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Rapid Onset Liver Injury Due to Azacitidine Through Possibly a Unique Mechanism of Hypoperfusion of the Liver

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Abstract

Azacitidine and venetoclax are important anti-neoplastic agents used in the treatment of acute myeloid leukemia. Azacitidine has been implicated to cause nonhepatic ischemic injury. Here we report a case of severe, short latency drug-induced liver injury following the infusion of azacitidine and venetoclax in a patient which was subsequently mitigated through pretreatment with a vasodilatory agent.

Keywords

acute liver injury, drug-induced liver injury, azacitidine, venetoclax, vasospasm, calcium channel blocker

Introduction

Drug-induced liver injury (DILI) is a common cause of liver toxicity where early recognition is important in preventing further clinical complications. DILI can be classified into 3 major categories of direct, indirect, or idiosyncratic hepatotoxicity.[1] An important characteristic of DILI includes the latency of onset which can range from rapid (within 24 hours) to delayed (months).[1] There are few drugs that are implicated in rapid, severe onset DILI; the most recognized of which is acetaminophen which classically causes rise in transaminases that are very high (>3500 IU/L for aspartate aminotransferase [AST] or alanine aminotransferase [ALT]) and occur with an onset of 24 to 36 hour following.[2]

Antineoplastic agents are commonly reported to cause DILI. In a retrospective cohort study of 284 patients undergoing chemotherapy, 6.1% were classified as having DILI, 82% of which were secondary to chemotherapy.[3] In another observational longitudinal study, among 49 patients deemed to have DILI secondary to anti-neoplastic agents the reported median latency period was 87.5 days (interquartile range: 36-291) with a mean ALT elevation of 511 IU/L (standard deviation: 541).[4] Within the class of antineoplastic agents is azacitidine, a cytidine nucleoside analog, that causes cytotoxicity through DNA and RNA hypomethylation. The combination of azacitidine with venetoclax, a BCL-2 inhibitor, is often used in the treatment of acute myeloid leukemia (AML). While there are some reports of hepatotoxicity related to azacitidine, there are no known reports of hepatotoxicity related to venetoclax.[5]

Here, we present a unique case of rapid and severe DILI following azacitidine and venetoclax administration, believed to be through a mechanism of hypoperfusion of the liver.

Case Presentation

A 70-year-old female with past medical history of hypertension, hyperlipidemia, and stem cell bone marrow transplant for AML was hospitalized due to concern for relapsed AML. She was initially diagnosed with AML at the age of 69 and underwent induction chemotherapy with 7 + 3 cytarabine and anthracycline with midostaurin. Due to failure of response, she proceeded to an allogeneic stem cell transplant 3 months after diagnosis. Six months following her transplant, she had evidence of disease relapse prompting this admission. The patient was 78.6 kg at the time of admission and received chemotherapy in the form of azacitidine 75 mg/m^2 infusion and oral 400 mg venetoclax daily. Prior to drug exposure, the patient's hepatic biochemical profile was normal. Routine laboratory data obtained 8 hours after infusion demonstrated sudden increase in transaminases (AST: 35 U/L, ALT: 26 IU/L to peak of AST: 1959 U/L, ALT: 1263 IU/L) as outlined in

