Inotuzumab Ozogamicin and Liver Toxicity: Something Old, Something New, and Something to Consider

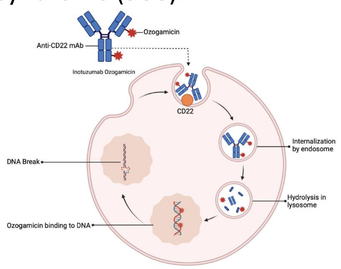
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Background

- Inotuzuamab ozogamicin (InO) is an approved treatment of relapsed or refractory B-cell acute lymphoblastic leukemia (B-ALL). INO is a monoclonal antibody targeted against the CD22 and conjugated to ozogamicin, a potent antitumor antibiotic.
- InO is associated with liver toxicity (LT) and sinusoidal obstructive syndrome (SOS).[1]



Case Presentation

- We report two patients with R/R B-ALL who received InO and developed LT, highly suspicious for SOS.
- Patient#1: 28-year-old female with past medical history of B-ALL (relapsed in 2018 and January 2022) and pilocytic astrocytoma resected in 2013. Treatment with InO and prophylactic intrathecal methotrexate was initiated in February 2022. At that time, she was also started on SOS prophylaxis with ursodiol.
- In October 2022, the patient reported right-sided abdominal pain, and was found to have elevated liver function tests. InO was discontinued due to concern for hepatotoxicity.
- An abdominal ultrasound showed hepatomegaly and increased hepatic parenchymal echogenicity, suggestive of parenchymal dysfunction.
- Patient#2: 42-year-old male with B-ALL, Ph+, who was on ponatinib and InO, had elevated liver enzymes. Hyperbilirubinemia and hyperammonemia were noted, and abdominal ultrasound showed hepatomegaly and portal hypertension, and subsequently, the patient passed away.
- A liver biopsy showed sinusoidal congestion for patient#1:

