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Altered Mental Status and Prolonged Hyperammonemia Associated with Inotuzumab Ozogamicin and Proposed Calicheamicin Syndrome: A Case Report

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Abstract

Background

Inotuzumab ozogamicin (InO) is a CD22-directed antibody-drug conjugate whose calicheamicin payload causes target-independent hepatic sinusoidal endothelial injury. Beyond the well-recognized risk of sinusoidal obstruction syndrome (SOS/VOD), a recently proposed phenotype characterized by hepatic sinusoidal congestion (HSC) without fulfilling diagnostic criteria for SOS/VOD has been referred to as calicheamicin syndrome. Reported features include the use of InO, elevated liver function tests, abnormal liver imaging, and thrombocytopenia. Altered mental status (AMS) and hyperammonemia have not previously been reported as manifestations of InO toxicity and calicheamicin syndrome.

Methods

A 28-year-old woman with relapsed CD22-positive B-ALL received 6 cycles of InO between February and September 2022. InO was discontinued due to hepatotoxicity and AMS. A core liver biopsy demonstrated HSC without evidence of SOS/VOD. Persistent

hyperammonemia was observed throughout 2023, with a peak serum ammonia level of 123 $\mu\text{mol/L}$, notably occurring several months after InO discontinuation. The hyperammonemia was managed with lactulose and resolved as hepatic function improved. During this period, she developed AMS, progressing to not able to feed herself, requiring gastrostomy tube (G-tube) placement. Brain imaging showed no acute abnormalities. Following discontinuation of InO and supportive management, the patient's AMS resolved, the G-tube was removed, hepatic function normalized, and her performance status returned to baseline over approximately 12 months.

Conclusion

We report prolonged hyperammonemia and AMS occurring in association with InO-related hepatotoxicity consistent with the proposed calicheamicin syndrome. To our knowledge, persistent hyperammonemia and significant AMS have not previously been described as part of this phenotype. Although causality cannot be established from this single case, these findings suggest that impaired hepatic ammonia clearance may contribute to neurologic manifestations of

InO-associated hepatotoxicity. Measurement of serum ammonia should be considered in patients receiving InO who develop otherwise

unexplained AMS, particularly in the setting of hepatic dysfunction or sinusoidal injury.

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