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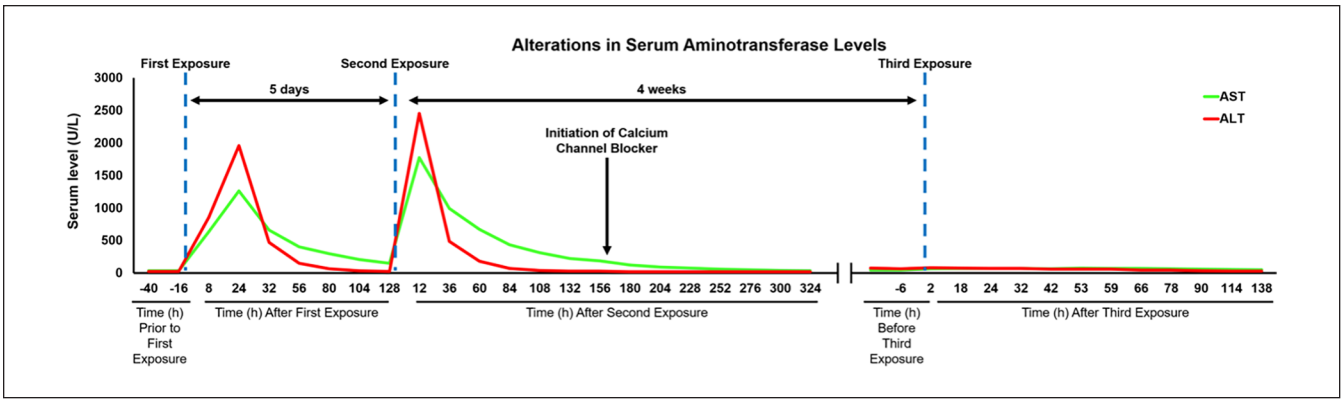

Figure 1. Alterations in serum levels of liver enzymes AST and ALT. ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Figure 1. Notably, the patient's alkaline phosphatase was mildly elevated to 324 IU/L from 136 IU/L with normal serum bilirubin. The patient's hepatic synthetic function was relatively preserved with an albumin of 4.2 g/dL and INR 1.4 (from 1.1). Upon further review, she had no personal or familial history of liver disease, new medications (including over the counter medication, herbal supplementation, or recent antibiotic exposure), history of significant alcohol use, intravenous drug use, or tattoos. There were no documented episodes of hemodynamic instability. Further imaging and laboratory work up included unremarkable hepatitis A (negative immunoglobulin M antibody), hepatitis B (surface antigen, immunoglobulin M and G core antibody), hepatitis C (IgG antibody) serologies as well as negative respiratory panel, cytomegalovirus, Epstein–Barr virus, and adenovirus PCR. An antismooth muscle antibody (1:40) and antinuclear antibody (negative) were also unrevealing. A right upper quadrant ultrasound with Doppler demonstrated patent portal and middle hepatic vein flow with appropriate direction. Transthoracic echocardiogram demonstrated normal cardiac function including ejection fraction of 60%, right atrial pressure of 3 mmHg, and normal size of the inferior vena cava.

Transaminases improved thus azacitidine and venetoclax were re-administered at the same dose 1 week later with a similar trend in significant rise in transaminases with short latency (Figure 1). In light of this, the patient was started on alternative therapy (gilteritinib, a tyrosine kinase inhibitor). However, patient did not respond, and the decision was made to re-trial azacitidine and venetoclax. Given necessity of treatment, pretreatment with vasodilatory medications prior to administration of chemotherapy was discussed. The rationale was that azacitidine may cause hepatic artery vasospasm and subsequent hypoperfusion injury based on previous observations of coronary artery spasm and ischemic colitis caused by azacitidine.[6,7] Thus, prior to the third infusion oral diltiazem sustained release 120 mg daily was started and the third infusion of 75 mg/m^2 of azacitidine was given. Notably, patient's venetoclax dosing was also reduced to 50 mg. Following the third infusion, there was no rise in transaminases.

Discussion

To the best of our knowledge, there are few published cases of DILI secondary to azacitidine. One of the earliest reports published in 1973, demonstrated in a cohort of 25 patients, liver function abnormalities in 7 individuals and progressive hepatic coma resulting in death in 4 individuals with prior hepatic metastasis after administration of 5-azacytidine.[6] Systemic vasoconstriction has been shown to cause rapid DILI along with other ischemic injury in substances like cocaine.[7] Interestingly, there have been several cases of non-hepatic azacitidine-induced ischemic toxicity including angina as well as ischemic colitis.[8] Further insight regarding this phenomenon can be obtained through the study of 5-fluorouracil (5-FU) which is an anti-neoplastic nucleoside analog similar to azacitidine that is strongly associated with cardiotoxicity secondary to vasospasm due to vascular smooth muscle dysfunction.[9] This suggests a possible shared mechanism between both agents causing end-organ hypoperfusion. Thus, we hypothesize that the primary mechanism of liver injury observed in this patient was secondary to ischemic hepatic liver injury given the short latency and pattern of liver injury.

