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Addition of High-Dose Cytarabine to Fludarabine-Based Conditioning for Hematopoietic Stem Cell Transplantation for Treating Fanconi Anemia Patients with Advanced Myeloid Malignancy: A Single-Center Experience and Literature Review

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A B S T R A C T

The complication of Fanconi anemia (FA) with acute leukemia is rare and challenging to treat because of high relapse rates, despite the improved outcome of hematopoietic stem cell transplantation with fludarabine-based conditioning for treating FA patients with hematological abnormalities. We added high-dose cytarabine to fludarabine-based conditioning to promote an enhanced antitumor effect and successfully subjected 4 patients with FA, including 3 with acute leukemia, to hematopoietic stem cell transplantation. All patients remain alive without treatment-related mortality or evidence of disease. Adding high-dose cytarabine to fludarabine-based conditioning may be tolerable and effective for treating FA patients with acute leukemia.

INTRODUCTION

Fanconi anemia (FA) is a rare inherited disorder characterized by congenital malformation, progressive bone marrow failure, and predisposition to malignancy. Rarely, FA may present with acute leukemia, which is difficult to treat. According to the European Society for Blood and Marrow Transplantation, only 4 of 795 patients with FA underwent transplantation for acute leukemia [1]. Among 113 patients with clonal evolution, myelodysplastic syndrome (MDS), or acute leukemia in the Center for International Blood and Marrow Transplant Research registry, only 14 presented with acute leukemia [2]. Although the outcome of hematopoietic stem cell transplantation (HSCT) for treating FA patients with hematological abnormalities has improved with fludarabine-based conditioning [1,3,4], HSCT in FA patients with acute leukemia is associated with treatment-related toxicity and a high relapse rate [2,5]. Allogeneic HSCT is the only curative treatment for FA patients with acute leukemia; however, a standard conditioning regimen has not been established for this small subgroup with a poor prognosis. We hypothesized that the high relapse rate in such patients results from inadequate tumor suppression consequent to reduced cyclophosphamide and irradiation doses, which are required to reduce treatment-related toxicity associated with FA.

To enhance the antitumor effect, we added high-dose cytarabine (HD-AraC) to fludarabine-based conditioning for treating FA patients with advanced myeloid malignancy. Through in vitro studies, AraC was shown to be as safe as fludarabine for patients with FA [6]; however, reports of AraC for conditioning are limited [7,8]. Herein, we report the toxicities and outcomes of HD-AraC–added conditioning for treating FA patients with advanced myeloid malignancy.

PATIENTS AND METHODS

Four FA patients (3 with acute leukemia; 1 with MDS, refractory anemia with excess blast [RAEB]-2) at Saitama Children's Medical Center underwent HSCT with HD-AraC plus fludarabine-based conditioning from 2001 to 2015. They were diagnosed with FA via mitomycin C sensitivity testing of peripheral blood lymphocytes. The complementation group was analyzed at Tokai University (Kanagawa, Japan). Detailed transplantation characteristics are shown in Table 1. The marrow grafts were unmanipulated. Adverse events and graft-versus-host disease (GVHD) were graded using the Common Terminology Criteria for Adverse Events, version 4 and Center for International Blood and Marrow Transplant Research criteria, respectively.

All patients underwent transplantation in high-efficiency particulate air-filtered rooms and received antibacterial and antifungal drugs and acyclovir as infection prophylaxis. GVHD prophylaxis involved continuous

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Table 1
Transplantation Characteristics and Outcomes

Characteristic	Patient No. 1	Patient No. 2	Patient No. 3	Patient No. 4
Age at HSCT, yr	8	13	6	7
FA complementation group	A	A	A	NA
Cytogenetic	47,XY,+i(1)(q10), add(10)(q26), del(17)(p11)	46,XX,del(1)(p34.3), add(7)(p11.2), del(9)(q13q22), add(14)(q32),-16,+mar	46,XX,del(1)(p32p34), add(2)(q33), del(3)(p13p21), add(5)(q22),add(7)(p13)	46,XX,del(1)(p34p36.1), add(5)(q31), add(6)(q21), add(18)(q21),der(21) t(1;21)(q21;q22)
Disease status at HSCT	MDS (blasts, 12%)	AML, CR	AML (blasts, 27%)	AML (blasts, 30%)
Stem cell source	Unrelated BM	Unrelated CB	Unrelated BM	Unrelated CB
HLA compatibility: antigen, allele	6/6, NA	4/6, 3/6	8/8, 6/8	5/6, 5/6
Total nucleated cell count,/kg	1.27×10^8	8.43×10^7	4.21×10^8	7.49×10^7
Conditioning (total dose, administration period)	AraC (20, day −12 to −8) Flu (150, day −7 to −3) CY (40, day −7 to −4)	AraC (8, day −6 to −3) Flu (120, day −6 to −3) CY (40, day −6 to −3) G-CSF (1500, day −7 to −3)	AraC (6, day −8 to −6) Flu (150, day −8 to −3) CY (40, day −5 to −2)	AraC (6, day −8 to −6) Flu (150, day −8 to −3) CY (40, day −5 to −2)
TBI (Gy), administration period	6, day −1 to 0	4.5, day −1 to 0	4.5, day −1 to 0	4.5, day −1 to 0
rATG (mg/kg), administration period	None	None	5, day −5 to −2	5, day −5 to −2
GVHD prophylaxis	Tac, sMTX	Tac, sMTX	Tac, sMTX	Tac, sMTX
Engraftment, d	28	18	31	18
Adverse events				
Grade 4	None	IPS	None	None
Grade 3	FN, bacteremia, mucositis	FN, HPS, bacteremia, mucositis, renal failure	FN, HPS, mucositis, diarrhea	None
Acute GVHD (organ, stage)	Grade I (skin, 2)	Grade I (skin, 1)	Grade II (skin, 3)	None
Chronic GVHD (organ, score)	Mild (skin, 1)	Mild (intestine, 1)	Mild (skin, 1)	None
Outcome	NED	NED	NED	NED
Follow up (months)	168	56	19	8

