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Case report

Low-dose cytarabine-induced hepatic and renal dysfunction in a patient with myelodysplastic syndrome

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We report a 49-year-old female patient with secondary myelodysplastic syndrome who developed liver dysfunction and acute renal failure caused by low-dose cytosine arabinoside (Ara-C) therapy. Treatment of low-dose Ara-C has widely been used for acute myelogeous leukemia and myelodysplastic syndrome, and it is thought to be a low toxicity except for myelosuppression. The patient complained of a transient adverse reaction in the second and third course of therapy. This rare case indicates that careful observation should be carried out during low-dose Ara-C therapy in view of allergic reactions. [© 1999 Lippincott Williams & Wilkins.]

Key words: Adverse effects, allergic reaction, low-dose cytosine arabinoside.

Introduction

Cytosine arabinoside (Ara-C) is one of the most effective agents against acute myeloblastic leukemia (AML).[1,2] Low-dose Ara-C at a dose of 10 mg/m^2 has proven efficacy in treating patients with AML, myelodysplastic syndromes (MDS) and secondary leukemia.[3–5] This regimen has primarily been used in elderly patients due to the low toxicity except for myelosuppression.[6,7] We report here a patient with secondary MDS who developed liver dysfunction and acute renal failure during treatment of low-dose Ara-C.

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Case report

A 45-year-old Japanese female was admitted with low-grade fever and general fatigue in September 1993. She had no history of allergy. The peripheral blood findings showed leukocytosis with monoblasts. A bone marrow aspiration also revealed an increase of monoblasts without myelodysplasia. Cytogenetic analysis of bone marrow showed normal female metaphases. She was diagnosed with acute monoblastic leukemia. Treatment with behenoyl-Ara-C, daunorubicin, 6-mercaptopurine and prednisolone led to a complete remission. She then received three sets of consolidation therapy with the same regimen except for prednisolone. She was discharged in April 1994.

In October 1997, the peripheral blood showed pancytopenia without blasts. She was admitted to our hospital again for further examination. The bone marrow showed hypoplasia with 10% of blasts. Cytogenetic analysis showed 47, XX, +8 in three metaphases and 46, XX in 17. Accordingly, therapy-related hypoplastic MDS was diagnosed. Low-dose Ara-C (10 mg/m^2) was injected s.c. every 12 h. She complained of high-grade fever on the 15th day of Ara-C therapy. Although there was no other reaction including hepatic and renal dysfunction, chemotherapy was discontinued on day 18 because fever was persistent. On day 29 after the treatment of low-dose Ara-C, hemoglobin was 9.3 g/dl, white blood cell count was 2100/μl (blast 0%) and platelet count was $9.4 \times 10^4/\mu$l. The marrow aspiration yielded normal cellularity with 2.0% of blasts. Normal female metaphases were obtained in all bone marrow cells. She received low-dose Ara-C for consolidation therapy on 21 January 1998. She had high-grade fever on day 2,

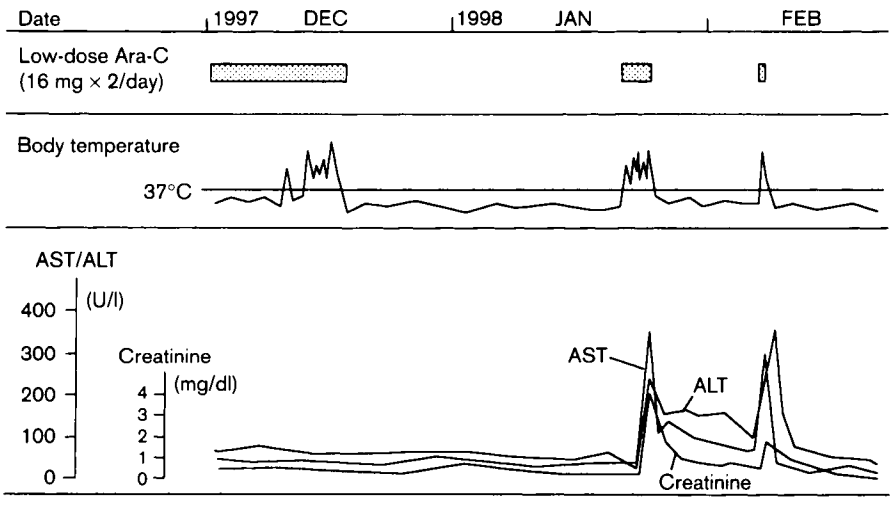

Figure 1. Clinical course of a patient receiving low-dose Ara-C for myelodysplastic syndrome.