The effect of coronary vasospasm occurring secondary to 5-FU therapy has been shown to be prevented using calcium channel blockers and long-acting nitrates prior to therapy.[10] Animal studies have also suggested a protective effect of calcium channel blocker on hepatic ischemia.[11,12] In the presented case, a calcium channel blocker was given prior to administration of the third dose of azacitidine resulting in prevention of an elevation in transaminases compared to prior infusions.

In conclusion, the degree of elevation coupled with the short latency of injury after exposure to azacitidine make this a unique case of likely hepatic hypoperfusion related drug-induced liver injury. This phenomenon may potentially

be prevented via pretreatment with vasodilatory agents such as calcium channel blockers.

Declaration of Conflicting Interests

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Verbal informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

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References

1. Fontana RJ, Liou I, Reuben A, et al. AASLD practice guidance on drug, herbal, and dietary supplement-induced liver injury. *Hepatology*. 2023;77:1036-1065. doi:10.1002/hep.32689
2. Tujios SR, Lee WM. Acute liver failure induced by idiosyncratic reaction to drugs: challenges in diagnosis and therapy. *Liver Int*. 2018;38:6-14. doi:10.1111/liv.13535
3. Azad A, Chang P, Devuni D, et al. Real world experience of drug induced liver injury in patients undergoing chemotherapy. *J Clin Gastroenterol Hepatol*. 2018;2:18. doi:10.21767/2575-7733.1000047
4. Chalasani N, Bonkovsky HL, Fontana R, et al. Features and outcomes of 899 patients with drug-induced liver injury: the DILIN Prospective Study. *Gastroenterology*. 2015;148:1340-1352.e1347. doi:10.1053/j.gastro.2015.03.006
5. King AC, Peterson TJ, Horvat TZ, et al. Venetoclax: a first-in-class oral BCL-2 inhibitor for the management of lymphoid malignancies. *Ann Pharmacother*. 2017;51:410-416. doi:10.1177/1060028016685803
6. Bellet RE, Mastrangelo MJ, Engstrom PF, et al. Hepatotoxicity of 5-azacytidine (NSC-102816) (a clinical and pathologic study). *Neoplasma*. 1973;20:303-309.
7. Dolkar T, Hamad AM, Han MM, Thu MB, Gayam VR. Cocaine and opioid-induced acute liver injury: a rare case report. *Cureus*. 2022;14:e23630. doi:10.7759/cureus.23630
8. Melchardt T, Weiss L, Pleyer L, et al. Complications of 5-azacytidine: three cases of severe ischemic colitis in elderly patients with myelodysplastic syndrome. *Oncol Lett*. 2013;6:1756-1758. doi:10.3892/ol.2013.1629
9. Kanduri J, More LA, Godishala A, Asnani A. Fluoropyrimidine-associated cardiotoxicity. *Cardiol Clin*. 2019;37:399-405. doi:10.1016/j.ccl.2019.07.004
10. Zafar A, Drobni ZD, Lei M, et al. The efficacy and safety of cardio-protective therapy in patients with 5-FU (Fluorouracil)-associated coronary vasospasm. *PLoS One*. 2022;17:e0265767. doi:10.1371/journal.pone.0265767
11. Chin S, Ikeda M, Ozaki M, Kameoka S. Protective effect of diltiazem on hepatic ischemia-reperfusion injury in rats by improving liver tissue blood flow. *Transplant Proc*. 2005;37:4556-4559. doi:10.1016/j.transproceed.2005.11.028
12. Uchida M, Takemoto Y, Nagasue N, Dhar DK, Kohno H, Nakamura T. Effect of verapamil on hepatic reperfusion injury after prolonged ischemia in pigs. *J Hepatol*. 1994;21:217-223. doi:10.1016/s0168-8278(05)80398-8