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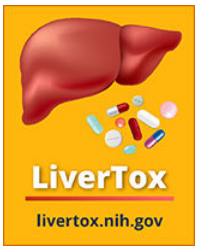

Inotuzumab Ozogamicin

Updated: January 15, 2024.

OVERVIEW

Introduction

Inotuzumab ozogamicin is a humanized monoclonal antibody-cytotoxin conjugate which is used in the therapy of refractory or relapsed acute lymphoblastic leukemia. Inotuzumab ozogamicin has been linked to frequent serum enzyme elevations during therapy and with instances of clinically apparent acute liver injury, including acute sinusoidal obstruction syndrome which can be severe and even fatal.

Background

Inotuzumab (in" oh tooz' ue mab) ozogamicin (oh" zoe ga mye' sin) is a humanized monoclonal antibody conjugate that is used in the therapy of B-cell precursor acute lymphoblastic leukemia. The monoclonal antibody is to the human CD22 cell surface marker which is highly expressed on malignant lymphoblastic leukemia cells. The monoclonal antibody is conjugated to a cytotoxic agent from a class of calicheamicins called ozogamicin. When inotuzumab binds to CD22, it is internalized and the ozogamicin is released by the action of lysosomal enzymes on the linker molecule that joins it to the monoclonal antibody. The released intracellular ozogamicin causes breaks in double stranded DNA that leads to apoptotic cell death. This monoclonal antibody conjugate has been shown to be effective in inducing remissions in relapsed or refractory B-cell precursor acute lymphoblastic leukemia and was given accelerated approval for this indication in the United States in 2017. Inotuzumab ozogamicin is available as 0.9 mg of lyophilized powder in single dose vials for reconstitution under the brand name Besponsa. The recommended dose regimen varies by body weight, day of therapy and whether treating refractory vs relapsed acute lymphoblastic leukemia. Inotuzumab ozogamicin is given intravenously typically on days 1, 8 and 15 of 21- or 28-day cycles. Premedication with a corticosteroid, antipyretic, and antihistamine is recommended before each dose. Common side effects include bone marrow suppression, infections, fatigue, fever, nausea, headache, abdominal pain and hemorrhage. Less common but potentially serious side effects include severe myelosuppression, severe infections, clinically significant bleeding and hemorrhage, infusion related reactions including anaphylaxis, QTc interval prolongation, and embryo-fetal toxicity. Inotuzumab ozogamicin should be prescribed and administered only by health care workers with expertise and experience in cancer chemotherapy and management of its adverse events.

Hepatotoxicity

In prelicensure clinical trials of inotuzumab ozogamicin, up to half of patients had serum ALT or AST elevations during therapy which were above 5 times the upper limit of normal (ULN) in 2% to 5%. Hyperbilirubinemia was also common during inotuzumab therapy, generally occurring without accompanying ALT or AST elevations. More importantly, a variable proportion of patients (ranging from 2% to 35%) developed clinically apparent

sinusoidal obstruction syndrome (SOS) after inotuzumab ozogamicin therapy. The proportion was even higher (15% to 25%) in patients who receive inotuzumab ozogamicin and subsequently underwent hematopoietic cell transplantation (HCT). Symptoms of nausea, right upper quadrant pain, weight gain and abdominal distension (from ascites) arose within 5 to 20 days of the infusion and were followed in some patients by progressive rises in bilirubin, serum aminotransferase and alkaline phosphatase levels. Clinically apparent SOS has a poor prognosis and the mortality rate is as high as 70%, most patients dying of multiorgan failure. Risk factors for developing SOS after inotuzumab therapy include allogenic hematopoietic cell transplantation, use of other antineoplastic agents, and presence of preexisting liver disease. While SOS is the usual cause of clinically apparent liver injury attributable to inotuzumab, cases of cholestatic hepatitis without evidence of sinusoidal cell injury have been described in up to 8% of treated subjects. The clinical features of this injury have not been well characterized. Patients being treated with inotuzumab ozogamicin are often receiving multiple medications and have other reasons for having acute liver injury (sepsis, shock, graft-vs-host disease, or hepatic metastases).

Likelihood score: A (well known cause of clinically apparent liver injury, generally due to sinusoidal obstruction syndrome).

Mechanism of Liver Injury

The cause of the serum enzyme elevations during inotuzumab ozogamicin therapy is not known, but they are likely due to direct toxicity of the conjugate. The propensity of inotuzumab ozogamicin to cause sinusoidal obstruction syndrome is perhaps due to the fact that the antibody conjugate may be taken up by these cells resulting in their damage and release of cellular apoptotic fragments into sinusoids causing obstruction.

