Acute Hepatotoxicity After High-Dose Cytarabine for the Treatment of Relapsed Acute Myeloid Leukemia: A Case Report

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Abstract

Purpose: Cytarabine is considered the standard of care for induction therapy in patients with acute myeloid leukemia (AML) who are preparing for bone marrow transplant. **Summary:** We report a case of a 72-year-old female presenting to the intensive care unit with hepatic failure after high-dose cytarabine (HiDAC) for the treatment of relapsed AML. The patient's liver function tests (LFTs) were elevated acutely, with a mildly elevated bilirubin and a normal alkaline phosphatase. HiDAC was discontinued but her LFTs remained high for 9 days post discontinuation, and the patient eventually expired due to sepsis and multiple organ failure. We estimated the probability of the hepatotoxicity observed with HiDAC as probable based on a score of 5 on the Naranjo scale. **Conclusion:** Clinicians should be aware of the potential hepatotoxicity associated with HiDAC for patients with AML, specifically in the elderly population.

Keywords

cytarabine, hepatotoxicity, liver failure

The current standard of care for induction therapy in the treatment of acute myeloid leukemia (AML) consists of a “7 + 3” regimen, which includes 7 days of cytarabine 100 to 200 mg/m² and 3 days of an anthracycline (daunorubicin, idarubicin) or an anthracenedione (mitoxantrone) over 7 days total of treatment. High-dose cytarabine (HiDAC; doses from 1-3 g/m²) is commonly used in AML patients who have relapsed or refractory response to induction therapy and may be preferred in patients younger than 60 years old, or with a high-performance status, due to toxicities.^{1,2}

The toxicity profile of cytarabine includes myelosuppression, nausea, vomiting, and neurotoxicity.³ Cytarabine is a synthetic pyrimidine nucleoside, which mimics endogenous nucleoside, cytidine, and deoxycytidine. Once the cellular uptake of cytarabine occurs, it inhibits DNA synthesis by inducing S Phase cell cycle arrest.^{4,6} Cytarabine is phosphorylated to its triphosphate form (ara-TP) in both normal and leukemic cells.⁶ It is then enzymatically degraded to its uracil form by cytidine deaminase; of which, significant levels are found in the liver, gastrointestinal mucosa, kidneys, and leukemic cells.^{6,7} The clinical rationale of using HiDAC relies upon ara-TP intracellular accumulation in leukemia cells versus plasma concentration as measured by area-under-the-curve.⁸ When plasma concentration remain within the range of 3 to 10 µmol/L, the rate of intracellular uptake remains linear. This desirable plasma concentration range is most likely to be achieved at doses no less than 0.5 g/m² and infused over 2

hours. It was demonstrated by the Southwest Oncology Group that patients receiving both HiDAC and anthracycline therapy have a superior 4-year survival and disease-free-survival compared with patients who received low-dose cytarabine for induction and consolidation therapy.¹ Thus, there are potential benefits in using HiDAC for patients with relapsed AML. Hepatotoxicity is not a commonly reported side effect of cytarabine as evidenced by the scant reports in the literature, yet clinicians should be mindful of this potential adverse effect when prescribing cytarabine.

Case Report

A 72-year-old Caucasian female (58 kg, 169 cm, body surface area [BSA] = 1.66 m²) was admitted to our bone marrow transplant (BMT) unit for a 7 + 3 induction chemotherapy with cytarabine 100 mg/m² (170 mg) infused over 24 hours and idarubicin 12 mg/m² (20 mg). Her most recent bone marrow biopsy (BMBX), done 9 days prior to admission, showed

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Figure 1. Liver function tests following cytarabine therapy.

residual AML with 40% to 50% blasts. Her notable past medical history includes breast cancer treated with lumpectomy and radiation therapy over 20 years ago. She also had a history of myelodysplastic syndrome for which she was treated with 6 cycles of parenteral azacitidine 75 mg/m² 5 months prior to admission. Following the azacitidine therapy course and approximately 5 weeks prior to admission, the patient was diagnosed with AML and had recently received 6 out of 10 planned days of decitabine 20 mg/m² (34 mg) intravenously (IV) every 24 hours. The decitabine regimen was complicated by neutropenic fever secondary to a tooth abscess, and her chemotherapy was halted after receiving only 6 doses. The patient's home medications at the time of admission were atorvastatin, hydrochlorothiazide-triamterene, isosorbide mononitrate, levothyroxine, lidocaine 2% mucous membrane solution, and metoprolol succinate.

