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Fludarabine-Based Reduced Intensity Conditioning for Stem Cell Transplantation of Fanconi Anemia Patients from Fully Matched Related and Unrelated Donors

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ABSTRACT

Reduced intensity conditioning has been suggested as a desirable therapeutic modality for the treatment of patients with malignant and nonmalignant indications, but it seems particularly attractive for patients with Fanconi anemia due to their increased sensitivity to chemoradiotherapy. Between November 1996 and September 2003, 7 patients (1 male and 6 female; age range, 3-31 years; median age, 9.5) were conditioned with a fludarabine-based protocol for stem cell transplantation without radiation. In vivo T-cell depletion was accomplished with anti-thymocytic globulin or Campath-1H (alemtuzumab). Graft-versus-host disease prophylaxis consisted of low-dose cyclosporine alone. Eight transplantations were carried out for 7 patients using bone marrow, peripheral blood, and/or cord blood as sources of stem cells. All patients received transplants from HLA-A, -B, -C, and -DR matched donors, 5 from family members and 2 from matched unrelated donors. One patient did not engraft her first matched unrelated donor and underwent a second transplantation from another matched unrelated donor, after which she engrafted well. All 7 patients are alive and well, fully reconstituted with donor cells, and with 100% performance status. In conclusion, fludarabine-based preparative protocols are well tolerated, facilitate rapid engraftment with minimal toxicity, and should be considered an essential component of choice for patients with Fanconi anemia.

KEY WORDS

Fanconi anemia • Reduced intensity conditioning • Stem cell transplantation • Fludarabine

INTRODUCTION

Fanconi anemia is an autosomal recessive disorder associated with congenital malformations, progressive marrow failure, and predisposition to acute myelogenous leukemia (AML) and other malignancies [1]. The syndrome is defined by genomic instability and cellular hypersensitivity to DNA cross-linking agents [2,3]. This hypersensitivity serves as a diagnostic test (using agents such as diepoxybutane) and allows diagnosis of Fanconi anemia in cases of subtle clinical features or no detectable congenital abnormalities [4]. Complementation studies have shown that there are ≥8 separate Fanconi anemia complementation groups, and the genes responsible for the defects in each group (A through G including D1 and D2) have been identified [5,6].

Stem cell transplantation (SCT) is the treatment of choice for Fanconi anemia patients with severe hematologic manifestations. Unfortunately, most probably due to their high chromosomal fragility, Fanconi anemia patients are very sensitive to conventional conditioning protocols. Since the early 1980s, when it was demonstrated by the Paris group [7,8], chemotherapy, especially alkylating agents and ionizing radiation, has been associated with a high incidence of transplantation-related toxicity and mortality [9]. Over the years, many transplantation centers have

used radiation as an integral part of conditioning to sidestep the use of chemotherapy. However, radiation is also associated with short- and long-term toxicities and possibly with an increased risk of secondary leukemia, to which Fanconi anemia patients are especially prone [10].

Reduced intensity conditioning (RIC) for SCT pioneered at our center for the treatment of malignant and nonmalignant disorders [11] and in other centers for high-risk patients with hematologic malignancies [12] constitutes a safer approach for hematologic reconstitution. These regimens are based on RIC that focuses on a window of immunosuppression for prevention of rejection of donor stem cells, thereby improving immediate and long-term transplantation outcomes by preventing or minimizing procedure-related toxicity and mortality. The well-known advantages of RIC based on cumulative experience in patients with malignant diseases are related to patients' general feeling of well-being throughout the procedure, independence from hyperalimentation, and low incidence of common immediate complications such as mucositis and fever due to intercurrent infections because of a shorter or no period of agranulocytosis and platelet dependence, and lesser risk of severe veno-occlusive disease of the liver, interstitial pneumonitis, and multiorgan failure resulting from combination of some or all of the above. The main component of most of these new conditioning regimens is fludarabine, a potent yet well-tolerated immunosuppressive agent [11,12].

