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Chemotherapy for Myeloid Malignancy in Children With Fanconi Anemia

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Background. Children with Fanconi anemia (FA) have a markedly increased risk of developing myeloid malignancies. Historically, patients with FA and myeloid malignancy have extremely poor outcomes. There are currently no clinical trials or case series addressing the use of chemotherapy for children with FA, except in the context of preparative regimens for stem cell transplantation (SCT). In this report we describe the toxicity of a chemotherapy approach for patients with FA and myeloid malignancy to achieve cytoreduction prior to SCT. ***Patients and Methods.*** Four patients with FA and myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) were treated with chemotherapy (fludarabine 30 mg/m^2 and cytosine arabinoside 300 mg/m^2 each on days 2–4 and granulocyte-colony stimulating factor (G-CSF) 5 μg/kg on days 1–5), termed reduced intensity FLAG prior to SCT. ***Results.*** The chemotherapy was well tolerated with expected hematologic toxicity and no measurable toxicity in other organs. Two of the three patients with AML cleared blasts from their bone marrow. Reduction in marrow cellularity was also achieved in one patient with hypercellular MDS. ***Conclusion.*** These data indicate that children with FA and myeloid malignancy can tolerate chemotherapy and achieve clearance of disease. It remains unclear whether pre-SCT chemotherapy improves currently poor survival rates for SCT in FA patients with myeloid malignancies and further studies are needed to determine if there is a clinical role for this strategy. Pediatr Blood Cancer 2007;48:668–672.

Key words: acute myeloid leukemia (AML); chemotherapy; Fanconi anemia

INTRODUCTION

Fanconi anemia (FA) is a genetic disorder characterized by congenital abnormalities, cancer predisposition, and progressive pancytopenia. The cellular phenotype of FA is characterized by increased sensitivity to DNA cross-linking or alkylating agents that block DNA replication and RNA transcription. FA patients have a very high risk of developing bone marrow failure along with an increased risk of development of malignancies. The most frequent malignancy in FA is acute myeloid leukemia (AML) with a cumulative incidence of 33% by 40 years of age [1]. The management of FA patients who develop myelodysplastic syndrome (MDS) or leukemia is challenging. Sensitivity to DNA-damaging agents limits therapy that can be administered to FA patients. Severe toxicity and marrow aplasia without hematological recovery have been described in single patient case reports [2,3]. Currently, the only definitive treatment for patients with FA and myeloid malignancy is stem cell transplantation (SCT) and there are no data to indicate whether cytoreduction with chemotherapy is beneficial prior to SCT in these patients. However, bulky leukemia may reduce the success of SCT. In addition, leukemia may need to be controlled while waiting for a transplant donor search.

The literature regarding conventional chemotherapy in FA patients with leukemia is limited, consisting of single case reports. Verbeek et al. [4] reported an adult AML patient with FA whose induction chemotherapy, consisting of sequential high-dose cytosine arabinoside (Ara-C) and mitoxantrone resulted in a complete but temporary hematological remission. Recently, Ikeda et al. [5] reported their experience of treating a 2-year-old boy with 100 mg 1-β-D-arabinofuranosylcytosine/m^2 for 7 days and 3 mg of mitoxantrone/m^2 for 5 days. This chemotherapy was well tolerated, except for development of mild mucositis.

Standard chemotherapy regimens for AML include agents such as alkylating agents and anthracyclines to which patients with FA have increased sensitivity. The combination of fludarabine, Ara-C, and granulocyte-colony stimulating factor (G-CSF), termed FLAG, has activity in children with AML without FA [6,7]. Fludarabine and Ara-C are nucleoside analogues that exert cytotoxicity by inhibition of DNA polymerase and ribonucleotide reductase, in turn inhibiting DNA synthesis [8]. We expected fludarabine and Ara-C to be better tolerated by patients with FA than anthracyclines and alkylating agents, as they exert cytotoxicity without direct DNA damage. We have tested a chemotherapy regimen for patients with FA who develop a myeloid malignancy that includes lower doses of Ara-C than standard FLAG chemotherapy (termed reduced intensity FLAG regimen). In this report we describe the toxicity and outcome of this approach in achieving cytoreduction prior to SCT.

PATIENTS AND METHODS

Patients

Between January 2003 and May 2005, four patients with FA and AML or hypercellular MDS were referred to the Fanconi Anemia Comprehensive Care Center at Cincinnati Children's Hospital Medical Center. The Cincinnati Children's Hospital Medical Center

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Institutional Review Board approved the retrospective review and reporting of these cases. The diagnosis of FA was confirmed by diepoxybutane (DEB) sensitivity testing in peripheral blood lymphocytes [9]. Complementation group assignment was made using published techniques [10,11]. The clinical and hematological characteristics of patients are summarized in Table I. Two children were male and two were female, with a median age of 13.9 years (range: 2–16.3 years). Patient 1 and 2 did not have any congenital anomalies. Patient 3 had microcephaly, café-au-lait spots, and an ear anomaly. Patient 4 had radial anomaly, extra right pelvic kidney, and hypothyroidism. Of note, Patient 3 is assigned to complementation group FANCD1, with biallelic mutations in the BRCA2 gene, typically associated with development of an early malignancy [12]. This child developed a stage 2b neuroblastoma at 16 months of age, which was treated with surgical resection alone at the referring institution. This patient subsequently presented with AML at the age of 20 months.

