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Case Report

Metronomic Maintenance Therapy in Refractory Acute Myeloblastic Leukemia with Monosomy 7

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ABSTRACT

Patients with acute myeloblastic leukemia (AML) with monosomy 7 are a group of patients with refractory AML who have a very poor prognosis. Therefore, rationally designed new therapies, including metronomic chemotherapy regimen with histidine deacetylase inhibitors (Valporic acid, ATRA) are being investigated as potential treatments for the population of refractory cases of AML. Herein, we report a patient with primary refractory AML who was treated with oral low-dose chemotherapy after standard systemic chemotherapy.

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Introduction

Hematological malignancies are usually primarily treated by systemic chemotherapy. Induction failure is still a dismal event in acute leukemia especially in those with chromosomal abnormalities such as monosomy 5 and 7. These patients often have low disease free survival rate after stem cell transplantation. Multidrug resistance is a major cause of treatment failure and death in them.[1]

Despite receiving combination chemotherapy, treatment failure and relapse occurrs in more than half of the cases with acute myeloid leukaemia (AML).[1] A few therapeutic strategies are recognized for treatment of AML to improve survival in patients with recurrent chromosomal abnormalities.

Inhibition of histone deacetylases (HDACs) with continuous low-dose all-trans retinoic acid (ATRA) and Valporic acid as differentiating agents has been proposed as alternative treatments in AML during the last decade. It is being used as metronomic chemotherapy which is intended to prevent tumor angiogenesis and induce apoptosis in myeloid blasts.[2] Herein, we report a patient with primary refractory AML who was treated with oral low-dose metronomic therapy after standard systemic chemotherapy.

Case Presentation

A 13-year-old Iranian boy was admitted to our hospital with pallor, fever and lethargy since 1 week previous to admission. Physical examination showed low grade fever, pallor without any neurologic sign, hepatosplenomegaly

or lymphadenopathy. CBC showed hemoglobin 3.5g/dL, platelets 64×10^9/µL, and leukocytes 55×10^9/µL with 4% blasts, 8% neutrophils, 80% lymphocytes, 6% monocytes and 2% eosinophil. Bone marrow aspiration showed 75% of total nucleated cells had myeloblastic phenotype (figure 1). Immunophenotyping analysis by flow cytometry was performed by a panel of antibodies. The blast cells were positive for CD45, CD13, CD117, CD34, CD19, HLA-DR and negative for other lymphoid markers including CD5, CD10 and also CD14. Negative controls were assessed by IgG1FITC/IgG1PE. Therefore, the patient was diagnosed as AML FAB-M_1 with aberrant expression of CD19 (figure 1). Karyotype study showed 45, XY,-7 compatible with monosomy 7 (figure 2).

The patient was considered a candidate for allogenic bone marrow transplantation after achieving first induction remission. He was initially treated by a course of MRC-12 protocol: Adriamycin (33.5 mg /m^2 , days 1,3,5), Cytarabine Arabinoside (100 mg /m^2 , days 1 to 10) and Etoposide (100 mg /m^2 , days 1 to 5) was the first course of induction phase which was not successful (induction failure) and then he was scheduled for 1st and 2nd course of FLAI protocol (Fludarabine (25 mg/m^2, days 1–4), Cytarabine Arabinoside (1000 mg/m^2, days 1–4) and Idarubicin (5 mg/m^2, days 1–3). However, he had no response to either 2 courses of FLAI protocol and repeated bone marrow aspiration and biopsy showed 60% myeloblast in bone marrow specimen. Then the patient was treated by alternative chemotherapy protocol including 5-day course of Cladribine (9 mg/m^2/dose) and Cytarabine Arabinoside as daily 2-hour infusions (500 mg/m^2/dose). But again he had no response to 1st course of the alternative protocol. Finally after explaining the situation for the patient and his parents, he was scheduled for our target regimen as oral metronomic chemotherapy in which Histone Deacetylase Inhibitors