With the expanding use of RIC for patients with malignant diseases, it seemed reasonable to apply a similar conditioning for nonmalignant diseases, particularly in patients known to be highly sensitive to chemotherapy or ionizing radiation, such as those with Fanconi anemia. Over the past few years, after our initial report [13], the use of fludarabine-based regimens for transplantation in patients with Fanconi anemia has become well established [14-21], and aspects are currently being raised regarding the use of cord blood as the source of stem cells [15,16], T-cell–depleted versus non–T-cell–depleted graft [17-19], or the relevance of including radiation in the preparative regimen [19-21]

Seven years ago, we published our first case of fludarabine-based RIC in a Fanconi anemia patient [13]. In this report, we summarize our cumulative experience in transplanting patients with Fanconi anemia from fully matched related or unrelated donors, using fludarabine-based conditioning regimens.

METHODS

Seven patients with Fanconi anemia (1 male and 6 female; age range, 3-31 years; median age, 9.5 years) underwent 8 SCT procedures. Four patients had organ malformations and marrow failure (Table 1). Percentages of marrow blasts at the time of transplantation are listed in Table 1. Four patients had aplastic anemia, 1 patient (who underwent 2 transplantations) had myelodysplastic syndrome, and 2 demonstrated transformation to AML. These 2 patients developed AML features shortly before, did not receive any antileukemia treatment, and were sent immediately for transplantation. Six patients received transfusions before transplantation. Of these, 5 received <10 U of packed red blood cells and 1 (UPN 1202) was heavily pretransfused with >40 U of packed red blood cells before transplantation. All patients received androgens at the period between diagnosis and admission for transplantation. Karnofsky performance status scores ranged from 90 to 100. Patients were referred to the Hadassah University Hospital for SCT between November 1996 and September 2003. Each participant signed an approved informed consent form and the protocol was approved by the institutional review board. All patients received transplants from HLA-A, -B, -C and high-resolution DRB1 fully matched donors; for patients who received transplants from unrelated donors, high-resolution DQ was also tested. Five patients received transplants from family members, and 2 from matched unrelated donors (MUDs;

Table 1. *Characteristics of Patients Who Underwent Fully Matched RIC With Fludarabine-Based Conditioning Regimens**

UPN	Age (y)	Organ Abnormal	Recipient	Donor	Donor/Recipient Relationship	Hematologic Status and Marrow Blasts (%) at Transplantation	Stem Cell Source
1114	10	No	F	M	Cousin	AML (20%)	BM
1202	12	Yes	F	F	Sibling	AA (0%)	CB
1420	10	Yes	F	F	Mother	AA (0%)	PB
1535	31	Yes	F	F	Sibling	AML (20%)	PB
1548	3	No	F	F	Unrelated	MDS (18%)	BM
1548a	3	No	F	M	Unrelated	MDS (18%)	BM
1698	9	Yes	M	M	Unrelated	AA (0%)	BM
1853	9	No	F	F	Sibling	AA (0%)	BM + CB

*UPN indicates unique patient number; F, female; M, male; AML, acute-myeloid leukemia; MDS, myelodysplastic syndrome; AA, aplastic anemia; BM, bone marrow; PB, peripheral blood; CB, cord blood.

Table 2. *Pretransplantation Conditioning Regimens Based on Fludarabine for Transplantation of Fanconi Anemia Patients**

