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Successful Outcome in Patients with Fanconi Anemia Undergoing T Cell-Replete Mismatched Related Donor Hematopoietic Cell Transplantation Using Reduced-Dose Cyclophosphamide Post-Transplantation

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A B S T R A C T

Allogeneic hematopoietic cell transplantation (HCT) has been shown to restore normal hematopoiesis in patients with Fanconi anemia (FA), with excellent results in matched related donor HCT. Outcomes of alternative donor HCT are less favorable, however. In patients without FA, several reports have documented stable engraftment and/or a low risk of graft-versus-host disease (GVHD) using unmanipulated HLA-mismatched related donors and post-HCT cyclophosphamide (PT-CY) for GVHD prophylaxis. Data on the use of this approach in patients with FA are scarce, and thus we launched a study of HLA-mismatched related donor HCT in these patient. Here we report our findings in 19 patients. The conditioning was fludarabine 30 mg/m^2/day for 5 days, antithymocyte globulin 5 mg/kg/day for 4 days, and total body irradiation (total dose, 200 cGy). GVHD prophylaxis was cyclosporine and mycophenolate and reduced doses of PT-CY, 25 mg/kg, on days +3 and +5. All patients exhibited absolute neutrophil count recovery. Grade III-IV acute GVHD occurred in 3 patients, and chronic GVHD occurred in 1 patient. At a mean follow-up of 38.3 ± 5.8 months, the 5-year probability of overall survival for our patients was 89.2% ± 7.2%. The regimen was well tolerated; hemorrhagic cystitis occurred in 7 patients, and severe mucositis occurred in 5 patients. There were 2 deaths; the primary cause of death was severe GVHD in 1 patient and leukemia recurrence in the other. We conclude that in patients with FA lacking a matched related donor, the use of mismatched related HCT with low-dose PT-CY is a viable option; it is well tolerated, with a high rate of engraftment and an acceptable incidence of GVHD.

INTRODUCTION

Fanconi anemia (FA) is relatively more common in the Kingdom of Saudi Arabia than elsewhere worldwide, due mainly to a high rate of consanguinity and interrelated marriages. FA is an autosomal recessive disorder belonging to the group of chromosomal instability syndromes [1-3]. Clinically, FA is characterized by congenital malformations, progressive marrow failure, and a predisposition to acute myelogenous leukemia and solid tumors [4-7]. Hematopoietic stem cell transplantation (HCT) remains the sole modality with the potential to restore normal hematopoiesis in these patients [8-11]. Although HCT from an HLA-matched related donor has been categorically associated with excellent outcomes in many patients, a higher incidence of treatment failure has been reported in recipients of unrelated donor HCT [11-14]. In recent years, haploidentical T cell-replete HCT with post-transplant cyclophosphamide (PT-CY) has become a valid alternative transplantation strategy for patients with both malignant and nonmalignant disorders who do not have a fully HLA-matched donor [15-19].

Patients with FA are a particularly suitable group for this modality, because without HCT, the prognosis is extremely poor because of the aggravated severity of the bone marrow failure with age and the increased incidence of leukemia; However, the DNA repair defects in these patients render them extremely sensitive to alkylating agents, and thus the PT-CY dose must be modified to reduce the risk of toxicity. Data on this approach in this patient population are still emerging. Here we report the results for 19 patients with FA who underwent HCT and were treated with reduced doses of PT-CY.

METHODS

Study Design

The study cohort comprised all patients with FA who underwent related mismatched donor HCT at King Faisal Specialist Hospital and Research Center (KFSH&RC) between January 2012 and June 2018. Clinical and laboratory data were prospectively collected from the KFSH&RC database. All patients and/or

