Gazi Tıp Dergisi / Gazi Medical Journal

OLGU SUNUMU - CASE REPORT

2008: Cilt 19: Sayı 4: 193-196

A PROBABLE CAUSE OF SEVERE HEPATOTOXICITY: CYTOSINE ARABINOSIDE

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ABSTRACT

Elevation in hepatic enzymes during the course of malignant hematological diseases may cause diagnostic difficulty. Here we present a patient who developed severe hepatotoxicity due to cytosine arabinoside (Ara-C) for treatment of acute myeloid leukemia. In the majority of patients, several drugs were used together with Ara-C during the course of treatment and blood transfusions were given. Therefore, it was difficult to differentiate which caused the hepatotoxicity. In our patient, hepatic damage might be related to Ara-C and other drugs such as sefepim, amikacin, meropenem, teicoplanin, and amphotericin B used in the first combination treatment. In conclusion, serious hepatotoxicity mimicking acute hepatitis may develop due to Ara-C for treatment of acute leukemia. However, in the second consolidation treatment, Ara-C was the only drug used and there were no other antibiotic or antifungal drugs. The elevation in hepatic enzymes was higher in the first combination treatment than in the second consolidation treatment with Ara-C. Therefore, hepatotoxicity due to Ara-C should also be considered in the differential diagnosis in leukemic patients with severe hepatic dysfunction.

Key Words: Liver Failure, Cytosine Arabinoside Palmitate.

CİDDİ HEPATOTOKSİSİTENİN OLASI BİR NEDENİ: SİTOZİN ARABİNOSİD

ÖZ

Malign hematolojik hastalıklarda karaciğer enzim yüksekliğinin ayırıcı tanısı zordur. Hematolojik malignitelerde akut hepatiti taklit eden ilaç iliskili hepatotoksitite gözlenebilir. Akut miyeloid lösemi (AML) tedavisinde sitozin arabinosid (Ara-C) kullanımına bağlı ciddi hepatotoksisite gözlenebilir. AML tedavisinde çok sayıda hasta Ara-C kullanımı sırasında baska ilaçlar kullanmakta ve kan transfüzyonu almaktadır. Bizim hastamızdaki hepatik hasar ilk kombinasyon tedavisinde Ara-C, sefepim, amikasin, meropenem, teikoplanin ve amfoterisin B gibi ilaçların kullanımı ile iliskili olabilir. Ancak ikinci konsolidasyon tedavisinde Ara-C'nin yanında herhangi bir antibiyotik ya da antifungal kullanılmadı. Karaciğer enzimlerindeki yükselme ilk kombinasyon tedavisinde konsolidasyon tedavisine göre daha fazlaydı. Bu nedenle lösemik hastalardaki ciddi hepatik disfonksiyonun ayırıcı tanısında Ara-C iliskili hepatotoksisite de göz önünde bulundurulmalıdır.

Anahtar Kelimeler: Hepatotoksisite, Sitozin Arabinosid.

Geliş Tarihi: 29/07/2008 *Kabul Tarihi: 01/12/2008*

Received: July 29, 2008 *Accepted: December 01, 2008*

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INTRODUCTION

Elevation in hepatic enzymes during the course of malignant hematological diseases is a common finding. This is due to viral hepatitides from frequent blood transfusions as well as leukemic infiltration of the liver or drug toxicity. Cytosine arabinoside (Ara-C) is an effective agent used for the treatment of malignant hematological diseases, and exhibits its activity by inhibiting DNA synthesis following conversion to 5-monophosphate nucleotide by the enzyme deoxycytidine kinase after being carried to the cytoplasm.[1-3] Its main side effects are myelosuppression, fever, alopecia, gastrointestinal ulceration, hyperpigmentation, neuropathy, and somnolence.[4] Hyperbilirubinemia, elevation in transaminases, and icterus have rarely been reported due to the use of Ara-C. The risk of hepatotoxicity increases with long-term use and high dosages of Ara-C. The diagnosis of hepatic toxicity due to Ara-C may be difficult.[5] We present a patient with severe hepatotoxicity due to cytosine arabinoside (Ara-C) for treatment of acute myeloid leukemia (AML).