Conditioning	Procedures, n	UPNs of Patients Transplanted with this Protocol
IV fludarabine 30 mg · m^{-2} · d^{-1} × 6 d; IV cyclophosphamide 5 mg · kg^{-1} · d^{-1} × 2 d; IV antithymocytic globulin† 10 mg · kg^{-1} · d^{-1} × 4 d	5	1114, 1202, 1420, 1535, 1548
IV fludarabine 30 mg · m^{-2} · d^{-1} × 6 d; IV busulfex 3.2 mg · kg^{-1} · d^{-1} × 2 d, alemtuzumab 5, 10, 20, 40 mg SC on days −4 to −1	1	1548a
IV fludarabine 30 mg · m^{-2} · d^{-1} × 6 d; IV cyclophosphamide 5 mg · kg^{-1} · d^{-1} × 2 d; IV busulfex 3.2mg/kg/day × 2 d; antithymocytic globulin† 10 mg · kg^{-1} · d^{-1} × 4 d	1	1698
IV fludarabine 30 mg · m^{-2} · d^{-1} × 6 d; IV cyclophosphamide 5 mg · kg^{-1} · d^{-1} × 1 d; IV busulfex 3.2 mg · kg^{-1} · d^{-1} × 2d; antithymocytic globulin†, 10 mg · kg^{-1} · d^{-1} × 4 d	1	1853‡
Total procedures	8	

*IV indicates intravenous; SC, subcutaneous; UPN, unique patient number.

†From Fresenius (Grafelfing, Germany).

‡This patient received only 1 dose of cyclophosphamide due to kidney dysfunction that developed in the days of conditioning. The dysfunction resolved spontaneously couple of days thereafter.

including 1 patient who underwent 2 procedures from different MUDs; Table 1).

Pretransplantation conditioning of all patients contained fludarabine plus other drugs, as indicated in Table 2. Five donors underwent bone marrow-derived stem cell harvesting in the operating room under full anesthesia on the day of transplantation. Two donors were injected subcutaneously with granulocyte colony-stimulating factor (G-Neupogen; Amgen AG, Lucerne, Switzerland), 5 μg/kg twice daily for 5 days, and mobilized peripheral blood stem cells were collected on days 5 and 6. Two donors donated cord blood stem cells and 1 of these also donated bone marrow-derived stem cells (this donor is also among the 5 bone marrow donors mentioned above). Details of the inocula are presented in Table 3.

Before transplantation, all patients received trimethoprim-sulfamethoxazole (10 mg · kg^{-1} · d^{-1}) on days −8 to −2, acyclovir (500 mg/m^2 3 times daily)

Table 3. *Graft Characteristics and Outcomes of Fanconi Anemia Patients**

UPN	Stem Cell Source	Nucleated Cells (10^8/kg)	$CD34^+$ Cells (10^6/kg)	$CD3^+$ T Cells (10^8/kg)	Days to ANC >0.5 × 10^9/L	Days to PLT >20 × 10^9/L	Place of Acute GVHD (Grade)	Chronic GVHD	Toxicity	Chimerism (Follow-up in Months After Transplantation)
1114	BM	4.8	34.08	Not available	12	19	No	No	Mild VOD, acute renal failure	Donor by amelogenine (96)
1202	CB	2 × 10^7	1 × 10^5	Not achieved	37	56	No	Mild	Mild VOD	Donor by VNTR (87)
1420	PB	43.0	25.7	10.8	11	9	No	No	No	Donor by VNTR (65)
1535	PB	37.7	24.6	13.6	15	12	Skin (II)	Extensive	Mild VOD, brain abscess	Donor by VNTR (50)
1548	BM	13.4	7.63	1.32	40	NA	No	No	No	Host by VNTR (49)
1548a	BM	6.66	1.79	0.37	13	19	No	No	No	Donor by amelogenine (45)
1698	BM	6.15	39.9	4.92	26	24	Skin (II)	Mild	No	Donor by VNTR (29)
1853	BM + CB	BM: 1.77 CB: 0.15	BM: 1.42 CB: 0.02	BM: 0.08 CB: 0.01	32	28	No	No	No	Donor by VNTR (14)

*UPN indicates unique patient number; BM, bone marrow; CB, cord blood; PB, peripheral blood; ANC, absolute neutrophil count; PLT, platelet count; VOD, veno-occlusive disease; VNTR, variable number of tandem repeats.

from day −8 to day +100, and allopurinol (300 mg/d) on days −8 to −1. Administration of trimethoprim-sulfamethoxazole twice weekly was resumed after recovery from neutropenia as a preventive measure against *Pneumocystis carinii* infection. Graft-versus-host disease (GVHD) prophylaxis consisted of low-dose cyclosporine (CSA) 3 mg/kg intravenously daily in 2 divided doses starting on day −4. Once patients were mobile, CSA was administered orally. CSA dosage was tapered during the fifth or sixth month after transplantation according to chimeric status and evidence of GVHD.