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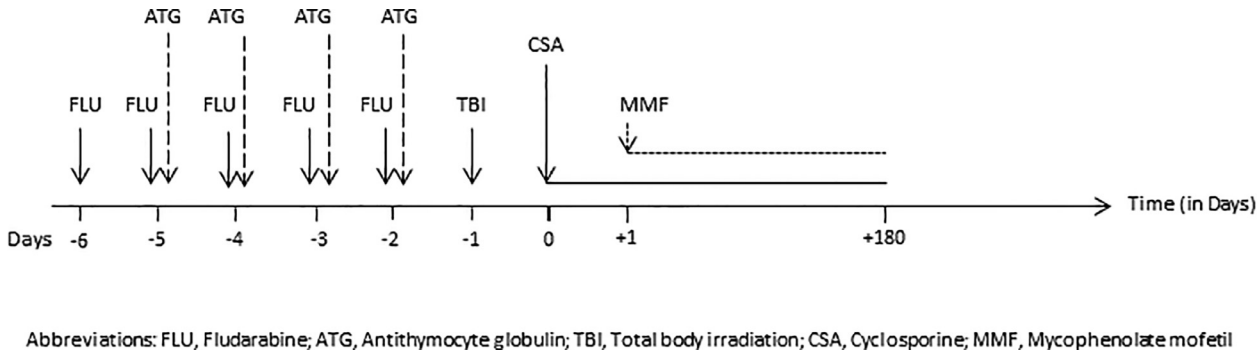

Figure 1. Conditioning regimen. FLU, fludarabine; CSA, cyclosporine.

their guardians provided signed informed consent. The study was approved by the KFSH&RC Research Advisory Committee (approval no. 2101048).

Patients

Patients with FA who had evidence of progressive bone marrow failure and were blood product-transfusion dependent (packed red blood cells and/or platelets) and patients with myelodysplastic syndrome and/or an abnormal clone or evidence of acute leukemia who required allogeneic HCT and did not have a full HLA-matched related donor were eligible. All patients had normal renal and cardiac function at the time of transplantation.

Transplantation Procedure

All patients received a conditioning regimen containing fludarabine 30 mg/m^2/day for 5 days given on days -6, -5, -4, -3, and -2; antithymocyte globulins (Fresenius, ATG) 5 mg/kg/day for 4 days given on days -5, -4, -3, and -2; and a single 200-cGy fraction of total body irradiation (TBI) on day -1. Graft-versus-host disease (GVHD) prophylaxis was provided with cyclosporine from day 0, mycophenolate from day +1, and PT-CY 25 mg/kg on days +3 and +5 (Figure 1). One patients received a modified PT-CY dose of 20 mg/kg on days +3 and +5. The donor was the father in 10 recipients, the mother in 3 recipients, a brother in 4 recipients, and a sister in 2 recipients. All donors were partially HLA-mismatched with the recipients; 12 were haploidentically mismatched, 5 were 2-antigen mismatched in 1 class I locus and HLA-DRB1, and 2 were 1 antigen mismatched in HLA-DRB1 only. The stem cell source was bone marrow in 17 patients and peripheral blood in 2 patients, and the median CD34 dose was 6.4×10^6/kg of recipient weight (range, 2.58 to 48.4×10^6/kg).

Patients were hospitalized in single rooms with high-efficiency particulate air filtration with positive pressure until neutrophil recovery. Patients received acyclovir prophylaxis if they were seropositive for herpes simplex virus and/or cytomegalovirus (CMV). Oral trimethoprim-sulfamethoxazole was given for *Pneumocystis* prophylaxis after engraftment for 1 year. Broad-spectrum i.v. antibacterial and antifungal and/or antiviral antimicrobials were administered for fevers as indicated. All patients received granulocyte colony-stimulating factor 5 μg/kg/day s.c., from the day after HCT until neutrophil recovery. CMV reactivation was monitored weekly until at least day 100 post-transplantation and preemptively treated with ganciclovir or foscarnet. No prophylactic rituximab was given.