The patient's baseline total bilirubin (T.bili) prior to cytarabine was 2.0 mg/dL (normal range 0.2-1.1 mg/dL) on hospital day 1 and fluctuated between 1 and 2.3 mg/dL during her prior treatment with decitabine. The initial elevation of T.bili occurred on hospital day 3 (during her cytarabine induction day 1) that rose from 1.5 mg/dL to 2.4 mg/dL, between hospital days 3 and 4. A direct Coombs test, lactate dehydrogenase (LDH), cold agglutinins came back negative for active hemolysis; however, a right upper quadrant ultrasound showed coarsened liver parenchyma. The patient's serum albumin and liver function tests (LFTs) such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (AP) remained unremarkable from hospital day 1 to 4. In light of the acute change of bilirubin, her atorvastatin was held on hospital day 4. She went on to finish her 7 + 3 induction regimen without further complications. The timeline of cytarabine exposure and trends of LFTs and T.bili are shown on Figure 1.

On hospital day 12, she developed neutropenic fever with a maximum recorded temperature (T_{max}) of 99.6°F and recorded a low blood pressure of 95/41 mmHg. An empiric 7-day regimen of cefepime was completed with no definitive source of infection identified. The patient's BMBX on hospital day 18 showed residual AML with 20% to 30% blasts, and HiDAC IV 1566 mg/m² (2600 mg) every 12 hours was initiated on hospital day 22. The dose was empirically reduced by 50% due to age greater than 60, per standard of care at our institution. She ultimately received 9 of 12 planned doses of HiDAC. LFTs on day 21 were within normal limits (WNL), with the exception of T.bili at 1.2 mg/dL, conjugated bilirubin (C.bili) of 0.3 mg/dL (normal range 0-0.2 mg/dL), and serum albumin of 2.4 g/dL (normal range 3.3-4.6 g/dL). On hospital day 24, she complained of pain at her peripherally inserted central catheter site, blood pressure was reported as 160/85 mmHg and a body temperature of 97.5°F but was tolerating chemotherapy well otherwise.

On hospital day 25 to day 27, the patient developed atrial fibrillation and progressive altered mental status. Physical exam findings were positive for newly onset jaundice and disorientation to time and place; however, her skin was warm and dry. Her morning HiDAC dose was held and eventually discontinued. On hospital day 27, the patient experienced respiratory distress, tachypnea (38 breaths/min), and an increased serum lactate of 12.4 mmol/L (normal value <2 mmol/L). Blood pressure remained unchanged from baseline which was slightly hypertensive with mean arterial pressure greater than 80 mmHg. The patient's respiratory status declined, requiring endotracheal intubation and transfer to our intensive care unit (ICU). Initial ventilator settings were pressure regulated volume control, with a tidal volume of 400 ml, respiratory rate (RR) 15 breaths/min, positive-end-expiratory pressure of 5 cm H₂O, and oxygen concentration at 100%. At the time of the

patient's admission to the ICU, AST had elevated to 153 U/L, ALT 169 U/L, AP 102 U/L, T.bili 2.3 mg/dL, C.bili 0.9, albumin 2.6 g/dL, and international normalized ratio (INR) of 2.0. See Figure 1 for LFT trend related to cytarabine doses. The patient received a total 9 of the planned 12 doses of HiDAC before it was discontinued on hospital day 27 due to her worsening condition. At the time of this acute change in LFTs, the patient was also on posaconazole oral 300 mg once daily given from hospital days 11 to 26, midazolam IV 6 mg on days 27 to 29, and a total of dose 1600 mcg of IV fentanyl between days 27 and 30.