NA indicates not available; CR, complete remission; BM, bone marrow; CB, cord blood; AraC, cytarabine (g/m^2); Flu, fludarabine (mg/m^2); CY, cyclophosphamide (mg/kg); G-CSF, granulocyte-colony stimulating factor($\mu g/m^2$); rATG, rabbit antithymocyte globulin; Tac, tacrolimus; sMTX, short-term methotrexate; FN, febrile neutropenia; HPS, hemophagocytic syndrome; NED, no evidence of disease.

intravenous .02 mg/kg tacrolimus from day −1 and short-term methotrexate at 15 mg/m^2 on day 1 and 10 mg/m^2 on days 3, 6, and 11 after bone marrow transplantation or half-dose short-term methotrexate on days 1, 3, and 6 after cord blood transplantation.

Patient number 1, an 8-year-old boy with short stature, was diagnosed with MDS (blasts, 16%) and FA and underwent transplantation with unrelated bone marrow 9 months after diagnosis without disease aggravation or any complications before HSCT. He received only red blood cell (RBC) and platelet transfusions and no chemotherapy before HSCT. We added 2 g/m^2 HD-AraC twice daily for 5 days before conditioning with fludarabine (30 mg/m^2, 5 days), cyclophosphamide (10 mg/kg, 4 days), and total body irradiation (TBI) (6 Gy in 4 fractions).

Patient number 2, a 13-year-old girl with scoliosis and operative thumb abnormalities, was initially diagnosed with acute myeloblastic leukemia (AML) complicated by cryptogenic organizing pneumonia (COP). Initial chemotherapy according to the Japanese Pediatric Leukemia/Lymphoma Study Group AML-05 protocol [9] was reduced because of pneumonia. After achieving remission, she was diagnosed with FA and underwent transplantation with unrelated cord blood after 3 cycles of reduced HCEI (HD-AraC, 3 g/m^2 twice daily on days 1 and 2; etoposide, 100 mg/m^2, days 1 to 3; idarubicine, 10 mg/m^2, day 1; and triple intrathecal therapy, day 1). Pneumonia persisted until HSCT. For conditioning, we prescribed FLAG regimen (fludarabine, 30 mg/m^2, 4 days; HD-AraC, 2 g/m^2, 4 days; and granulocyte-colony stimulating factor, 300 $\mu g/m^2$, 5 days) [10], cyclophosphamide (10 mg/kg, 4 days), and TBI (4.5 Gy in 3 fractions).

Patient number 3, a 5-year-old girl with short stature, skin pigmentation, and an operative imperforate anus, was diagnosed with MDS (blasts, 8%) and FA and underwent transplantation with unrelated bone marrow 5 months after diagnosis. During regular RBC and platelet transfusions, disease aggravation led to AML complicated by pneumonia and odontogenic infection 1 month before and disseminated intravascular coagulation 1 week before HSCT. We added HD-AraC (2 g/m^2, 3 days) to the conditioning regimen of fludarabine (25 mg/m^2, 6 days), cyclophosphamide (10 mg/kg, 4 days), TBI (4.5 Gy in 3 fractions), and rabbit antithymocyte globulin (Thymoglobulin [Sanofi, Lyon, France]; 1.25 mg/kg, 4 days) [3,11,12].

Patient number 4, a 7-year-old girl with short stature, skin pigmentation, scaphocephaly, and micrognathia was diagnosed with MDS (blasts, 5%) and FA. Two months after diagnosis, acute lymphoblastic leukemia (ALL) developed (blasts, 97%) and she was treated with reduced induction therapy comprising prednisolone, vincristine, l-asparaginase, and triple intrathecal therapy. After achieving remission of ALL, AML and low gastrointestinal hemorrhage developed as complications 6 weeks after starting the induction therapy for ALL and the patient underwent transplantation with unrelated cord blood. We prescribed the same conditioning regimen as described for patient number 3.

RESULTS

All 4 FA patients underwent HSCT with HD-AraC plus fludarabine-based conditioning without treatment-related mortality (TRM). Only patient number 2, who received 3 cycles of chemotherapy before HSCT and experienced complicating COP, developed grade 4 idiopathic pneumonia syndrome (IPS), followed by grade 3 renal failure. She required 12 days of mechanical ventilation and administration of etanercept for IPS. All patients developed grade 3 mucositis and febrile neutropenia. Two cases each of bacteremia and hemophagocytic syndrome developed, although none exceeded grade 3 (Table 1).

All 4 patients survived to the last follow-up without evidence of disease, including secondary malignancy. There were no graft failures, although 2 patients developed grade I acute GVHD (stage 1 skin and stage 2 skin) and 1 patient developed grade II GVHD (stage 3 skin). All of these events were followed by mild chronic GVHD (2 of score 1 skin and 1 of score 1 intestinal GVHD).

DISCUSSION

In addition to our cases, we have summarized studies and outcomes of multiple FA patients who underwent transplantation with fludarabine-based or AraC-added conditioning for acute leukemia in Table 2 [2,5,7,11,13-16]. This summary demonstrates that a high relapse rate, as well as high TRM, reduces overall survival among FA