Endpoint Definitions

The time to neutrophil recovery was defined as the first of 3 consecutive days on which the absolute neutrophil count (ANC) was $\geq .5 \times 10^9$/L. Primary graft failure was defined as failure to achieve an ANC of $.5 \times 10^9$/L by day 42, and secondary graft failure was defined as an ANC $< .5 \times 10^9$/L for 3 consecutive days or 0% donor chimerism by PCR in patients who have achieved an ANC $\geq .5 \times 10^9$/L. Time to platelet recovery was the first of 3 consecutive days on which the platelet count was $> 20 \times 10^9$/L without transfusions for 7 days before the first measurement. GVHD was graded by standard criteria. Acute leukemia relapse was disease recurrence and supported by cytogenetic and molecular analyses. Survival was defined as the time from HCT to death from any cause.

Statistical Considerations

All continuous data are presented as median with range and mean ± SD as appropriate, and discrete data are provided as number and percentage. Kaplan-Meier survival analysis was used to draw the overall survival curve for our cohort.

RESULTS

A total of 19 patients with FA aged ≤14 years (13 females; 68.4%) who underwent mismatched unmanipulated related HCT at KFSH&RC were prospectively enrolled in this study. The median age at HCT was 9.1 years (Table 1). Eighteen patients underwent HCT because of pancytopenia and had no evidence of myelodysplasia on the pre-HCT cytogenetic analysis of bone marrow, although 2 of them had +3q and 1 had 11q23. One patient had acute lymphoblastic leukemia with 21q22 and was treated with a 3-drug induction regimen (vincristine, L-asparaginase, and methylprednisolone); he went in remission and then underwent HCT.

Engraftment/Chimerism

ANC recovery occurred in all patients, at a median of 14 days (range, 10 to 19 days), while platelet transfusion independence occurred in 18 patients, at a median of 20.5 days (range, 16 to 112 days). At the last follow-up visit, 18 patients had 100% donor chimerism and 1 patient had 97% chimerism (lymphocytes).

GVHD

The cumulative incidence of acute GVHD (aGVHD) was 42.1% (8 patients). Five patients had grade I-II aGVHD (skin, n = 3; liver/gut, n = 2), and 3 had grade III-IV aGVHD (skin, n = 2; liver, n = 1; gut, n = 1). All 8 patients were treated with steroids

Table 1
Patient Characteristics and Transplantation-Related Parameters (N = 19)

Parameter	Value
Age at HCT, yr	
Median (range)	9.1 (2.8-12.3)
Mean ± SD	8.6 ± 2.8
Sex, n (%)	
Male	6 (31.6)
Female	13 (68.4)
CD34 cell count, $\times 10^6$ per kg, median	6.4
Stem cell source, n (%)	
Bone marrow	17 (89.5)
PBSCs	2 (10.5)
Donor, n (%)	
Father	10 (52.6)
Mother	3 (15.8)
Brother	4 (21.1)
Sister	2 (10.5)
Time to ANC recovery, d, median	14
Time to platelet recovery, d, median	20.5
Survival status, n (%)	
Alive	17 (89.5)
Deceased	2 (10.5)
Follow-up, mo from infusion, median	38.3
95% confidence interval	27.0-49.6

PBSCs, peripheral blood stem cells.

and responded, except 1 patient who progressed into severe hemorrhagic gut GVHD and died. Extensive chronic GVHD (cGVHD) occurred in only 1 patient (5.3%) with skin and gut involvement; she received a prolonged course of steroid therapy in addition to cyclosporine and mycophenolate mofetil (MMF) and was in remission at the time of this report.

Regimen-Related Toxicity

Hemorrhagic cystitis occurred in 7 patients (36.8%), and BK virus was detected in 4 of them. In 1 patient, the BK-associated hemorrhagic cystitis was associated with BK nephritis and led to long-term renal impairment; the others recovered after conservative treatment. CMV infection developed in 17 patients (89.5%), with a median time to infection of 41 days (range, 26 to 253 days). Two of these 17 patients died, 1 within .7 month and the other within 2.6 months of the PCR-documented infection. CMV was not the primary cause of death in either of these patients. Epstein-Barr virus reactivation occurred in 3 patients. Severe mucositis (grade ≥III) developed in 5 patients (26.3%) and resolved on ANC recovery. One patient developed sinusoidal obstruction syndrome that was successfully treated with defibrotide.