CASE

A 57-year-old woman presented with fever. There was no history of alcohol consumption or liver disease. Her blood pressure was 120/80 mmHg, fever 38.8 °C, and her skin and mucous membranes were pale. Laboratory findings were a hemoglobin level of 79 g/l, a white blood cell count of 2800/mm3, a platelet count of 58,000/mm3, a mean of erythrocyte volume of 94.4 fL, a reticulocyte count of 1%, and an erythrocyte sedimentation rate of 70 mm/h. Peripheral blood cell examination revealed 12% neutrophils, 44% lymphocytes, 40% blasticcells, 4% metamyelocytes, and 1% normoblasts. Moreover,hypochromia was observed in the erythrocytes. Bone marrow aspiration and biopsy revealed 59% of big blastic cells with narrow cytoplasm, vacuoles, granulations, fine nuclear chromatin, and prominent nucleoli and without Auer bodies. Blastic cells were stained with Sudan Black-B. CD45, CD13, and CD33 were positive on flow cytometry on bone marrow aspiration. No cytogenetic abnormality in bone marrow was detected using G banding. Acute myeloid leukemia (AML-M1) was diagnosed in the patient. The patient was given 12 mg/m2 Idarubicin for 3 days and cytosine 100 mg/m2 arabinoside for 7 days (Ara-C) as induction chemotherapy.[6] Before chemotherapy the liver function tests were normal. Elevations in the aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were noted on the 6th day of chemotherapy. Because of the detection of gram-positive bacilli in the blood culture during the febrile period, 4 g/d sefepim was started, according to the Neutropenic Fever Guidelines of the Infectious Diseases Society of America.[7] Then 1 g/d amikacin and 400 mg/g teicoplanin were added, because the fever continued. We did not detect any microorganism in cultures. On the 13th day of chemotherapy, sefepim was discontinued and 3 g/d meropenem was started. Teicoplanin and amikacin were disconti-

Table 1: Changes in hemogram and biochemical parameters with two different Ara-C therapies.

	1. ARA-C Day 0	Day 45*	2. ARA-C Day 0	Day 17*
Urea (mg/dl)	52	18	27	33
Creatinine (mg/dl)	0.6	0.6	0.6	0.6
ALT (IU/L)	37	837	24	310
AST (IU/L)	27	934	25	198
GGT (IU/L)	13	206	19	38
ALP (IU/L)	162	336	93	93
T. Bil. (mg/dl)	0.2	0.8	0.4	0.4
D. Bil. (mg/dl)	0.1	0.5	0.2	0.3
Hemoglobin (g/dl)	9.3	10.4	9.7	8.6
Hematocrit (%)	27.0	30.7	28.8	24.5
Leukocyte (/µL)	2500	3200	4200	1200
Neutrophil (/µL)	800	2100	3600	400
Platelet (/µL)	50000	175000	394000	107000

* The days during which levels of hepatic enzymes were highest in the two treatment courses with Ara-C.