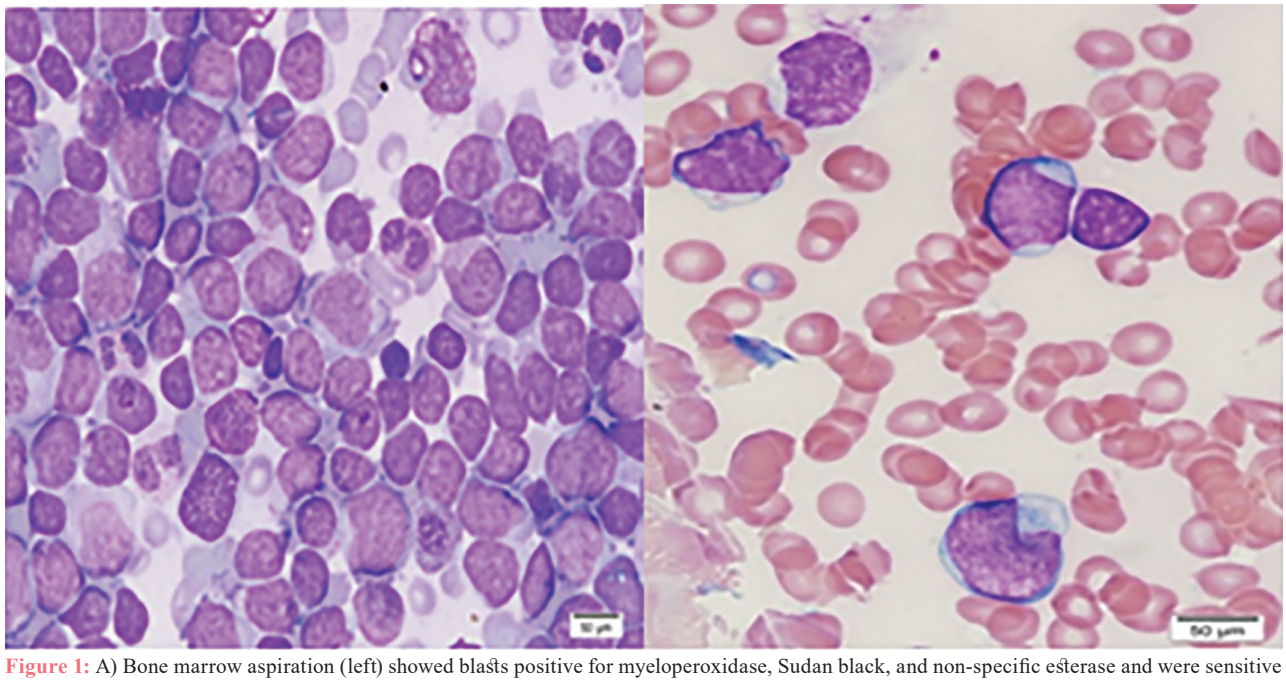

Figure 1: A) Bone marrow aspiration (left) showed blasts positive for myeloperoxidase, Sudan black, and non-specific esterase and were sensitive to fluoride inhibition. B) Peripheral blood showed myeloblasts.

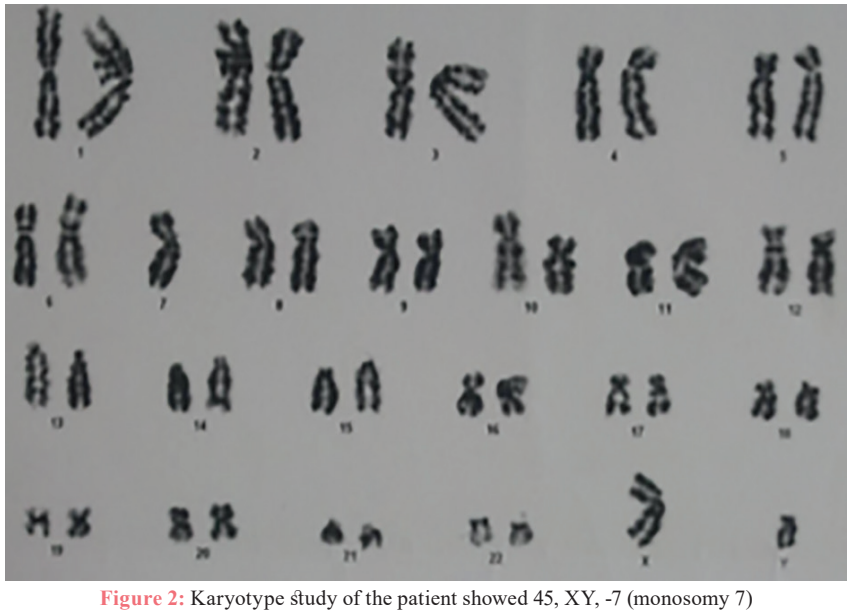

Figure 2: Karyotype study of the patient showed 45, XY, -7 (monosomy 7)

(HDAI) were included: 6-Thioguanin 40 mg/m^2 for 21 days, Prednisolone 40 mg/m^2 for 5 days, oral Etoposide 50 mg/m^2/day for 21 days plus ATRA 45mg/m^2/day and Valproic acid 2.5-5 mg/kg/day for the first 14 days of month followed by 7 days of rest.