Three patients had AML and one had MDS/chronic myelomonocytic leukemia (CMMoL). Patients 1 and 2 had FAB M5 AML with 51% and 80% blasts in the bone marrow, respectively. Patient 3 had 49.5% blasts and FAB M2 AML. Median white blood cell count prior to chemotherapy was 4.35×10^9/L (range $0.9–68 \times 10^9$/L), and median hematocrit and platelet count were 25.6 (range 22.3–34.2) and 123.5×10^9/L (range $14–962 \times 10^9$/L), respectively. All patients included in this study had clonal chromosomal abnormalities (defined as >10% of cells harboring a single abnormality) with the most frequent being loss of all or part of chromosome 7 as described in Table I. When referred with AML, Patient 1 had central diabetes insipidus and thrombocytosis, as described in other, non-FA patients with AML and rearrangements of chromosome 3 and monosomy 7 [13–18]. The diabetes insipidus resolved slowly after treatment with reduced intensity FLAG chemotherapy and SCT. All patients required red blood cell transfusions prior to referral, as all had evidence of bone marrow failure before developing malignancy.

Chemotherapy Received Prior to Reduced Intensity FLAG

Two patients had received other chemotherapy prior to reduced intensity FLAG therapy (Patients 2 and 3). Patient 2, diagnosed with AML, received one course of Ara-C alone, 200 mg/m^2/day for 4 days with no toxicity, but without any response. This was followed by a course of Ara-C 100 mg/m^2/day and etoposide 200 mg/m^2/day for 3 days, again with no toxicity and no response prior to treatment with reduced intensity FLAG. Patient 4, diagnosed with CMMoL, received daily hydroxyurea (500 mg), and then oral etoposide (50 mg on alternate days) prior to the reduced intensity FLAG regimen to reduce an elevated white cell count.

Reduced Intensity FLAG Regimen

Patients received fludarabine 30 mg/m^2 at hour 0–0.5 on days 2–4, and Ara-C 300 mg/m^2 as a 4-hr infusion starting at hour 4 on days 2–4 along with G-CSF 5 μg/kg on days 1–5 as shown in Figure 1. Each patient received only one course of reduced intensity FLAG and all except Patient 3 (who received additional chemotherapy) proceeded to allogeneic SCT after treatment with reduced intensity FLAG.

Stem Cell Transplant Regimen

All patients received unrelated donor peripheral blood stem cells that had undergone T-cell depletion by the use of Isolex 300i column CD 34+ cell selection or unmanipulated cord blood cells. The transplant preparative regimen included fludarabine (35 mg/m^2, days −6 to −3), cyclophosphamide (10 mg/kg, days −5 to −2), and total body irradiation (450 cGy on day −1). In addition patients also received 30 mg/kg of lymphocyte immune globulin (ATGAM) on days −6 to −2 to prevent graft rejection. Cyclosporine and methylprednisolone were used for Graft versus host disease prophylaxis. GCSF support was provided from day +5 until ANC > 2000 × 3 days.

Supportive Treatment

The clinical support received by the patients during chemotherapy treatment was according to the standard procedures at this institution. All patients were treated in single HEPA-filtered rooms. Cotrimoxazole or pentamidine and liposomal amphotericin B (AmBisome®) were administered to all patients as prophylaxis against pneumocystis carinii (PCP) infection and fungal infection, respectively.

Outcome Analysis

Bone marrow aspiration for evaluation of response was performed 10 days after completion of the course of reduced intensity FLAG. In patients with AML, response was defined as a bone marrow with <5% blasts and the absence of extramedullary

TABLE I. Patient Characteristics Before Reduced Intensity FLAG Chemotherapy

	Patient 1	Patient 2	Patient 3	Patient 4
Age at FA diagnosis	14 yrs	6 yrs	1 yr	4 yrs
Age at chemotherapy	16 yrs 3 months	14 yrs 2 months	2 yrs	13 yrs 7 months
Gender	Male	Female	Male	Female
Race/ethnic origin	Hispanic	African American	Caucasian	Hispanic
Complementation group	FANCA	FANCA	FANCD1	FANCJ
Prior malignancy	None	None	Neuroblastoma	None
Cytogenetics	45, XY, t(2;3)(p23;q27),	47, XX, t(6;11), idic (15)(q11.1)	Add (1)(q21) del(7)(q21)	46, XX deletion(7)(q22)
Morphology	AML; 51% blasts	AML; 80% blasts	AML; 49.5% blasts	CMMoL

