 795 FA patients who underwent HSCT across Europe, cGVHD was an independent risk factor and time dependent co-variate factor for development of secondary malignancy.<sup>22</sup> Although neither of our patients had cGVHD, they did receive TBI-based regimens before transplant. Ionizing radiation is a known carcinogen, inducing double strand breaks in DNA, leading to chromosomal translocations and genomic instability. Irradiation-containing conditioning regimens have been identified as a risk factor for post-transplant malignancy in patients with FA.<sup>23</sup> In a study by Rosenberg et al., there was a trend towards increasing malignancy in patients with FA receiving TBI based regimen.<sup>17</sup>

Iron overload after HSCT can lead to cardiac, liver, pituitary and thyroid related morbidity. Patients with FA who are frequently transfused have elevated ferritin levels pre-transplant, and high serum ferritin has been reported to be associated with inferior outcomes after HSCT.<sup>24</sup> However, in our cohort, there was no significant difference in OS and DFS comparing the 13 patients who had pre-transplant ferritin >500 ng/ml, to the 9 patients with pre-transplant ferritin <500 ng/ml, like other reported studies.<sup>25</sup> Liver iron content (LIC) measured by liver magnetic resonance (T2\*-MRI) is more specific and a more accurate measure of body iron stores.<sup>26</sup> We follow LIC by T2\*-MRI in patients with FA undergoing HSCT at MSK having high serum ferritin levels. We initiated chelation with phlebotomy in six patients with iron overload in the post transplant period. Given the non-compliance in this small group we still noticed an appreciable decrease (although not statistically significant) in ferritin levels post transplant compared to six others lost to follow-up and who did not undergo any chelation. The use of iron chelators is a potential alternative option to phlebotomy in patients who have venous access issues, or can be used in addition to phlebotomy in patients with prolonged elevated iron levels. However, one has to weigh the potential benefits with the risks of hepatic and/or renal toxicity that we can see post transplant.



Endocrinopathies including growth hormone deficiency, thyroid dysfunction and glucose intolerance are commonly observed in patients with FA independent of stem cell transplantation.<sup>10</sup> In a series of 120 patients with FA, 48% of patients who had not undergone HSCT and 53% of patients who had undergone transplant were found to have hypothyroidism.<sup>27</sup> Similarly we observed a high incidence of hypothyroidism in our patients (45%), although half of these patients had evidence of hypothyroidism prior to HSCT. Thyroid hormone replacement may improve growth velocity in children with borderline thyroid function and FA,<sup>28</sup> and hence close thyroid monitoring and early treatment is recommended. Glucose intolerance/insulin resistance has previously been reported in 40–80% of patients with FA independent of HSCT.<sup>10, 27</sup> In our cohort, nine of 18 patients (50%) who received a TBI-based regimen had insulin resistance/IDDM. Impairment of glucose metabolism and insulin resistance in HSCT survivors is common, particularly after TBI-based cytoreductive regimens.<sup>8, 29–31</sup> TBI has been reported to increase the risk of metabolic syndrome by nearly fourfold among leukemia survivors treated with HSCT.<sup>32</sup> Moreover, exposure to TBI may be associated with hypertriglyceridemia, one component of the metabolic syndrome, as seen in 30% of our patients following TBI.

Patients with FA undergoing transplant are at high risk of gonadal dysfunction and infertility after high dose alkylating agent-based chemotherapy or TBI-based regimens. In this cohort 67% of postpubertal evaluable males had evidence of gonadal dysfunction, which is comparable to an earlier reported study.<sup>27</sup> Recovery of spermatogenesis has been reported in HSCT recipients treated with low doses of cyclophosphamide (<120mg/Kg) and absence of cGVHD.<sup>33, 34</sup> Among 5 evaluable females in our cohort, 4 (80%) had ovarian failure. The most important risk factor predicting ovarian dysfunction was patient age at time of treatment with TBI. Essentially all female patients older than 10 years at the time of TBI, and 50% of prepubertal girls at the time of TBI will have irreversible ovarian failure.<sup>35</sup> Female FA patients, even without transplant have shortened reproductive life with late menarche, early menopause and subfertility. Pregnancy after HSCT for FA is relatively rare. Among 285 female patients with FA who underwent HSCT with Cy/TBI or Cy (N=3), ten had a pregnancy.<sup>36</sup> In our cohort one patient who had evidence of ovarian failure requiring hormone replacement therapy achieved a pregnancy and gave birth to a healthy infant.