and developed dyspnea, hepatic dysfunction and acute renal failure on day 4 of chemotherapy. C-reactive protein (CRP) increased to 26.4 mg/dl, total bilirubin to 1.3 mg/dl, serum AST to 368 U/l, ALT to 232 U/l and serum creatinine to 4.38 mg/dl. Therefore, low-dose Ara-C was discontinued on day 5 of the second course. She was treated with diuretics for reducing pulmonary edema. Abnormalities of laboratory data rapidly improved after discontinuation of chemotherapy. She received the third course of chemotherapy with 10 mg prednisolone in February. However, she had high-grade fever within several hours after the injection of Ara-C. Because hepatic and renal dysfunction was observed on the next day, the administration of Ara-C was discontinued. Within a few days after discontinuation of Ara-C, fever and abnormalities on the biochemical examination improved immediately. Although a drug lymphocyte stimulation test using Ara-C was done, it was unsuccessful because of lack of lymphocyte count. She was discharged without further chemotherapy (Figure 1).

Discussion

Widespread use of Ara-C for leukemia has led to the recognition of various adverse effects related to its use.[8] Major toxicities are myelosuppression, gastrointestinal toxicity, cardiopulmonary failure and neurotoxicity. Moreover, allergic reactions such as fever, exanthema and elevation of hepatic enzymes are relatively frequent. In this paper, the patient developed high-grade fever, elevation of CRP, hepatic dysfunction and renal failure during low-dose Ara-C therapy. Although the pathogenesis of these Ara-C-induced adverse reactions is unclear, it is suspected that these transient symptoms were caused by Ara-C or its metabolite in this case.

It is generally used at a standard dosage (100–200 mg/m^2/day as a continuous i.v. infusion for 7–10 days) in combination with anthracyclines.[1] Intermediate and high doses of Ara-C are employed to eliminate drug-resistant leukemic cells in refractory and relapsing AML. In the case of myelosuppression, gastrointestinal symptom and neurotoxicity, there is an obvious relationship between the degree of toxicity and both of dosage and duration of exposure of Ara-C. Hepatic dysfunction is suspected in 20–70% of patients with high-dose Ara-C, owing to an elevation of hepatic enzymes and bilirubin.[8] However, it should be considered that other cytotoxic agents are employed with Ara-C in many cases. Slavin *et al.* have reported that a 55–85% incidence of nephrotoxicity was found in patients with Ara-C, defined as an elevation of serum creatinine and/or a fall in creatinine clearance.[11] Furthermore, histologic findings suggest that Ara-C interferes with DNA synthesis at the tubular epithelial cell level.[12] A notable finding in the present case is the rapid improvement of laboratory data after discontinuation of Ara-C. It appears that pathogenesis of hepatic and renal dysfunction in low-dose Ara-C may be different from those in standard and/or high-dose Ara-C.

On the other hand, allergic reactions are not generally dependent on dose and duration of exposure. In addition, anaphylactic reaction to Ara-C has

been observed in several case reports.[9,10] Evidence of a specific antibody to Ara-C and the efficacy of desensitization in a patient with anaphylaxis to Ara-C have been demonstrated by Rassiga *et al.*[10] It was not anaphylaxis in our case, but an immunologic mechanism might act on the adverse reactions because symptoms developed coincident with second and third exposure to Ara-C.

In conclusion, we described a case of hepatic and renal dysfunction caused by low-dose Ara-C therapy. This form of allergic reaction has not been previously described in patients with low-dose Ara-C. Clinicians caring for such patients must be alerted to this type of adverse reaction, although this chemotherapy is generally well tolerated.

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