

# Successful combination chemotherapy involving clofarabine, cyclophosphamide, and etoposide for pediatric relapsed acute myeloid leukemia: A case report

SAGE Open Medical Case Reports  
Volume 9: 1–4  
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DOI: 10.1177/2050313X211015511  
journals.sagepub.com/home/sco



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## Abstract

Limited salvage chemotherapies are available for relapsed/refractory acute myeloid leukemia. Herein, we described successful reinduction chemotherapy, involving a combination of clofarabine, cyclophosphamide, and etoposide, in a 12-year-old male with relapsed acute myeloid leukemia prior to allogeneic bone marrow transplantation from his father. Although treatment with a combination of fludarabine, cytarabine, granulocyte colony-stimulating factor, idarubicin, and gemtuzumab ozogamicin had no positive effects, the aforementioned clofarabine-based chemotherapy induced complete remission and allowed the transplantation to go ahead. The abovementioned regimen may be useful for induction chemotherapy prior to hematopoietic stem cell transplantation for refractory/relapsed acute myeloid leukemia.

## Keywords

Clofarabine, pediatric, relapsed acute myeloid leukemia

Date received: 18 November 2020; accepted: 16 April 2021

## Introduction

The prognosis of relapsed/refractory acute myeloid leukemia (AML) is extremely poor, except when hematopoietic stem cell transplantation (HSCT) is successfully performed after complete remission (CR) has been achieved through salvage induction chemotherapy.<sup>1</sup> Presently, the salvage chemotherapy options for relapsed/refractory AML are limited. They include fludarabine, cytarabine, and granulocyte colony-stimulating factor (FLAG); FLAG-idarubicin (FLAG-IDA); and FLAG-IDA-gemtuzumab ozogamicin (FLAG-IDA-GO).<sup>2–6</sup>

Studies have shown that clofarabine is effective against pediatric acute leukemia,<sup>7,8</sup> and that its combination with cytarabine was effective against AML.<sup>9–12</sup> Moreover, a few studies have indicated that combination chemotherapy involving clofarabine, cyclophosphamide, and etoposide was effective against relapsed/refractory acute lymphocytic leukemia (ALL) and AML.<sup>13–16</sup> However, the enrolled cases primarily involved ALL, due to the low number of registered AML cases. Hence, the efficacy of such combination chemotherapy against AML remains unclear.

Herein, we detailed our experience with combination chemotherapy involving clofarabine, cyclophosphamide, and etoposide in a 12-year-old male with relapsed AML, which was administered prior to allogeneic bone marrow transplantation (BMT).

## Case

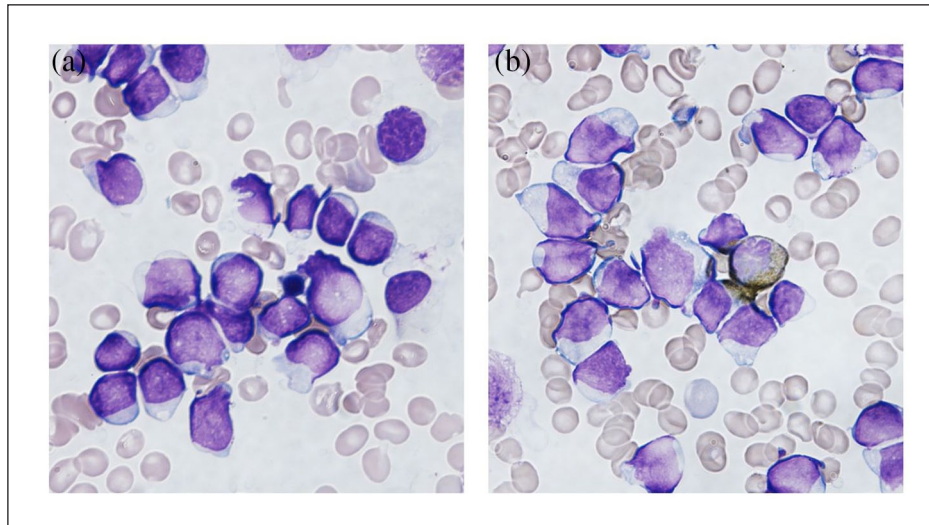
Our case involved a 12-year-old male, who was diagnosed with relapsed AML 4 months after treatment. He was initially diagnosed with AML (French-American-British (FAB) classification: M0) 11 months prior to the relapse. Bone marrow aspiration (BMA) performed after the relapse revealed a blast frequency of 93.6% (FAB classification: M0).