Immune Recovery

Immune reconstitution data were available for 9 of the 17 surviving patients. Normal T cell function (phytohemagglutinin proliferation) and CD3 count recovery were documented in all 9 patients at 18 months post-HCT.

Survival

At a median follow-up of 38.3 ± 5.8 months, the cumulative probability of overall survival at 5 years for our cohort was 89.2 ± 7.2% (Figure 2). At the time of this report, 17 patients (89.5%) were alive with normal hematopoiesis.

Secondary Malignancy

None of the surviving patients developed a secondary malignancy during the follow-up period.

Causes of Death

One death, due to severe GVHD, occurred within 100 days from the day of transplantation (100 day-mortality of 5%). Another death was due to recurrence of leukemia at 5 months from the date of HCT.

DISCUSSION

HCT in patients with FA is particularly challenging due to these patients' underlying DNA repair defects that render them more susceptible to chemotherapy and radiation toxicity [20,21]. However, the last 2 to 3 decades have seen a revolutionary shift in the understanding of the underlying pathophysiology of FA,

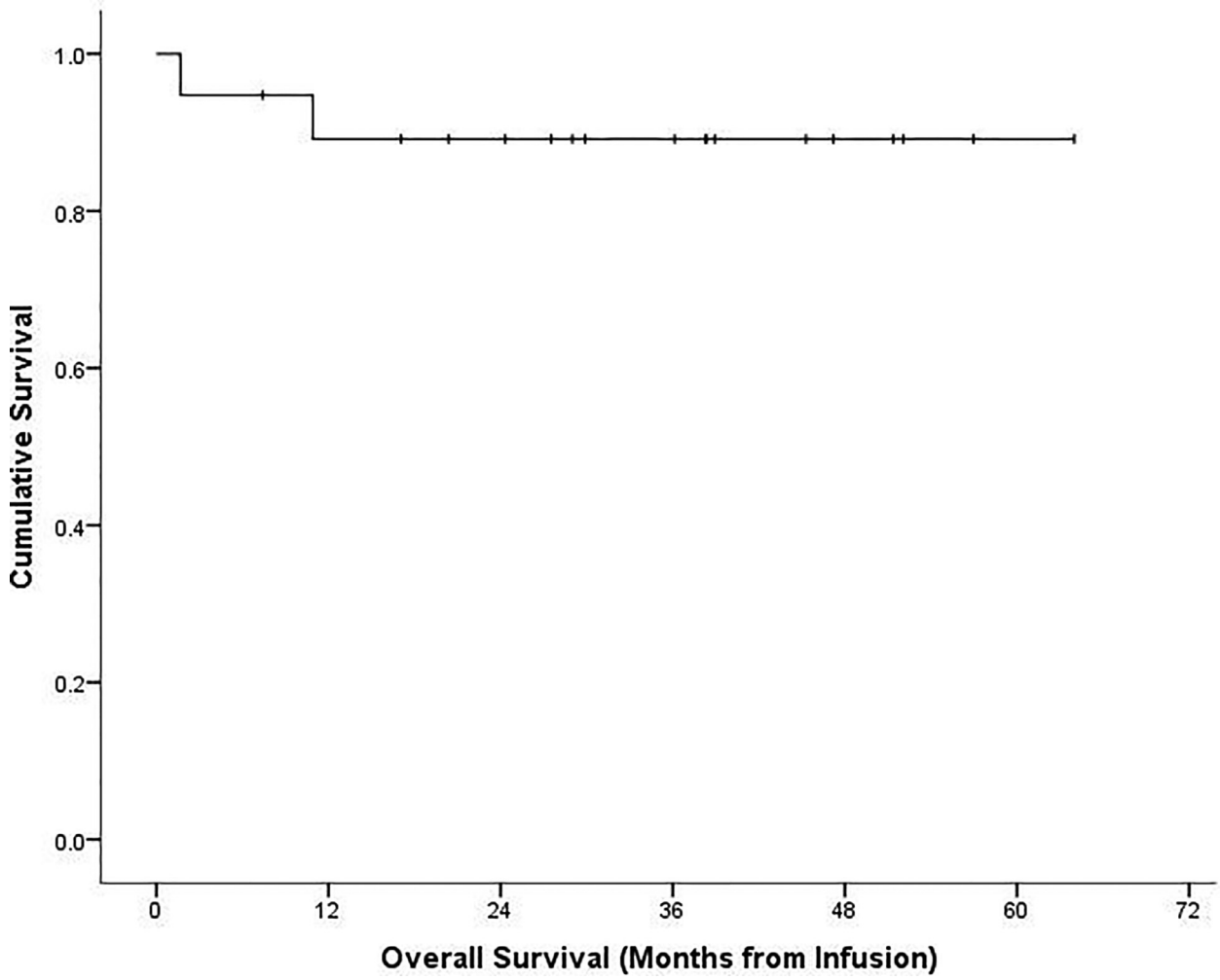

Figure 2. Overall survival.

resulting in a marked reduction in the doses of agents used in HCT preparatory regimens [1-3,8-11]. The use of low-dose cyclophosphamide and, more recently, the introduction of fludarabine have radically improved HCT outcomes in patients with FA. HCT from an HLA-matched related donor is now known to restore normal hematopoiesis in many patients, with excellent long-term survival [9-11,22-24].

On the other hand, initial results of alternative donor transplantation from matched unrelated donors in patients with FA were less encouraging [12], and unrelated cord blood transplant results were equally discouraging [13]. Our own experience at KFSH&RC with unrelated cord blood transplantation in patients with FA is comparable to the published literature [11,14]; however, more favorable results for unrelated donor HCT in these patients have been reported recently [25].