Our cohort carried significant baseline psychiatric comorbidity (55% (n=12) of patients with significant symptoms requiring psychiatric evaluation) much of which persisted beyond a year post-transplant, (45%, n=10), even when compared to other long-term survivors following stem cell transplantation (HSCT) (5–40% with anxiety and/or depression).<sup>37,38</sup> As we lacked validation of psychiatric diagnoses or controls, our retrospective psychiatric data must be considered exploratory. However, several risk factors and stressors for psychiatric distress have been identified in patients with FA, above and beyond those of the typical HSCT survivor<sup>39</sup>; these include the fear of second cancers, other sequelae of genetic disease, parental guilt due to genetic transmission of FA, the possibility of having affected siblings or experience of sibling loss due to FA, the use of androgens, and post traumatic stress disorder following HSCT. Additionally, patients with FA may have associated neurodevelopmental and learning issues that predispose them to poor coping and difficulties with academic, occupational and social reintegration after transplant. A prior review of pre-transplant psychiatric evaluations of patients with FA at our center was also concerning for high rates

of non-adherence to treatment and other risky health behaviors in FA patients undergoing HSCT.

Patients with FA undergoing transplant are at risk for late effects including hemochromatosis, endocrinopathies and psychological issues. Those treated with TBI-based regimens appear to be at greater risk for adverse treatment-related complications, but patients treated with busulfan-based regimens were fewer and had a shorter follow-up; this will need to be studied in larger patient cohorts. Ten of the 18 patients receiving TBI-based regimens had greater than two late effects, while eight had none at all. (Table 2) Patients who experienced these late effects were more likely to be older than 10 years at time of transplant and have MDS or AML.

Over the last two decades, outcome post HSCT for patients with FA has significantly improved, with an increased OS. Patients with FA who pass the one year mark post transplant have a very good outcome. Patients with FA are at risk for late effects from (1) cytoreduction, (2) allogeneic transplantation and (3) disease-associated complications. Multidisciplinary follow-up of patients with FA (including cancer screening) is essential for the early detection and management of late complications, and the improvement of the long-term outcome. FA patients continue to be at risk for solid tumors of the head and neck and anogenital area post transplant. We have adopted two approaches to decrease this risk including T-cell depleted grafts as described in this series, and the development of a chemotherapy-only cytoreductive regimen without TBI which is now being studied in a US multi-center HSCT trial.

## Acknowledgments

We would like to thank the fellows, residents, nurses and nurse practitioners of the Department of Pediatrics at MSK and Rachel Lehrman and Joseph Olechnowicz for data management and editorial assistance.

Support: Anur Praveen is the recipient of a St. Baldrick's Fellowship. We wish to thank the Fanconi Anemia Research Fund for their support. This research was funded in part through the NIH/NCI Cancer Center Support Grant P30 CA008748.

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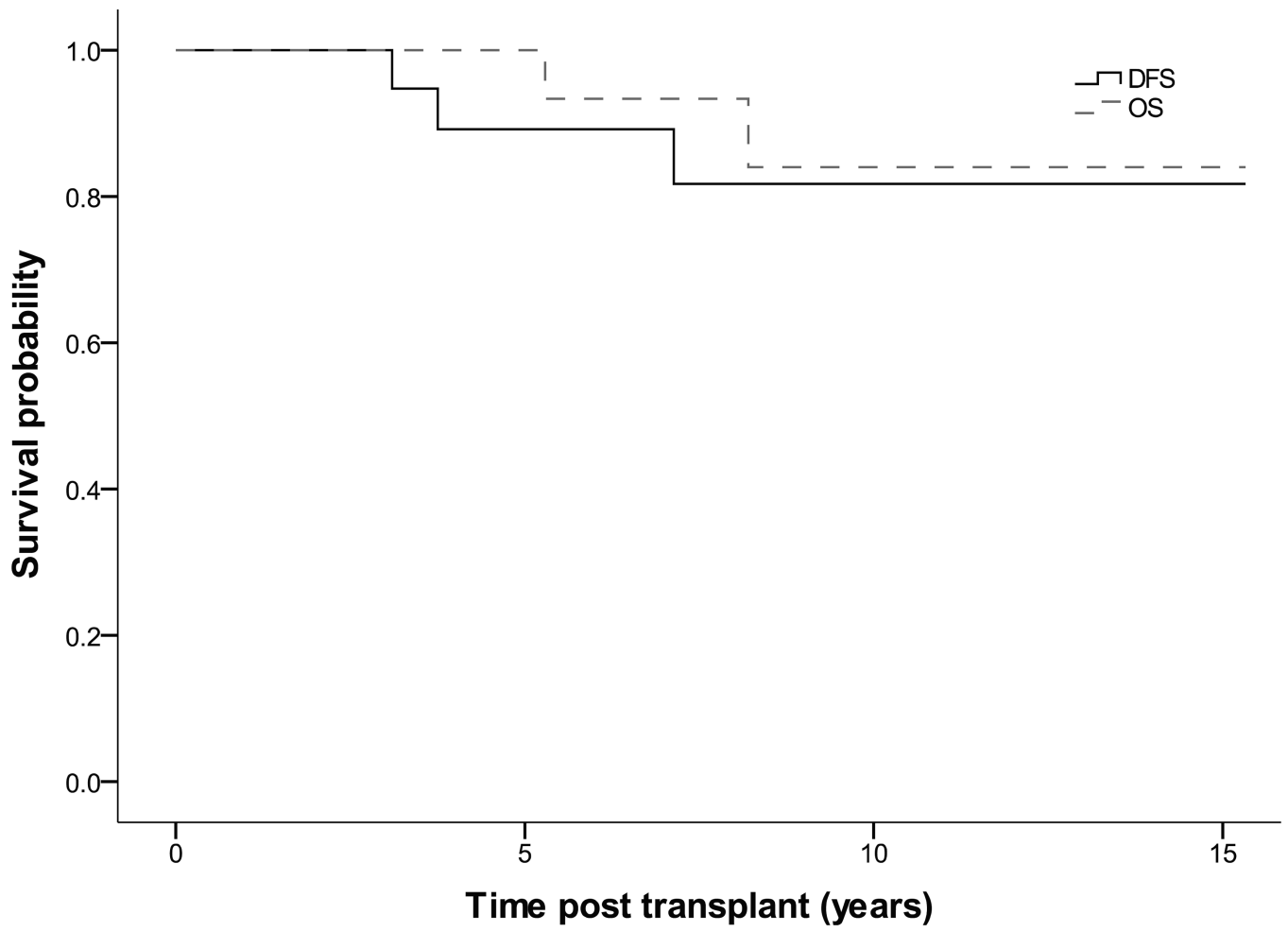
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**Figure 1.** Disease free and overall survival for patients survivors at least one year post transplant



