Cytarabine-Induced Hyperbilirubinemia in a Pregnant Patient with Acute Myeloid Leukemia

Abdelwahab Ahmed, MD,[1] Yalda Dehghan, MD,[1] Ji-Cheng Hsieh, BS,[2] Christopher Moore, MD[3]

[1]Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [2]Northwestern University Feinberg School of Medicine, Chicago, IL, USA, [3]Division of Gastroenterology and Hepatology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

BACKGROUND

Cytarabine is a mainstay chemotherapeutic agent used in the management of acute myeloid leukemia (AML).[1] The adverse reactions of cytarabine discussed in the literature include bone marrow suppression,[2] non-cardiogenic pulmonary edema,[2] neurotoxicity,[3,4] and cytarabine syndrome,[5] which causes fevers, myalgias, and rash. Liver injury, including jaundice, has also been reported.[1,2,6] In particular, there is a growing body of literature reporting rare instances of direct hyperbilirubinemia without elevated transaminases or coagulopathy in patients undergoing treatment with cytarabine.

Here, we present the first reported case of direct hyperbilirubinemia in pregnancy without evidence of synthetic liver dysfunction in a patient recently initiated on a 7+3 regimen for inv16 AML.

PATIENT PRESENTATION

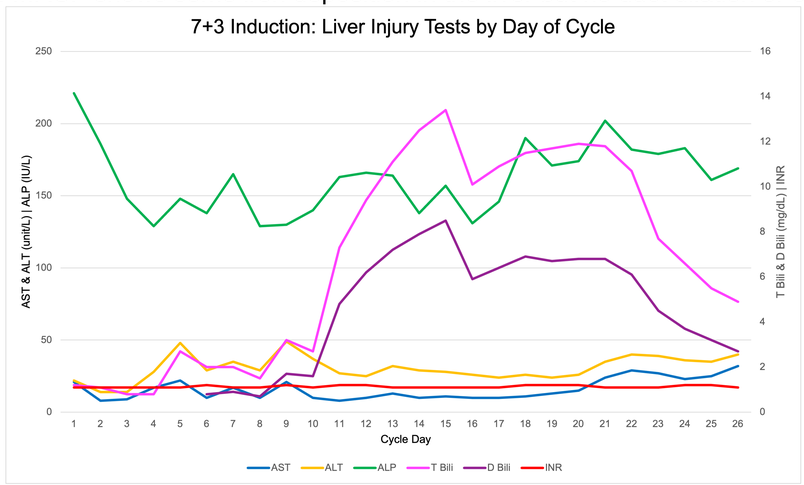
A 33-year-old G2P1 female at 19 weeks gestation with a history of gestational hypertension presents with 4 days of dyspnea on exertion.

She was found to have a WBC count of 86.6, hemoglobin of 5.5, and platelet count of 18. Differential revealed 80% circulating blast cells. PE, pneumonia, ACS, and other etiologies of DOE were ruled out. The patient was then admitted to the hematology-oncology service and bone marrow biopsy confirmed inversion 16 +22 AML.

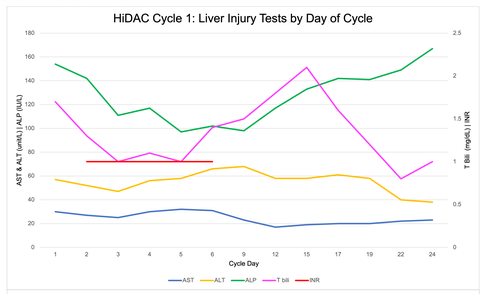
Maternal-fetal medicine was consulted to better characterize contraindications of various chemotherapeutic regimens. It was decided that patient would receive induction therapy with daunorubicin and cytarabine.