On hospital day 28 (ICU day 2), the patient's AST has increased to above the upper limit of detection at greater than 7000 U/L, ALT 4638 U/L, T.bili 2.8 mg/dL, INR 2.1, however the AP was WNL at 85 U/L. The patient was diagnosed with severe sepsis as evidenced by tachycardia (heart rate [HR] in the 140s), T_{max} of 103.2°F. Blood cultures drawn at the time of transfer returned positive for *Rothia Mucilaginosa*. The patient's hepatitis antibody panel (A, B, C) were negative. Additional ICU admission diagnosis included acute hypoxic respiratory failure and lactic acidosis.

On hospital day 29 (ICU day 3), the patient's LFTs began to trend down, but remained elevated (AST 3934 U/L, ALT 3984 U/L), AP remained WNL at 99 U/L, T.bili 3.4 mg/dL, and INR 1.8. By hospital day 32 (ICU day 6), LFTs improved marginally, but were still abnormally high, respiratory status had improved, and she was liberated from mechanical ventilation.

Soon after extubation, the patient deteriorated, developed hypoxic, tachycardic, and acutely encephalopathy. At this time, the family decided to pursue comfort care measures only, and the patient passed away on hospital day 38. Her AST eventually came down to below 100s U/L on days 35 and 36.

Discussion

This report represents a rare adverse drug reaction of HiDAC associated severe hepatic damage without a major elevation in bilirubin in an elder patient with AML. A list of PubMed search (1950 to March 2018) with search terms “(cytarabine* OR ara-C* OR arabinosyl cytosine* OR high-dose cytarabine*) AND hepatotoxicity” yielded 5 previous case reports of cytarabine and hepatotoxicity-related reactions (Table 1).

The severity of hepatotoxicity was classified as World Health Organization (WHO) grade 4 by AST and ALT ($>10\times$ ULN), grade 2 hyperbilirubinemia ($2.3\times$ ULN), grade 1 blood urea nitrogen (BUN) ($1.8\times$ ULN), and grade 0 by AP and creatinine (WNL).⁵ The isolated incident of hyperbilirubinemia prior to her HiDAC therapy is likely due to her previous decitabine treatment, given the lack of confounding factors. While the exact metabolism of decitabine is unknown, it does undergo deamination mediated by cytidine deaminase much like cytarabine.¹³ It is possible that decitabine predisposed the patient to the observed hepatotoxicity during HiDAC therapy due to its actions on cytidine deaminase.

Posaconazole could also have been a contributing factor in the patient's hepatotoxicity, as it was given on hospital days 11 to 26 for a total of 16 doses. However, the patient's LFTs remained WNLs from hospital day 11 to day 26, thus posaconazole is unlikely to be culprit behind the observed acute hepatotoxicity.

To assess the probability of a drug-related adverse reaction of cytarabine and the observed hepatotoxicity, we used the Naranjo Adverse Drug Reaction Scale (score = 5), which indicated the relationship between hepatotoxicity and cytarabine observed in our patient was probable.¹⁴ However, it is inconclusive as to whether this adverse effect was dose related.