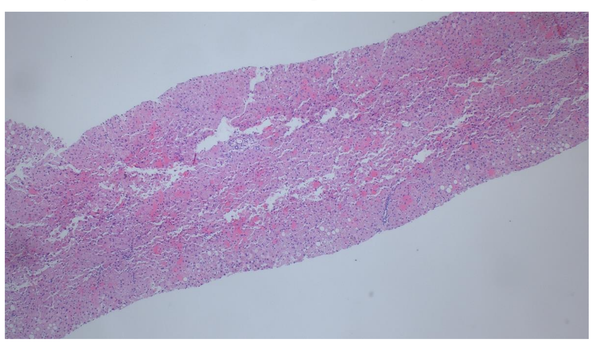


Figure 1: 4x magnification of liver biopsy showing hepatic congestion

Pathophysiology

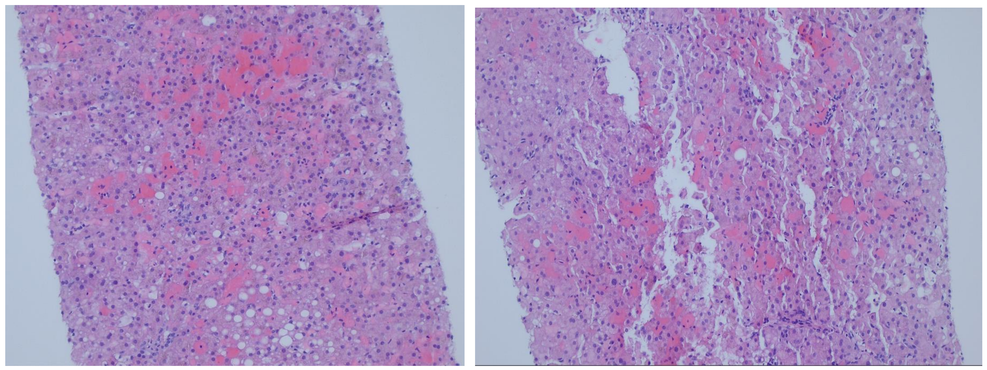


Figure 2: 10x magnification of liver biopsy showing hepatic congestion

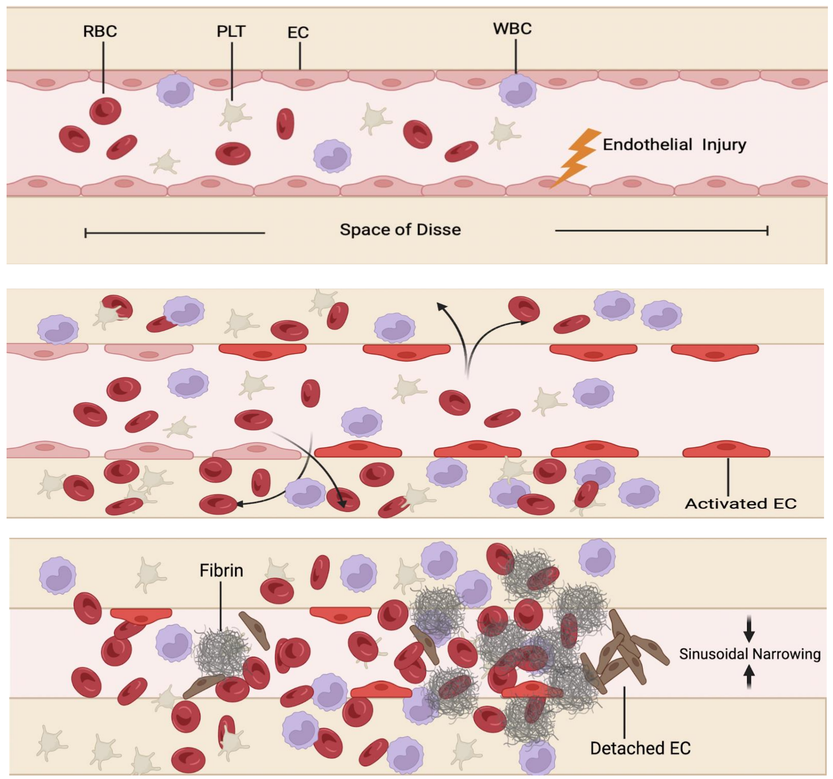


Figure (Pathophysiology of SOS): Toxic metabolites generated by hepatotoxic drugs such as alkylating agents in transplant conditioning regimens, ionizing radiation, or hepatotoxins cause damage to sinusoidal endothelial cells and hepatocytes in the hepatic acinus.[2,3] The damage causes gaps in the sinusoidal barrier, allowing cells and cellular debris to pass into the space of Disse beneath the endothelial cells.[2,3] Narrowing of the venous lumen reduces sinusoidal venous outflow, resulting in postsinusoidal portal hypertension, widespread liver zonal disruption, and centrilobular hemorrhagic necrosis.[2,3]

Discussion

- SOS is a potentially lethal complication of InO and may be under-recognized in the clinical setting.
- When using InO, prophylaxis with ursodeoxycholic acid 300mg twice daily has been shown to significantly decrease the incidence of SOS.[4]
- Defibrotide is currently only FDA-approved for the treatment of SOS in patients undergoing hematopoietic stem cell transplant (HSCT).[5]
- Conditioning regimens containing dual alkylating agents as well as hepatotoxic drugs in combination with high-dose alkylating agents should be avoided when using InO. Cycles of InO should be limited to 2 is possible.[7]
- Aspartate transaminase, alanine transaminase, bilirubin, platelets, and daily weights should be closely monitored as they may be indicative of developing SOS.
- If there is suspicion for LT and the development of SOS, InO should be discontinued.
- All patients on InO should be on prophylactic ursodeoxycholic acid regardless of transplant history.
- The aim of this two cases is to emphasize the significance of LT with InO in patients with R/R B-ALL and to propose a prophylactic regimen with ursodeoxycholic acid 300mg twice daily in order to reduce the risk of LT.

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