**Table 1**

## Patients Characteristic

	N = 22
<b>Gender</b>	
Female	14
Male	8
<b>FA Complementation group</b>	
A	11
C	2
D2	1
G	3
Other - Unknown	5
<b>Age at HSCT (years)</b>	
Median	12.1
Range	5.4 – 35.6
<b>Hematologic Diagnosis</b>	
SAA	11
MDS	6
AML	5
<b>Prior Treatment</b>	
Androgens	15
>20 red blood cell transfusions	7
<b>Conditioning regimen</b>	
TBI/Flu/Cy	18
Dose of TBI	(450 cGy)
Bu/Flu/Cy	4
<b>Donor N (%)</b>	
Unrelated Matched	9
Unrelated Mismatched	5
Related Mismatched	8
<b>Follow-up (years)</b>	
Median	7.4
TBI cohort	9.1
Bu cohort	2.8
Range	2.3 – 15.3

**Table 2**  
Summary of Treatment Exposures and Late Medical Outcomes for all Patients (N=22)

Patient ID	Cytoreduction	Age at BMI(yrs)	Gender	Follow-up (Years)	Disease	Ferritin	Hypothyroid	Insulin Resistance	Triglycerides	Gonadal Dysfunction
1	TBI/Flu/Cy	5.6	M	15.3	AA	Y	N	N	N	N
2		6.9	F	9.9	AA	Y	N	N	N	N
3		8.5	M	7.8	AA	Y	N	N	N	N
4		10.1	F	10.8	AA	N	N	Y	Y	Y
5		9.9	M	6.5	AA	Y	N	N	N	N
6		10.8	M	15.3	MDS	Y	Y	Y	Y	Y
7		9.5	F	13.5	MDS	N	Y	IDDM	N	Y
8		11.7	M	7.1	AA	N	N	N	N	Y
9		12.4	M	10.7	AML	Y	Y	Y	N	Y
10		12.8	M	14.3	MDS	Y	Y	Y	N	N
11		13	M	5.1	AA	Y	N	N	N	N
12		15.1	F	11.4	AA	Y	N	IDDM	Y	Y
13		16.8	M	5.2	MDS	N	Y	Y	Y	Y
14		19.3	M	3.1	MDS	N	N	N	N	Y
15		21.8	F	8.2	AML	Y	Y	Y	Y	Y
16		24	F	5.3	AML	N	N	N	N	NE
17		24.8	M	10.9	AML	Y	Y	N	N	Y
18		35.6	F	3.0	AML	N	N	N	Y	Y
19		5.4	F	5.2	MDS	N	Y	N	N	NE
20		7.4	M	2.3	AA	N	Y	N	N	NE
21		7.8	M	3.3	AA	Y	Y	N	N	NE
22		31.4	M	2.3	AA	N	N	N	N	N

**Disease Stage:** AA-Aplastic Anemia, MDS-Myelodysplastic Syndrome, AML-Acute Myeloid Leukemia; N-Not Present, Y-Yes Present, Y-Yes Present, NE-not evaluable, IDDM-Insulin Dependent Diabetes mellitus;