Neutropenic patients with culture-negative fever received a combination of gentamicin, cefazolin, and mezlocillin or piperacillin as a first-line antibiotic protocol. Persisting fever was treated with amikacin and Tazocin as a second-line protocol, and meropenem and vancomycin were used as a third-line protocol. In cases of persistent fever that did not respond to antibiotic therapy within 5 days, amphotericin B (1 mg/kg every other day) was added until the neutropenia resolved.

As of day −8, patients were monitored with a DNA polymerase chain reaction (PCR) test to detect cytomegalovirus; later in the study period, when pp65 antigenemia was introduced, this test was carried out on a weekly basis. Two consecutive positive PCR results or 1 documented antigenemia test with >1 cell positive for pp65 served as an indication for replacing acyclovir with ganciclovir, 10 mg $\cdot$ kg^{-1} $\cdot$ d^{-1}, until ≥2 negative tests were obtained. Patients were treated with reverse isolation in rooms equipped with HEPA filters, and they received a regular diet. Additional supportive measures, such as parenteral nutrition and blood component transfusions, were administered as necessary.

Acute and chronic GVHD were graded according to criteria of Glucksberg et al [22]. Immediately after the appearance of GVHD symptoms, intravenous methylprednisolone (2 mg/kg) and CSA were administered.

To assess engraftment, degree of chimerism, minimal residual disease, and early relapse, patients were monitored at regular intervals by cytogenetic analysis, donor- and host-specific DNA markers using male and female amelogenin gene PCR bands [23], and by variable number of tandem repeats/PCR assay [24].

RESULTS

All 7 patients were alive, well, and free of disease 19 to 101 months after transplantation. Seven patients underwent 8 allogeneic transplantation procedures (patient UPN 1548 received 2 transplants). RIC protocols were well tolerated. No severe hepatic veno-occlusive disease (VOD) occurred in any patient. Mild to moderate VOD was documented in 3 of 8 procedures and subsided with hydration (3000-4000 mL $\cdot$ m^{-2} $\cdot$ d^{-1}) combined with diuresis. No VOD episode caused further complications. All patients developed fever, with a median of 1 febrile episode (range, 1-2) and a median of 6 febrile days (range, 3-14). Oral mucositis was mild, and only 50% of patients required supplemental parenteral nutrition for a median of 11 days (range, 9-26). During the other 4 procedures, patients were maintained on normal oral intake.

Engraftment

Six patients displayed evidence of stable 3-lineage engraftment. One patient (UPN 1548), a recipient of a MUD transplant, exhibited immune-mediated graft rejection and immediately underwent a second transplantation from another MUD; engraftment of this donation occurred 13 days later.

The lowest white blood cell count was .1 × 10^9/L (range, .1-.2). Recovery of absolute neutrophil counts ≥.5 and ≥1.0 × 10^9/L took 11-40 days (median, 20.5) and 12-40 days (median, 27.5), respectively. The lowest platelet count was 7 × 10^9/L (range, 2-10). Intervals to platelet recovery (≥20 and ≥50 × 10^9/L) were 9-56 days (median, 19) and 11-67 days (median, 35), respectively. Median number of packed red cell transfusions was 4.5 U (range, 2-14) and median platelet transfusions from single and random donors was 13.5 U (range, 2-107).

Transplant-Related Morbidity and Mortality

There was no severe transplant-related toxicity and no mortality.