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**Figure 1.** Bone marrow aspiration performed during relapse peroxidase staining showed blasts did that not contain Auer bodies (FAB classification: M0): (a) Giemsa staining and (b) peroxidase staining.

Peroxidase staining showed that the blasts did not contain any Auer bodies (Figure 1), and the blasts were positive for CD13 (29.8%), CD33 (99.8%), CD11b (98.4%), and CD34 (99.7%) and negative for cytoplasmic myeloperoxidase. Chromosomal analysis of the bone marrow revealed the following karyotype: 46, X, -Y, t(7; 12)(p15; p12), +10[4]/46, XY[7]. *FLT3*-ITD, a specific chimeric gene; chromosomal abnormalities (affecting chromosomes 5, 7, and 8); and central nervous system metastasis were not detected during the initial diagnosis or at relapse. After the initial diagnosis, the patient received five courses of chemotherapy (cytarabine, etoposide, and anthracycline) on the basis of his standard risk profile (the core-binding factor was not affected).

After the diagnosis of relapse, the patient received a course of FLAG-IDA-GO (30 mg/m<sup>2</sup> fludarabine, 5 days; 2 g/m<sup>2</sup> cytarabine, 5 days; 10 mg/m<sup>2</sup> idarubicin, 1 day; and 3 mg/m<sup>2</sup> gemtuzumab ozogamicin, 1 day) and one intrathecal injection (IT) [7]. Since a BMA examination performed after bone marrow recovery, that is, at 1 month after the first course of FLAG-IDA-GO indicated a non-CR (50.4%), we added a week of azacytidine. Thereafter, BMA showed a blast frequency of 87.8%, and chromosomal analysis revealed a karyotype of 46, X, -Y, t(7; 12)(p15; p13), +10[6]/46, XY[5]. Since in vitro drug sensitivity tests suggested that antimetabolic agents, such as clofarabine, and alkylating agents, such as cyclophosphamide and etoposide, would be effective, we then attempted combination chemotherapy involving clofarabine, cyclophosphamide, and etoposide (40 mg/m<sup>2</sup> clofarabine, 5 days; 440 mg/m<sup>2</sup> cyclophosphamide, 5 days; and 100 mg/m<sup>2</sup> etoposide, 5 days) and one IT. After approximately 1 month, BMA indicated that CR and normal chromosomal findings had been achieved. Then, a second course of the same regimen (cyclophosphamide was administered at half the previous dose) was administered. After two courses of clofarabine had been

administered, no severe clofarabine-associated adverse events were noted, except for febrile neutropenia, which was controlled with antimicrobial drugs (common terminology criteria for adverse events (CTCAE) grade 3); hepatotoxicity (increased aspartate aminotransferase levels (CTCAE grade 2) and increased alanine aminotransferase levels (CTCAE grade 2)); and bone marrow suppression (anemia and decreased neutrophil, white blood cell, and platelet counts (CTCAE grade 4 for all events)). After the second course of clofarabine, cyclophosphamide, and etoposide, the patient underwent allogeneic BMT from his father (completely matched for the human leukocyte antigen DNA type), which involved a preparatory regimen comprising total body irradiation (TBI) (12 Gy) and cyclophosphamide (60 mg/kg, 2 days). The BMT was successful and did not result in severe complications, and neutrophil engraftment was confirmed on day 29. Grade 4 acute graft-versus-host-disease (GVHD), involving intestinal symptoms, was temporarily observed and controlled with cyclosporin and prednisolone. Gradual amelioration of the acute GVHD was achieved through immunotherapy. BMA revealed a normocellular bone marrow without blasts, and hematological CR was maintained for 12 months after the BMT. Also, complete chimerism was detected using short-tandem-repeat analysis, and chromosomal analysis revealed a karyotype of 46, XY[20/20].

