Retrospective Analysis of Hepatotoxicity Associated with Inotuzumab Therapy in B-Cell Acute Lymphoblastic Leukemia: Describing a New Clinical Phenomenon Called Calicheamicin Syndrome

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Introduction

- Inotuzumab ozogamicin (InO) is a CD22-directed antibody-drug conjugate (ADC), which is FDA approved for the treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia (B-ALL) in adult and pediatric patients ≥1 year of age
- Hepatotoxicity and sinusoidal obstruction syndrome (SOS) are known InO complications
- ***Calicheamicin syndrome*** characterized by:
  - History of InO use
  - Elevated liver function tests (LFTs)
  - Thrombocytopenia
  - Abnormal liver imaging

Aim

- To characterize hepatic sinusoidal congestion (HSC) as a distinct, non-SOS hepatotoxicity pattern associated with InO use in patients with relapsed/refractory B-ALL

Objectives

- To characterize HSC among InO-treated R/R B-ALL patients at a single institution restrospective study.
- To describe the clinical, laboratory, imaging, and histopathologic features of HSC.
- To assess outcomes and resolution of liver injury following InO cessation.
- To expand and build on diagnostic awareness for a novel hepatic toxicity: *calicheamicin syndrome.*

Methods

- Single-center retrospective review of 21 patients with R/R B-ALL treated with InO from 2018 to 2024.
- Clinical data, LFTs, imaging, and liver bx were reviewed.
  - Patients underwent liver biopsy (Bx) to rule out SOS when clinically indicated.
- Hepatotoxicity defined as elevated LFTs with or without right upper quadrant pain.
- Patients were stratified by severity of LFT elevation, abnormal liver imaging, and histopathology.

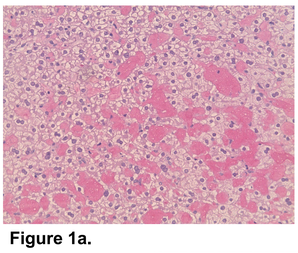


Figure 1a.

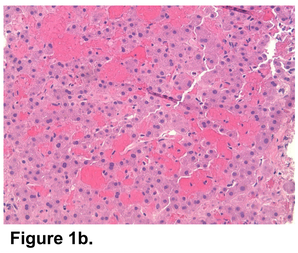


Figure 1b.

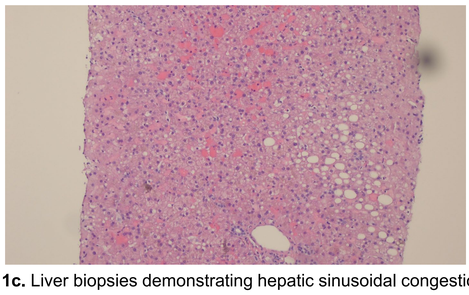


Figure 1c. Liver biopsies demonstrating hepatic sinusoidal congestion

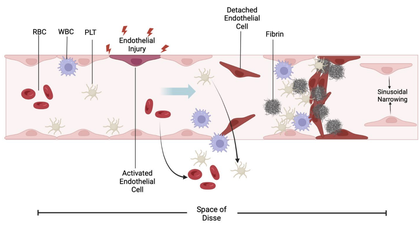


Figure 2. Proposed mechanism of liver injury from InO

Results

- 21 patients with relapsed/refractory B-ALL were treated with InO
- 100% (21/21) developed abnormal LFTs
- **28.6%** (6/21) underwent liver Bx, which showed **HSC without SOS** or other alternative hepatic pathologies
- Common findings amongst patients:
  - Persistent LFT elevation
  - Thrombocytopenia
  - Right upper quadrant pain
  - Abnormal liver imaging: CT abdomen and pelvis showed hepatomegaly and heterogenous liver enhancement
  - Did not meet full diagnostic criteria for SOS

	Pre-InO	InO	Post-InO
AST (U/L)	24.5	59.0	55.0
ALT (U/L)	17.0	40.0	25.0
Alk Phos (U/L)	95.0	192.0	184.0
Total Bilirubin (mg/dL)	0.3	1.1	0.8

Table 1. Median Liver Function Tests Across Timepoints

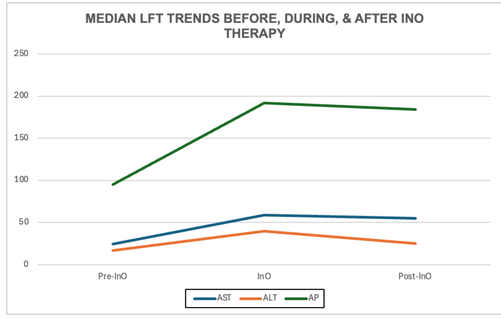


Figure 3. Median Liver Function Tests Trends Pre-, During, and Post-InO

Discussion

- 6 of 21 patients with InO-treated R/R B-ALL developed HSC without meeting criteria for SOS
- Patients were symptomatic with persistent LFT elevation and thrombocytopenia
- Liver biopsy confirmed **HSC in the absence of SOS** or other alternative liver pathologies
  - Standard SOS criteria may miss this distinct hepatotoxicity pattern, leading to under-diagnosis
- ***Calicheamicin syndrome*** may reflect calicheamicin-induced microvascular injury
- In several patients, LFT abnormalities improved after InO discontinuation and supportive care.

Clinical implications:

- Remain diligent about HSC in patients with unexplained liver injury during InO therapy
- Consider early biopsy when SOS is suspected but diagnostic criteria are unmet
- Monitor future ADC toxicities, risk stratification, and drug development

Summary

- InO can cause HSC without meeting criteria for SOS
- This distinct pattern, termed *calicheamicin syndrome*, may be underrecognized
  - Presents with elevated LFTs, thrombocytopenia, and abnormal liver imaging
- Liver biopsy is important for diagnosis
- Recognizing this entity can guide management, prevent progression, and refine ADC toxicity profiles

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