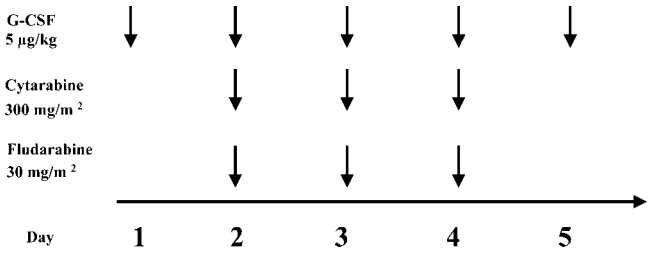

Fig. 1. Schema for the administration of reduced intensity FLAG.

leukemia. Patients proceeded to SCT once cytoreduction of malignant cells was achieved, because it was anticipated that recovery of normal hematopoiesis after chemotherapy was likely to be prolonged, or might not occur. It is therefore not possible to assess recovery of normal hematopoiesis or durability of response to chemotherapy alone in these cases.

RESULTS

Toxicity of Chemotherapy

Overall, reduced intensity FLAG was well tolerated, with no mucositis or measurable toxicity to other organs. Common Terminology Criteria for Adverse Events (CTCAE) grade 4 hematopoietic toxicity occurred in all patients, with neutropenia and a requirement for platelet and red cell transfusions. One patient developed severe infection (klebsiella sepsis requiring intensive care unit admission) during the pre-transplant preparative therapy that could have been a consequence of neutropenia induced by the reduced intensity FLAG chemotherapy. Patient 3 developed a typical skin rash in response to Ara-C that resolved after cessation of chemotherapy.

Response to Chemotherapy

Two of the three patients (Patients 1 and 2) with AML had a good response (reduction of blasts to <5%) after reduced intensity FLAG (Table II). Patient 3 with AML, had 49.5% blasts prior to and 36% blasts after reduced intensity FLAG. This child also had no response to a subsequent course of Ara-C (200 mg/m^2/day for 3 days), etoposide (200 mg/m^2/day for 3 days), and dexamethasone (6 mg/m^2/day for 3 days), but went on to achieve complete clearance of blasts after a further course of anthracycline-containing chemotherapy (daunorubicin 22.5 mg/m^2/day for 3 days and Ara-C 50 mg/m^2/day for 7 days). The patient with CMMoL achieved cytoreduction with reduced marrow cellularity of the bone marrow biopsy.

Toxicity and SCT

The use of pre-transplant chemotherapy did not increase toxicity related to SCT. During transplant all patients had CTC grade 3 mucositis and grade 3 pain as expected. One patient had grade 3 endocrine toxicity (diabetes requiring insulin), and four patients had a grade 3 elevation of GGT. Patient 2 had grade 4 mucositis and grade 5 infection after a second preparative regimen given for graft failure; as this was 5 months after reduced intensity FLAG, these toxicities were likely related to the preparative regimen.

Survival

All four patients started the transplant preparative regimen at a median of 11 days (range 9–49 days) after completion of the reduced intensity FLAG chemotherapy. Of the three patients with AML, Patients 1 and 3, achieved good hematopoietic recovery (normal blood counts without transfusion) with full donor chimerism. Three out of four patients developed acute GVHD. Patient 1 developed stage 2 skin and stage 1 liver GVHD, Patient 2 had stage 1 skin GVHD (after her third transplant) and Patient 3 developed stage 2 skin GVHD. Patient 1 is alive without evidence of leukemia 8 months post transplant. Patient 3, who had a BRCA2/FANCD1 defect, had relapse of leukemia 4 months post transplant and subsequently died of disease. Patient 2 failed to engraft after a cord blood transplant, received a second cord blood unit without engraftment and finally achieved full donor chimerism after infusion of peripheral blood stem cells from a one antigen mismatched unrelated donor. The patient, however, died of adenovirus infection 5 months after transplant and 6 months after reduced intensity FLAG without recurrence of leukemia. The patient with CMMoL achieved good hematopoietic recovery and full donor chimerism after SCT with no evidence of clonal abnormality of chromosome 7 by FISH. However, she died of reactivation of toxoplasmosis 2 months after SCT without recurrence of her disease.