Transplant-related complications occurred in the course of 2 of 8 (25%) procedures and consisted of 1 case of brain abscess and 1 case of acute renal failure. In the case of brain abscess (UPN 1535), the presenting sign was grand-mal seizure followed by fever. Computed tomography showed a focal lesion in the left parieto-occipital hemisphere of the cerebrum. Lumber puncture done after excluding hazardous high intracranial pressure and/or pending herniation revealed a high protein level and a large number of inflammatory cells. Culture of this specimen grew *Aspergillus*. The pathologic lesion was then stereotactically biopsied and showed a granulomatotic process compatible with *Aspergillus* infection. The patient was treated with intravenous liposomal amphotericin, with good response. In the case of renal failure (UPN 1114), this patient did not have renal problems before transplantation and was treated by hydration (3000-4000 mL $\cdot$ m^{-2} $\cdot$ d^{-1}) and holding any possible nephrotoxic drug (acyclovir and CSA) until renal function was improved. Both conditions subsided without any long-term deficit.

Infectious episodes that occurred from the day of transplantation and up to 1 year after transplantation

Table 4. *Infectious Episodes in Fanconi Anemia Patients up to One Year After Transplantation**

UPN	Days After Transplantation	Site of Infection	Name of Causative Strain	Treatment
1114	None	NR	NR	NR
1202	None	NR	NR	NR
1420	None	NR	NR	NR
1535	+10	Brain	*Aspergillus*	Liposomal amphotericin
	+127	Palate	Herpes simplex	Acyclovir
1548	+7	Blood	*Staphylococcus* coagulase negative	Antibiotic protocols†
1548a	+6	Blood	*Pseudomonas aeruginosa*	Antibiotic protocols†
1698	+60	Throat	*Candida albicans*	Fluconazole
1853	None	NR	NR	NR

*UPN indicates unique patient number; None, no infection occurred until 1 year after transplantation; NR, no relevance due to no occurrence of infection.
†See Methods section.

are presented in Table 4. No reactivation of cytomegalovirus was seen in patients during their hospital stay. All patients were discharged for continuing outpatient treatment after a median hospital stay of 48.5 days (range, 23-77). They continue to be followed on an ambulatory basis. The median follow-up period to date is 49.5 months (range, 14-96).

Incidence and Severity of GVHD

No patient developed severe (grade III-IV) acute GVHD. Two patients developed mild (grade II) acute GVHD, which later progressed to mild chronic GVHD. The first patient (UPN 1535) had grade II skin involvement that started at day +62 after transplantation. It was treated by CSA and corticosteroids but progressed to extensive chronic GVHD with skin, mouth leukoplakia, and liver involvements. After corticosteroidal treatment, all involved areas stabilized and improved but did not completely resolve. The other patient (UPN 1698) also developed grade II skin involvement that started on day +28 after transplantation. As with the first patient, he was treated with combination of CSA and corticosteroids but progressed to limited chronic GVHD that affected his skin. This was treated with corticosteroids and resolved completely. One patient (UPN 1202) developed limited de novo chronic GVHD with liver involvement. She was treated with corticosteroids and had a good response, with complete resolution of the event.