Now after 1 year since beginning of metronomic chemotherapy, he occasionally receives only supportive care such as antibiotics and transfusions of blood products; however, there is no evidence of remission in bone marrow and peripheral blood smear. The patient did not experience any adverse event related to treatment with ATRA (dryness of mucosa, headache and increased transaminases or triglycerides).

Metronomic chemotherapy as maintenance was continued for the patient due to lack of response to standard systemic chemotherapy in order to to prolong survival and improve patient's quality of life.

Discussion

Metronomic chemotherapy is continuous systemic administration of non-toxic doses of drugs that attack proliferating endothelial cells as targets during tumor angiogenesis. This strategy was innovated 40 years ago in adult oncology, but experiences in pediatric oncology are scanty especially in hematological cancers. This strategy often is used in management of solid tumors by co-administration of anti-angiogenic drugs plus low-dose continous chemotherapy instead of high dose intermittent chemotherapy.[3]

Currently, PrET protocol (Prednisolone, Etoposide and Thioguanine) is a well-known metronomic regimen for refractory AML patients. The anti-angiogenic ability of 6TG, together with its antimetabolite activity toward tumor cells has a major role supporting efficacy of this method.[4]

In one study, a 68-year-old man was reported who had AML with high-risk cytogenetic features such as our patient who achieved complete remission during induction phase by oral metronomic chemotherapy by similar regimen in an outpatient settings. He was then treated with high-dose cytarabine Arabinoside (HDAC) as consolidation followed by maintenance therapy with PrET protocol. He was survived 35 months since diagnosis and 21 months off treatment.[5]

Our patient did not achieve remission despite different kinds of salvage regimens he received (FLAI, Cladribine and HDAC). As a result, he was determined to be treated by PrET protocol as palliative treatment. Two components of our treatment were administration of Histone deacetylase inhibitors (HDACI) including valporic acid (VPA) and All-trans retinoic acid (ATRA) that were co-administered as metronomic chemotherapy.

Valporic acid (VPA) has antileukemic effects in AML used in combination with other antileukemic agents.[4] This treatment can induce a clinically relevant improvement in peripheral blood cell counts and stabilization of the clinical status for a subset of AML patients, as well as reducing the risk of clinically relevant toxicity. Although our patient had a stable clinical status, the most cell population in peripheral blood and bone marrow was myeloblasts.

It seems that VPA could induce differentiation and has anti-proliferative and pro-apoptotic effects in AML cell lines. However, patients are most likely heterogeneous in terms of susceptibility to VPA and molecular mechanisms mediating its antileukemic effects. Direct effect of the drug on leukemic cells seems to be the most important, but there may be indirect effects mediated through increased antileukemic immune reactivity.[6,7]

ATRA is also a HDAC inhibitor which its differentiating effect on human acute promyelocytic leukemia (APL) cells in vitro has been well established.[7] In APL, absence of ATRA leads to HDAC activities, inducing chromatin condensation and transcriptional repression.[4] ATRA induces a conformational change in the promyelocytic leukemia (PML)/retinoic acid receptor α (RARα) fusion oncoprotein, thereby allowing the release of HDAC complexes and recruitment of transcription. Treatment with ATRA has dramatically improved prognosis of APL and has also been used in the treatment of non-APL AML.[2]

We used combination of PrET metronomic chemotherapy along with ATRA and VPA after failure of various intensive salvage protocols for this patient, since he had no chance for continuation of treatment and prolonged survival; however, this method of led to improved survival and increased quality of life.

Synchronous prescription of ATRA and VPA can be combined with low-dose cytotoxic drugs such as Cytarabine Arabinoside.[8] Hydroxyurea and 6-thioguanine,[6] can also induce remission according to the Myelodysplastic Syndrome (MDS) response criteria and complete hematological remission. Our patient showed evidence of clinical stability with metronomic strategy despite lack of signs of remission induction on bone marrow. Satisfactory results with other combinations of oral metronomic therapies such as melphalan and lenalidomide but without HDAC inhibitiors has been reported.[9-12] It seems this method could induce a lifesaving dormancy condition in the patient preventing from flare up of the primary disease.

Conclusion

Metronomic chemotherapy with HDAC inhibitors can be employed as a therapeutic strategy particularly in refractory AML cases not responsive to other treatments. This case report suggests the probable efficacy of combination of oral low-intensity metronomic chemotherapy by HDAC inhibitors in AML patients with induction failure.

Conflict of Interest: None declared.

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