The most common adverse effects of cytarabine include myelosuppression, nausea, vomiting, diarrhea, and immune-suppression related infection.^{5,9} There is minimal published literature to establish a definitive link between cytarabine and hepatotoxicity. This is further complicated by the varying dosages of HiDAC. As a case in point, our patient suffered severe hepatotoxicity at an empirically reduced dose for her age (50% reduction). We discovered 5 patient case reports on hepatic dysfunction associated with the use of cytarabine. The 2 patients reported by George et al developed hepatic dysfunction 7 to 14 days after HiDAC, both patients exhibited hyperbilirubinemia, elevated AP, but a normal AST/ALT.¹⁰ Tanaka et al discussed a patient who received low-dose cytarabine who developed hepatic dysfunction during the course of chemotherapy by an elevated AST/ALT ($10\times$ and $7\times$ ULN, respectively), slight elevation of T.bili and acute renal failure.¹¹ Our patient had an abnormally high AST/ALT, a mild increase of serum creatinine, and although our patient exhibited mildly elevated bilirubin, it was during and before the discontinuation of HiDAC. A fourth reported case reported by Nachbaur et al was a young female patient who went into fulminant hepatic failure 25 days after the second course of HiDAC and mitoxantrone (HAM) treatment for a second relapse of AML. Hepatotoxicity (WHO grade I with ALT of 110 U/L) was first observed 14 days after the first cycle of HAM. The patient received a second course of HAM for consolidation therapy after the normalization of her LFTs, where a WHO grade II hepatotoxicity was observed at the end of the treatment. Twenty-five days after the end of her second course of HAM, she developed severe abdominal pain, vomiting, diarrhea, jaundice, a grade I encephalopathy, and grade III-IV hepatotoxicity as outlined by the laboratory findings in Table 1.¹² However, the presence of elevated bilirubin does not necessarily predict hepatotoxicity in patients on cytarabine. Barker et al demonstrated a safe use of reduced dose of HiDAC for a patient with a bilirubin in the range of 10 mg/dL; notably LFTs were not reported.¹⁵ Nonetheless, the patient was declared leukemia free after cytarabine therapy.

There is no consensus in the literature as to the definition of hepatic dysfunction in patients receiving cytarabine. It is unclear whether elevated bilirubin or other markers of hepatic dysfunction can be used to reduce the dose of

Table 1. Reported Cases of Hepatotoxicity Following Cytarabine Therapy.

Patient	Presentation	Other concurrent hepatotoxic medications	Cytarabine exposure	Pertinent laboratory or other findings	Outcome
A 72-year-old female with acute myeloid leukemia with 40% to 50% blasts ^(our case)	Became jaundiced and experienced AMS 5 days after HiDAC	Posaconazole 300 mg once daily on day 21 to day 26 Micafungin 100 mg once daily on day 30 to day 34	Nine doses of HiDAC 1.5 g/m ² given Q12H	Liver baseline: Normal with slightly elevated T.bili Liver dysfunction following cytarabine: AST 7000 U/L, ALT 4638 U/L, T.bili 2.3 mg/dL	Care withdrawn per family's request
A 45-year-old male with Philadelphia chromosome positive chronic myelogenous leukemia. ⁹	Became jaundiced second week after chemotherapy	Prochlorperazine 10 mg for the first 6 days of chemotherapy Allopurinol, dosage and frequency not reported	Twelve doses of HiDAC 3 g/m ² given Q12H	Liver baseline: WNL on admission Liver dysfunction following cytarabine: AST 39 U/L, AP 393 U/L, LDH 133 U/L, T.bili 21 mg/dL. U/S negative for gallstones or biliary system dilatation. Postmortem showed no evidence of septic cholangitis or abscess	Expired due to sepsis
A 31-year-old male with T-cell lymphoblastic leukemia. ⁹	Became jaundiced 7 days after chemotherapy	Prochlorperazine 10 mg for the first 6 days of chemotherapy Allopurinol, dosage and frequency not reported	Twelve doses of HiDAC 3 g/m ² given Q12H	Liver baseline: Not reported Liver dysfunction following cytarabine: AST 10 U/L, AP 103 U/L, LDH 131 U/L, T.bili 23 mg/dL. U/S normal	Expired due to septic shock
A 45-year-old Japanese female with secondary myelodysplastic syndrome. ¹⁰	High-grade fever, dyspnea, acute renal failure on Day 4 of chemotherapy	None or not reported	Low-dose cytarabine 10 mg/m ² SQ Q12H. Discontinued after 9 doses	Liver baseline: WNL Liver dysfunction following cytarabine: AST 368 U/L, ALT 232 U/L, T.bili 1.3 mg/dL	Discharged without further chemotherapy
A 15-year-old female with relapsed AML. ¹¹	Severe abdominal pain, vomiting, diarrhea, jaundice and grade I encephalopathy 25 days after chemotherapy	Two doses of mitoxantrone 12 mg/m ²	Six doses of HiDAC 3 g/m ² given Q12H	Liver baseline: ALT 110 U/L (WHO grade I), AP 2x ULN Liver dysfunction following cytarabine: AST 4500 U/L, ALT 3330 U/L, LDH 15030 U/L, AP 324 U/L, bilirubin up to 2.6 mg% (WHO grade III-IV). U/S positive for hepatomegaly	Patient developed encephalopathy and expired
A 46-year-old male with Janus kinase 2 positive, BCR-ABL negative myelofibrosis. ¹²	Not reported	None or not reported	Three doses of reduced dose of HiDAC 1 g/m ²	Liver baseline: bilirubin 15.9 mg/dL Liver dysfunction following cytarabine: Bilirubin of 7.6 mg/dL and 3.2 mg/dL on day 6 and 18 of cytarabine therapy, respectively.	Leukemia-free greater than 2 years posttransplant