## Discussion

The prognosis of pediatric AML has continued to improve, with event-free survival (EFS) rates of 60% and overall survival (OS) rates of 70%. However, 5%–10% of all patients experience induction failure, while around 30% of all patients who achieve CR relapse after induction therapy.<sup>4,17</sup> Moreover, studies have shown that relapsed/refractory AML is associated

with poor OS (under 40%).<sup>1</sup> Nonetheless, achieving a second CR and undergoing HSCT have been identified as the most significant predictors of a better prognosis.<sup>18</sup>

Clofarabine, a second-generation purine nucleoside analog, which is structurally related to fludarabine and cladribine,<sup>7,8</sup> exhibits significant anti-leukemic activity. Phase II trials of clofarabine monotherapy among pediatric patients with ALL or AML showed an overall response (OR) rate (CR or CR without platelet recovery (CRp)) of 20% in ALL and a CR rate of 26% in AML [20, 21]. Clofarabine was approved by the United States Food and Drug Administration (FDA) in 2004, specifically as a treatment for pediatric relapsed/refractory ALL.<sup>8,19</sup>

Combination regimens involving clofarabine and traditional anti-leukemic drugs have been extensively investigated. Clofarabine increases the anti-leukemic activity of cytarabine,<sup>9</sup> and recent studies have provided evidence in support of its effectiveness against both adult and pediatric AML.<sup>10–12,21,22</sup> Accordingly, Rubnitz et al.<sup>23</sup> suggested that clofarabine could be used instead of anthracycline and etoposide during remission therapy for childhood AML, while Molteni et al.<sup>11</sup> showed the potential of clofarabine-based chemotherapy as a bridge toward transplantation in patients with refractory/relapsed AML, especially after fludarabine-based salvage chemotherapy has been attempted.

A few studies have investigated the use of combination chemotherapy involving clofarabine, cyclophosphamide, and etoposide for acute pediatric leukemia, including ALL and AML.<sup>13–16</sup> A phase I study by Hijiya et al.<sup>13</sup> reported an OR rate of 64% (ALL: 55% and AML: 100%) for 20 patients with ALL and 5 patients with AML. The aforementioned study concluded that this combination was well tolerated and effective against pediatric relapsed/refractory acute leukemia. A phase II study by Miano et al.<sup>15</sup>, involving 40 children (16 AML and 24 ALL) who received salvage therapy, revealed a 24-month OS rate of 25% for all cases and CR, minimal residual disease CR, and CRp rates of 0%, 0%, and 31.2%, respectively, for the AML cases after the first course. After further therapy including transplantation, Messinger et al.<sup>16</sup> reported that this combination chemotherapy for refractory/relapsed childhood and adolescent AML resulted in an EFS of 24% (after a median follow-up period of 60 months).

Since *in vitro* drug sensitivity tests indicated that clofarabine and cyclophosphamide would be effective in this case, we administered clofarabine, cyclophosphamide, and etoposide, and the patient achieved CR. Also, the TBI-cyclophosphamide regimen was used as a conditioning regimen, based on the results of the drug sensitivity tests. The patient developed grade 4 GVHD, specifically diarrhea. It was considered that this might have been due to excess inflammation related to intestinal damage caused by the cumulative toxicity of cyclophosphamide. Although it has only been used in a small number of cases, this regimen has demonstrated adequate potential as a salvage chemotherapy

regimen for relapsed/refractory AML. However, given that the FDA and other regulatory agencies in many countries have only approved clofarabine as a treatment for ALL, recent studies on the efficacy of combinations of clofarabine and other drugs against AML have been insufficient.

Previous studies paid close attention to hepatotoxicity, the systemic inflammatory response, cytokine release-like events, capillary leak syndrome, severe tumor lysis syndrome, and infection-related complications as potential adverse events.<sup>7</sup> While hepatotoxicity and febrile neutropenia developed in the present case, both were controlled, and no severe complications occurred.

This study described the clinical course of a patient with relapsed AML, who received combination chemotherapy involving clofarabine, cyclophosphamide, and etoposide. Despite the ineffectiveness of FLAG-IDA-GO and the lack of other options for relapsed AML, the aforementioned regimen induced CR, which allowed HSCT to subsequently be performed.

## Conclusion

A clofarabine-based regimen, involving cyclophosphamide and etoposide, has potential as a reinduction therapy for relapsed/refractory AML. Nonetheless, further investigations are needed due to the limited number of cases in which this regimen has been used.

## Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Ethical approval

The administration of clofarabine was approved by the institutional review board of Showa University Fujigaoka Hospital, Japan

## Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

## Informed consent

Written informed consent for the use of clofarabine was obtained from the patient and his guardians.

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