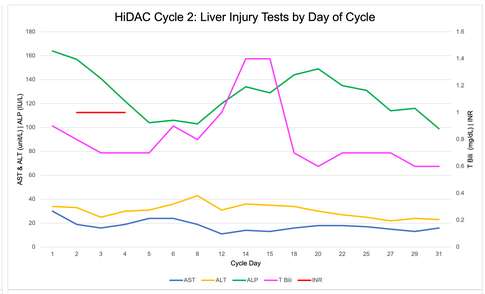
HOSPITAL COURSE

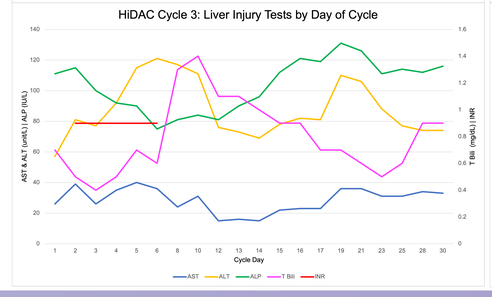
- **Induction regimen:** Daunorubicin 60mg/m^2 (day 1-3) + cytarabine 100mg/m^2 (day 1-7)
- **Day 5:** patient develops T Bili of 2.7 mg/dL
  - Right upper quadrant ultrasound with no evidence of dilation
- **Day 14:** MRCP shows some iron deposition in the liver but no duct dilation or obstruction

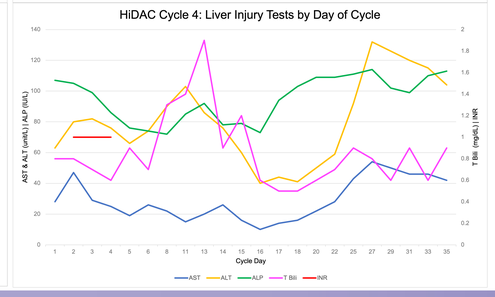


- Following induction, patient received 4 more cycles of high dose cytarabine (HiDAC) at a reduced dose









DISCUSSION

Here we present the first reported case of cytarabine-induced hyperbilirubinemia in a pregnant patient without evidence of synthetic liver dysfunction. The patient presented with primarily direct hyperbilirubinemia and did not exhibit coagulopathy or elevated transaminases. Additional workup was negative for other obvious etiologies of direct hyperbilirubinemia, including autoimmune causes, obstruction, infection, and other drug-induced liver injury. She was largely asymptomatic except for pruritis, which was treated with ursodiol.

It is worth noting that due to the patient's pregnancy, liver biopsy was deferred due to concerns that this would harm her fetus. In another report of cytarabine-induced direct hyperbilirubinemia, a liver biopsy was performed and did not show any abnormality.[7]

Following induction therapy, the patient completed consolidation chemotherapy which typically involves a higher dose of cytarabine. Due to the hyperbilirubinemia during induction, a lower dose was used for the consolidation phase. On this lower dose, the total bilirubin was never higher than 2 mg/dL. This suggests a correlation between drug dose and degree of bilirubin elevation, though this is in the absence of coagulopathy or transaminase elevation. In this patient, the modified dose did not affect her remaining cancer treatment and she has been in remission since April 2022.

References

1. Coutsouvelis J, Corallo CE. The management of prolonged, isolated hyperbilirubinemia following cytarabine-based chemotherapy for acute myeloid leukaemia. J Oncol Pharm Pract. Jun 2009;15(2):107-10. doi:10.1177/1078155208097633
2. Stentoft J. The toxicity of cytarabine. Drug Saf. Jan-Feb 1990;5(1):7-27. doi:10.2165/00002018-199005010-00003
3. Baker WJ, Royer GL, Jr., Weiss RB. Cytarabine and neurologic toxicity. J Clin Oncol. Apr 1991;9(4):679-93. doi:10.1200/JCO.1991.9.4.679
4. Dotson JL, Jamil MO. Successful treatment of cytarabine-related neurotoxicity with corticosteroids, a case series. Int J Hematol. Nov 2018;108(5):554-557. doi:10.1007/s12185-018-2485-4
5. Jirasek MA, Herrington JD. Cytarabine syndrome despite corticosteroid premedication in an adult undergoing induction treatment for acute myelogenous leukemia. J Oncol Pharm Pract. Dec 2016;22(6):795-800. doi:10.1177/1078155215607090
6. Altundag O, Altundag K, Celik I, Turker A, Kars A. Isolated hyperbilirubinemia following standard dose cytosine arabinoside in a patient with relapsed acute myeloid leukemia. Am J Hematol. Apr 2004;75(4):263-4. doi:10.1002/ajh.20029
7. Cheung M, Bhagat V, Pawa S. A Case of Isolated Direct Hyperbilirubinemia Associated with High Dose Cytarabine: 1354. Official journal of the American College of Gastroenterology | ACG. 2018;113:S776.