In recent years, haploidentical HCT has become a valid alternative transplantation strategy for patients with malignant or nonmalignant disorders without an HLA-matched donor with T cell depletion in vivo or ex vivo [15-19,26,27]. In patients with FA, evidence of the feasibility of the use of haploidentical donors has been gradually mounting [28-36]. Zecca et al [33] reported the outcomes of 12 consecutive pediatric patients with FA who were given T cell-depleted, $CD34^+$ positively selected cells from a haploidentical related donor after a reduced-intensity fludarabine-based conditioning regimen. Engraftment was achieved in 9 of 12 patients (75%), and the cumulative incidence of graft rejection was 17%. The cumulative incidences of grade II-IV aGVHD and cGVHD were 17% and 35%, respectively, and the 5-year overall survival, event-free survival, and disease-free survival were 83%, 67%, and 83%, respectively. Similarly, Mehta et al [34] reported excellent outcomes in 45 patients with FA who underwent a radiation-free conditioning regimen with a T cell-depleted graft; the median age was 8.2 years, and the regimen included busulfan, cyclophosphamide, fludarabine, and rabbit ATG. Donors were matched unrelated in 25 patients, mismatched unrelated in 14, and mismatched related in 6. The 1-year probabilities of overall and disease-free survival for the entire cohort were 80 $\pm$ 6% and 77.7 $\pm$ 6.2%, respectively. The median duration of follow-up was 41 months, and no patient developed grade II-IV aGVHD.

Several published studies have also addressed the use of T cell-replete peripheral blood or bone marrow from haploidentical donors as a stem cell source patients with nonmalignant disorders and reported favorable outcomes using GVHD prophylaxis consisting of high-dose PT-CY), tacrolimus, and MMF [15-17,37,38]. A high rate of stable engraftment together with a low risk of GVHD have been documented. Klein et al [17] evaluated 11 pediatric patients with life-threatening nonmalignant conditions who underwent HCT using reduced-intensity conditioning, alternative donors, and PT-CY alone or in combination with tacrolimus and MMF and reported favorable outcomes, with limited GVHD and no treatment-related mortality.