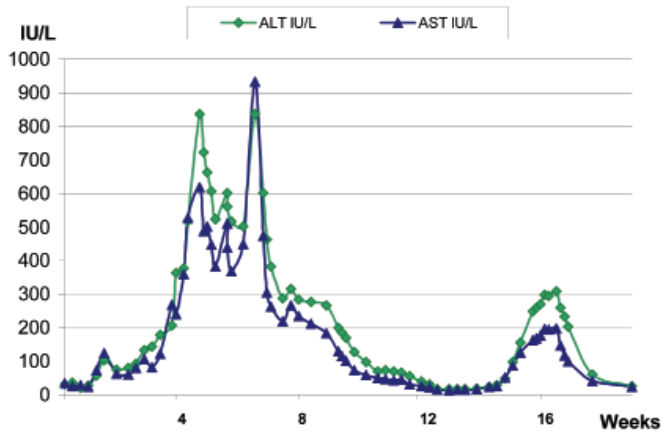
nued on the 5th and 9th days of chemotherapy, respectively. Because the fever continued, 0.5 mg/kg amphotericin deoxycolate was started, but she did not tolerate this drug and the treatment was changed to 3 mg/kg liposomal amphotericin B.[6] The bone marrow biopsy and aspiration performed on the 21st day of the chemotherapy showed that the patient wasin remission. Meropenem and liposomal amphotericin were discontinued after 2 weeks. The elevation in the hepatic enzymes was continuing on the 45th day of chemotherapy (Table1). Based on the Toxicity Criteria of the National Cancer Institute, the patient was considered as having grade-4 hepatotoxicity (rise in AST/ALT more than 20-fold).[8] Hepatitis B surface antigen, antibodies to Hepatitis-A virus, Hepatitis-B core antigen IgM, total Hepatitis-B core antigen, Hepatitis-C virus, Hepatitis E virus, cytomegalovirus IgM, and Transfusion Transmitted Virus, Viral Hepatitis-B virus DNA, and Hepatitis-G Viral RNA were negative. Anti-LKM-2 (liver kidney microsomal antibody type 2) was negative.[9] The liver biopsy revealed hydropic degeneration, ground-glass appearance, and micro- and macro-vesicular steatosis in the hepatocytes, a few apoptotic bodies, evidence of cholestasis, foci of spotty necrosis, and low-grade mononuclear cell infiltration including eosinophils in the portal areas (Figure 1). Hepatic enzymes decreased to normal on the 3rd month (Diagram 1). Then 2 g/m2 Ara-C on days 1, 3 and 5 as consolidation therapy was started.[10] An elevation in hepatic enzymes was observed again on the 4th day of chemotherapy with high-dose Ara-C.

Hepatic enzymes normalized in the 4th week of consolidation therapy. At the time of writing the patient was in remission in the 18th month of diagnosis and receiving high dose Ara-C in the same dosages as maintenance therapy with 3-month intervals.

Liver biopsy revealed hydropic degeneration, ground-glass appearance, and micro- and macro-vesicular steatosis in the hepatocytes, a few apoptotic bodies, evidence of cholestasis, foci of spotty necrosis and low grade of mononuclear cell infiltration including eosinophils in the portal areas.

DISCUSSION

We treated our patient with Ara-C and idarubicin as consolidation treatment for acute leukemia. Moreover, the patient received several antibiotics and antifungal treatment because



Diyagram 1: The days during which levels of transaminases were in two treatment courses with Ara-C.

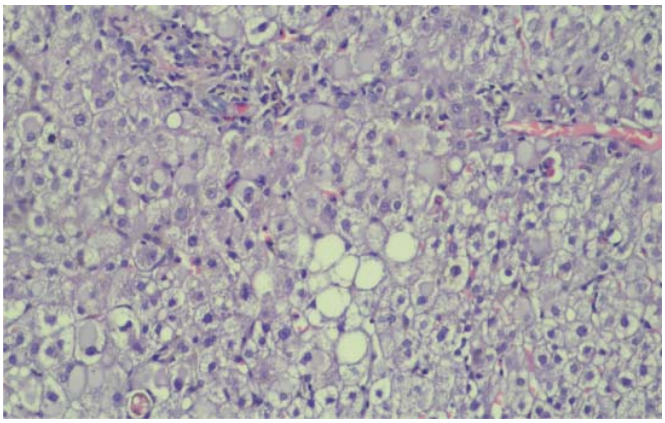


Figure 1: View of hepatic biopsy (H&E, x 200).

of febrile neutropenia after induction therapy. During this treatment, hepatic enzymes were markedly elevated. We thought that this elevation in the hepatic enzymes may be related to the drugs, but idarubicin-induced hepatotoxicity has not been reported in the literature.[8]