DISCUSSION

Fanconi anemia is a systemic disease that is frequently associated with congenital malformations, severe progressive stem cell failure, and high incidence of leukemia. Allogeneic SCT is the only known curative procedure for hematologic abnormalities. To circumvent short- and long-term procedure-related risks, particularly in patients with Fanconi anemia, it is imperative to minimize or prevent peri- and post-transplantation morbidity resulting from alkylating chemotherapy and ionizing radiations. Nevertheless, many yet unknown parameters may play a role in the survival of such patients. Thus, it seems that Fanconi anemia patients reconstituted with matched sibling-derived stem cells are doing much better in terms of survival after transplantation compared with patients engrafted from alternative, unrelated donors [25]. Based on our first reported case [13], it seemed that fludarabine-based protocols may be particularly suitable for improving dramatically the outcome of Fanconi anemia patients in need of SCT. As anticipated, the fludarabine-based transplantation procedures used appeared to be much better tolerated and all patients are alive with excellent performance status. This holds true regardless of the recipient-donor relations. The group of patients presented is somewhat heterogeneous in terms of conditioning regimens, but the heterogeneity of the protocols, with fludarabine as the single unchanged medication, emphasizes its pivotal role in ensuring a safe engraftment in this cohort of patients. Only 1 patient with a MUD transplant rejected the graft but her second transplantation from another MUD, after additional conditioning, was successful. She did not undergo heavy pretransfusion before the first transplantation, had 18% blasts in bone marrow with myelodysplastic syndrome features, and was treated with CSA 3 mg/kg from day −4, which was continued after transplantation as the sole anti-GVHD prophylaxis after transplantation of bone marrow-derived stem cells. A safe and uneventful outcome after the second transplantation is additional evidence of the excellent tolerability of the first fludarabine-based transplantation procedure. The second recipient of SCT from a MUD had successful outcome after using the modified RIC protocol that was used for the first MUD recipient.

In contrast to previously used regimens [26], the successful protocols described in this report, which

avoided the use of radiation and/or high-dose alkylating agents, may decrease not only the immediate risks of transplantation but also the long-term risk of secondary malignancies caused by chromosomal instability. Neither HLA alloimmunization, due to multiple transfusions of blood products, nor previous treatment with androgens [27] compromised engraftment in our patients.

As in the use of RIC regimens in patients without Fanconi anemia, all patients experienced a relatively easy and uneventful course of hospitalization that was marked by a low incidence of fever, minimal requirement for hyperalimentation, and a low incidence of acute GVHD. However, time to engraftment was mildly prolonged than expected after receiving RIC. A possible explanation is that patients with Fanconi anemia do not tolerate standard conditioning regimens [7,8], so RIC may be more harmful to bone marrow than in patients without Fanconi anemia. Therefore, although intensity was decreased, the protocols described in this study may have caused the relatively late engraftment. This is emphasized by the lack of correlation between duration of engraftment in each patient and stem cell source, stem cell dose, and preparative therapy.

Zanis-Neto et al [28] reported that patients with Fanconi anemia can tolerate cyclophosphamide at doses up to 80 mg/kg, which is much higher than the 10-mg/kg dose given in our study. However, in our study cyclophosphamide was only part of the conditioning regimen, which included ≥1 more agent, whereas cyclophosphamide was the only chemotherapy used in the study by Zanis-Neto et al.

One patient developed acute GVHD with an acute infectious event of brain abscess during transplantation hospitalization. This led us to decrease dramatically the immune-suppression medications and may have led to the development of acute GVHD. Because patients with Fanconi anemia without evidence of AML or other cancer at time of transplantation do not need induction of graft-versus-leukemia or graft-versus-malignancy effects that may be associated with GVHD, and because GVHD carries the risk of secondary head and neck carcinomas developing over the long term [29], minimizing the incidence of GVHD in patients with Fanconi anemia seems desirable. Hence, using some degree of in vivo T-cell depletion of donor alloreactive T cells, in addition to host alloreactive lymphocytes by anti-thymocytic globulin or alemtuzumab, as used in the present cohort, seems justified. Moreover, the use of intravenous busulfan, a myeloablative agent with limited toxicity to mature lymphocytes, further keep some host T cells, potentially with veto capacity, and thus decreases even more the risk of GVHD in this cohort of patients [30]. However, excessive T-cell depletion after grafting should be considered cautiously or avoided due to the increased risk of allograft rejection because T cells play a significant role in facilitation of engraftment, especially in recipients who are conditioned with a nonmyeloablative regimen.

In conclusion, the present results based on a small cohort of patients support the use of fludarabine-based RIC in preparation for SCT for patients with Fanconi anemia. However, larger cohorts of patients should be evaluated for longer follow-up periods to define the optimal RIC for patients with Fanconi anemia in need of SCT.

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