Despite the success of the PT-CY regimen using 2 doses of 50 mg/kg on days +3 and +5 after HCT in patients without FA, concerns that high dose alkylating agents in FA patients may be associated with increased toxicity and potential mortality must be addressed; on the other hand, however, lower doses of PT-CY may lead to increased risk of GVHD. Therefore, until recently, the optimal dose of PT-CY in patients with FA was undetermined. Klein et al [17] gave 2 patients with dyskeratosis congenita undergoing T cell-replete haploidentical HCT PT-CY 50 mg/kg on day +3 only, and both patients engrafted with no GVHD. Thakar et al [31,39] developed a protocol for patients with FA with PT-CY using a conditioning regimen of CY 10 mg/kg, fludarabine 150 mg/m^2, and TBI 200 cGy. PT-CY was delivered in 2 doses on days +3 and +4 at 25 mg/kg/dose, with no ATG. In their series, all 6 patients with FA engrafted; 4 survived long-term with 100% donor chimerism and excellent performance status, and the 2 who died had multiple comorbidities and late referral.

On a larger scale, Bonfim et al [40] reported on 30 patients with FA, also using fludarabine 150 mg/m^2 plus TBI 200 to 300 cGy with or without CY 10 mg/kg and with or without rabbit ATG. Twenty-six patients underwent HCT upfront, and 4 patients were rescued after primary or secondary graft failure after related or unrelated donor transplantation; all received PT-CY at 25 mg/kg/day on days +3 and +5, along with cyclosporine and MMF. Fourteen patients did not receive ATG; they engrafted, but their course was complicated by high rates of aGVHD and cGVHD, and 8 of them were alive at the time of the report. The remaining 16 patients received ATG; 14 of them had sustained engraftment, with a lower rate of severe GVHD, and 13 were alive at the time of the report. Hemorrhagic cystitis occurred in 50% of the patients, and CMV reactivation occurred in 75%. One-year overall survival for the entire cohort was 73% [40].

At KFSH&RC, we adopted a similar approach in 2012 for our patients with FA and report here a relatively large number of patients treated with a uniform regimen at a single institution. We used fludarabine and TBI for conditioning and PT-CY. None of our patients received CY pre-HCT, which did not appear to affect engraftment, suggesting that the use of CY pre-HCT is not necessary for engraftment. All patients received ATG, which could have contributed to the lower incidence of severe GVHD. The use of ATG reflects a form of in vivo T cell depletion, which concomitantly depletes host T cells that survive the conditioning regimen and reduces the risk of rejection while depleting newly infused donor T cells, thereby potentially reducing GVHD [41]. In this study, we used the same low-dose PT-CY regimen for GVHD prophylaxis as has been reported for patients with FA, but we continued immunosuppressive therapy with cyclosporine and MMF for 6 months and then tapered it gradually in those without active GVHD. Based on our results, we recommend this strategy. Of note, we tried a lower dose of PT-CY in 1 patient; she received CY 20 mg/kg on days +3 and +5 but developed severe GVHD of the skin and gut. At the time of this report, she was well with full engraftment, but given the good results with PT-CY 25 mg/kg on days +3 and +5, we have not adopted, nor do we recommend, this reduction. Toxicity was acceptable in our study; concerns have been raised about an increased incidence of hemorrhagic cystitis after haploidentical HCT [42]. Theoretically, the risk of hemorrhagic cystitis also may be higher post-HCT in patients with FA; we report here an incidence of 36.8% in comparison to the 50% incidence reported by Bonfim et al [40]. In 4 of our patients, it appeared to be associated with BK virus. CMV infection developed in the majority of our patients (n = 17; 89.5%); the 2 patients who died had CMV infection, but it was not the cause of death in either patient. In all other patients, CMV infection resolved with therapy. The severe immunosuppression necessary for the procedure most likely contributed to this high incidence of CMV and BK infection.

In summary, our report further corroborates the strategy of using T cell-replete related mismatched and haploidentical HCT for patients with FA who have no suitable matched related donor, appearing to be associated with very favorable outcomes and tolerable toxicity. Furthermore, the fact that reduced CY doses in this patient population who received stem cells from donors without FA are associated with favorable outcomes suggest that this dosing of CY might also be considered even in patients without FA.

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