DISCUSSION

Children with FA have a strong predisposition to development of bone marrow failure, myeloid malignancies, and malignancies at sites outside of the bone marrow [1]. The most consistent

TABLE II. Toxicity and Outcome After Reduced Intensity FLAG Chemotherapy

	Patient 1	Patient 2	Patient 3	Patient 4
Toxicity of chemotherapy	Klebsiella sepsis during post-chemo neutropenia & SCT preparative regimen	No organ toxicity	No organ toxicity, reversible skin rash with Ara-C	No organ toxicity
Marrow morphology post FLAG chemotherapy	No residual blasts, markedly hypocellular marrow	<5% blasts, hypocellular marrow	Blasts reduced to 36%, blasts cleared with daunomycin+Ara-C	CMMoL, moderately hypocellular marrow
Increased SCT-related toxicity	No	No	No	No
Final outcome post-SCT	Alive 8 months post-SCT	Died of infection 5 months post-SCT	Relapse and death—4 months post-SCT	Died of reactivation of toxoplasmosis—2 months post-SCT

characteristic of FA cells is increased sensitivity to DNA-damaging agents, in particular agents such as mitomycin-C and DEB that are the basis of the in vitro test for FA [9,19].

Despite the considerable experience that has lead to improved, although not always satisfactory, dosing of cyclophosphamide, radiation and more recently fludarabine, for bone marrow transplant in FA, there are few reports of the use of chemotherapy in FA [20–25]. The majority of reports describe children in whom the diagnosis of FA was made only after the occurrence of severe and unexpected toxicity after conventional dose chemotherapy given for malignancy. Goldsby et al. [2] described excessive pulmonary toxicity after cyclophosphamide, daunorubicin, prednisone, and PEG-asparaginase in a child with T-cell lymphoblastic lymphoma and unrecognized FA. Similarly, Ruud and Wesenberg [3] reported severe marrow aplasia, infections, fever and renal impairment in a child treated with conventional doses of alkylating agents for medulloblastoma who subsequently proved to have FA.

In the current study, we used a uniform chemotherapy regimen that we expected to be well tolerated by children with FA as an initial step in exploring cytoreduction for patients with myeloid malignancy prior to SCT. We were interested in exploring this strategy because outcomes for patients with myeloid malignancy and FA are unsatisfactory. In addition, control of AML is sometimes needed during a prolonged transplant donor search. A report from the International Fanconi Anemia Registry (IFAR), described extremely poor outcome in 35 cases with FA and AML [26]. In this IFAR report, 5 of the 35 AML cases were transplanted; of the remaining 30 cases, 26 died within 3 months of diagnosis. In addition, patients with FA transplanted with overt leukemia have poor survival, and children who relapse after SCT generally do not survive [27]. We selected a chemotherapy regimen, that is, a modification of published reports of a combination of fludarabine, Ara-C, and G-CSF (FLAG), and does not include anthracyclines, alkylating agents, or topoisomerase inhibitors likely to cause excessive toxicity.

Our ability to judge response in this study is limited, as our goal was to achieve cytoreduction with minimum toxicity, then proceed to SCT without waiting for recovery of normal hematopoiesis. Patients 1 and 2 in this report, who had AML, cleared their marrows of blasts completely after a single course of reduced intensity FLAG. In contrast, Patient 3 required higher doses of chemotherapy, and inclusion of a significant dose (22.5 mg/m^2) of daunorubicin, approximately 50% of conventional dosing, to clear the blasts. Interestingly, this dose of daunorubicin was tolerated in this single patient with minimal toxicity; in particular there was no significant gastrointestinal toxicity and there was complete clearance of blasts. These data illustrate the heterogeneity of FA patients in terms of sensitivity to DNA damaging agents, and suggests that heterogeneity is also reflected in malignant blasts arising in FA patients. It is currently unclear whether this heterogeneity is due to intra- or intergenic variability in FA mutant protein function, but there are reported genotypic variations in both the onset of marrow failure and the occurrence of leukemia in this disease [1,12]. This broad range of sensitivity presents a challenge in formulating appropriate treatment regimens for patients with FA. Also, our understanding of biochemical and genetic characteristics of AML blasts from FA patients is very limited. It is not known whether these blasts retain the chemotherapy hypersensitivity like the patients with FA or they are more resistant, again limiting our ability to clear them with chemotherapy. It would be interesting to measure Ara-C metabolites in patients with FA treated with reduced intensity FLAG chemotherapy. It should also be noted that there is also a range of toxicity and response to chemotherapy seen in non-FA patients with AML, a proportion of whom fail to achieve remission or die of toxicity with standard induction regimens.

In summary, our experience suggests that reduced intensity FLAG chemotherapy has minimal toxicity but heterogeneous responses in children with FA. In the future, use of a uniform chemotherapy strategy in children unable to proceed to immediate BMT may advance our understanding of the clinical role of chemotherapy in patients with FA and AML/advanced MDS and possibly help identify predictors of response. In addition, studies will be needed to determine whether cytoreduction prior to SCT improves outcome and whether more effective chemotherapy regimens can be developed that improve overall survival and possibly have less toxicity compared to SCT.

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