Note. HiDAC = high-dose cytarabine; T.bili = total bilirubin; AST = aspartate aminotransferase; ALT = alanine aminotransferase; WNL = within normal limit; AP = alkaline phosphatase; LDH = lactate dehydrogenase; U/S = ultrasound; WHO = World Health Organization; ULN = upper limit of normal; AMS = altered mental status; Q12H = every 12 hours.

cytarabine, or to what extent.^{5,15,16} It is important to note that while the existing case reports have similarity to our patient, none of them exhibited the same degree of severity and quick onset of hepatotoxicity. The inconsistency between the reported laboratory values of LFTs and T.bili levels compared with the observed manifestation and severity of hepatotoxicity in the literature does not provide a clear cause–effect relationship. Based on our patient's presentation, and published reports, there is not enough evidence to suggest that bilirubin alone could have been a predictive marker in hepatic injury for our patient.

The patient was not hypotensive during her HiDAC therapy, nor did she have a significant history of hepatic injury or a positive hepatitis panel. It is possible given the age of our patient, she was at a higher risk of hepatic injury, however; data are lacking to prove this hypothesis. In addition, she received a reduced dose of cytarabine empirically due to her increased age. A recent study suggested that patients who have a homozygous variant TT of *NT5C2*, a gene that

encodes metabolic enzymes for cytarabine, are at a higher risk of hepatotoxicity. Within that retrospective study cohort, a higher frequency of this homozygous variant was observed in patients 65 years or older.¹⁷ Our patient was the oldest at age 72 where other patient cases reported in the literature were all below the age of 65. It is possible that our patient had the homozygous TT variant of the *NT5C2* gene and thus was at a higher risk of cytarabine-related toxicity. Although our patient was previously exposed to a lower dose of cytarabine, the extensive hepatic injury did not manifest until the higher dose was given. The half-life of cytarabine is relatively short, within 1 to 3 hours in the elimination phase.¹¹ Without other obvious concurrent hepatotoxic medications or causes of the acute hepatic injury and lactic acidosis, we assigned this drug reaction a score of 5 on the Naranjo scale; it was probable that cytarabine, specifically, HiDAC, was associated with the observed hepatotoxicity. Clinicians should exercise caution when using cytarabine in elderly patients with and without preexisting hepatic conditions.

Conclusion

We report a case of HiDAC-induced acute liver failure in a relapsed AML patient who developed respiratory failure, AMS, very abnormal LFTs, and who eventually expired. The existing literature linking cytarabine to hepatotoxicity is sparse; the manifestations and laboratory findings remain heterogeneous, thus making this adverse effect difficult to predict. While cytarabine remains the backbone of treatment options for patients with AML, special considerations should be taken into account for elderly patients regardless of preexisting or concurrent hepatic injury. Additional studies are needed to determine specific risk factors and dose reduction strategies to mitigate hepatotoxicity during cytarabine therapy.

Declaration of Conflicting Interests

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