Serious hepatotoxicity due to allopurinole has developed during treatment of leukemia but is rare. There are 7 such cases in the literature. Granulomas have often been observed in hepatic biopsies in these cases.[11] Serious hepatotoxicity due to aminoglycosides and glycopeptides are rarely seen.[12] Hepatic dysfunction has been considered a typical adverse reaction to amphotericin B but the incidence of serious hepatotoxicity due to this drug is very low.[13] In our patient, bilirubin levels were within normal limits and viral markers such as Hepatitis-B, Hepatitis-C, Hepatitis-G, transfusion-transmitted viral antibody, and cytomegalovirus IgM were negative. Thus, the possibility of hepatides related to transfusion was excluded. We did not detect any evidence of leukemic infiltration in the liver biopsy. There was no hemolysis in our patient. Moreover, the patient received multiple blood transfusions. Thus it was very difficult to know what had caused the hepatotoxicity. However, in the second consolidation treatment Ara-C was the only drug used and there were no other antibiotic or antifungal drugs.

Elevation in the hepatic enzymes was higher in the first combination treatment than in the second consolidation treatment with Ara-C. When all the possibilities are considered, hepatic damage might be related to Ara-C, and other drugs such as sefepim, amikacin, meropenem, teicoplanin, and amphotericin B used in the first combination treatment might have contributed to the hepatic damage. The Naranjo ADR probability scale showed that a relation between hepatotoxicity and Ara-C was probable.[14]

During the treatment of AML, elevation of hepatic enzymes usually occurs due to hepatitis viruses and leukemic infiltration rather than drug toxicity. Drug-related hepatotoxicity in AML is uncommon.[15] The diagnosis may be difficult, unless a known hepatotoxic drug or a hepatitis picture related to transfusions is present.[5,8] Hepatotoxicity due to Ara-C may rarely occur and is usually associated with jaundice and hyperbilirubinemia.[5]

Herzig et al. reported hepatotoxicity due to Ara-C, but hepatotoxicity in these patients presented as slight elevations in the levels of aminotransferases, alkaline phosphatase (ALP), and bilirubin.[10] Hepatotoxicity was transient and not dose-limiting and serious jaundice has not been reported. Donehower et al. detected hepatic dysfunction in 24 of 27 patients receiving a high-dose of Ara-C through infusion for 72 hours.[16] Hepatotoxicity was reversible and it was not necessary to warrant dose limitation. Amadori et al.[17] found mild hepatotoxicity in 2 of 8 patients treated with high-dose Ara-C and L-asparaginase for lymphoma and leukemia of the central nervous system. Popov et al. observed grade-3 hepatotoxicity in one of 37 patients using cisplatin and high-dose Ara-C for advanced gastric and colonic carcinoma.[18] Babaoglu et al. reported hepatotoxicity due to the interaction between Ara-C and dipiridamol in one patient.[3] Hepatotoxicity was explained by the inhibition of extracellular transportation of Ara-C by dipiridamol and increased intracellular level of Ara-C in the hepatocytes. Although hepatic dysfunction due to high-dose Ara-C has been reported in 20% to 70% of the patients, no information was given on the level of toxicity. Moreover several drugs were used together with Ara-C in the majority of patients.[2,19] In an early report, hepatic dysfunction was found in 37 of 85 patients with leukemia receiving Ara-C.[20] but in the majority of patients, there was hepatic dysfunction prior to the treatment or confounding factors such as sepsis or hemolysis; therefore no definite evidence of hepatotoxicity could be found.

In conclusion, serious hepatotoxicity mimicking acute hepatitis may develop due to Ara-C given for treatment of acute leukemia. In our patient, we think that Ara-C was the probable cause of the hepatotoxicity. Hence, hepatotoxicity due to Ara-C should be considered in the differential diagnosis in leukemic patients with severe hepatic dysfunction.

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