Outcome and Management

The mild-to-moderate serum aminotransferase elevations that occur during inotuzumab ozogamicin therapy are generally transient and asymptomatic and do not require dose modification or delay in therapy. Elevations above 5 times the upper limit of normal should lead to more careful monitoring and suspension of further infusions, at least until levels return to normal or near normal levels. The product label for inotuzumab ozogamicin has a black boxed warning for the risk of severe sinusoidal obstruction syndrome and recommends monitoring routine liver tests before administering each dose of the antibody-drug conjugate. Management of SOS generally rests on careful attention to fluid balance and treatment of complications. There are no proven means of prevention or treatment of SOS due to inotuzumab ozogamicin, although pretreatment with ursodiol and acute management with defibrotide are often employed. The adverse events profile and hepatotoxicity of inotuzumab ozogamicin are similar to those caused by gemtuzumab ozogamicin, a similar monoclonal antibody-conjugate directed to CD33 that is used to treat refractory or relapsed acute myeloid leukemia.

Drug Class: Antineoplastic Agents; Monoclonal Antibodies

Other Monoclonal Antibody Conjugates: Benlantamab Mafodotin, Brentuximab Vedotin, Enfortumab Vedotin, Gemtuzumab Ozogamicin, Polatuzumab Vedotin, Sacituzumab Govitecan, Tisotumab Vedotin, Trastuzumab Deruxtecan, Trastuzumab Emtansine

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Inotuzumab Ozogamicin – Besponsa®

DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Inotuzumab Ozogamicin	635715-01-4	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 15 January 2024

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; GvH, graft-vs-host; HCT, hematopoietic cell transplantation; SOS, sinusoidal obstruction syndrome (also known as hepatic veno-occlusive disease).

DeLeve LD. Gemtuzumab ozogamicin. Liver sinusoidal endothelial cells and liver injury. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2011, pp. 142-3.

(Review of agents that damage liver sinusoidal cells including gemtuzumab ozogamicin; mentions that CD33 which is present on leukemic blast cells is also present on liver sinusoidal endothelial cells).

Wellstein A, Giaccone G, Atkins MB, Sausville EA. Pathway-targeted therapies: monoclonal antibodies, protein kinase inhibitors, and various small molecules. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 1203-36.

(Textbook of pharmacology and therapeutics).

FDA. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761040Orig1s000MultidisciplineR.pdf

(FDA Drug Approvals website that has product labels [package inserts], letters of approval and full FDA scientific review of the new drug application for safety and efficacy which mentions that ALT elevations occur in up to 50% of inotuzumab ozogamicin treated subjects and are above 5 times ULN in 2% to 5%, but these abnormalities are generally are self-limited and without symptoms or jaundice, but that SOS occurs in 3% of treated subjects not undergoing HCT and as many as 22% of those with HCT [before or after treatment]).

Rajvanshi P, Shulman HM, Sievers EL, McDonald GB. Hepatic sinusoidal obstruction after gemtuzumab ozogamicin (Mylotarg) therapy. Blood 2002; 99: 2310-4. PubMed PMID: 11895761.

(Among 23 patients with relapsed, refractory acute myeloid leukemia [AML] treated with gemtuzumab ozogamicin, liver injury suggestive of SOS developed in 11, 7 of whom died of hepatic failure 8-47 days after the infusion).

Leopold LH, Berger MS, Feingold J. Acute and long-term toxicities associated with gemtuzumab ozogamicin (Mylotarg) therapy of acute myeloid leukemia. Clin Lymphoma 2002; 2 Suppl 1 : S29-34. PubMed PMID: 11970768.

(Review of adverse side effects of gemtuzumab ozogamicin therapy; mentions mild ALT and AST [Grade 1 and 2] elevations in 26% and elevations ≥5 times ULN in 16% and clinically apparent SOS in 2-12% of patients, risk factors for this complication being HCT, concurrent cytotoxic therapies, higher and more frequent doses and underlying liver disease).

McDonald GB. Management of hepatic sinusoidal obstruction syndrome following treatment with gemtuzumab ozogamicin (Mylotarg). Clin Lymphoma 2002; 2 Suppl 1 : S35-9. PubMed PMID: 11970769.

(Review of management of SOS).

Kantarjian H, Thomas D, Jorgensen J, Jabbour E, Kebriaei P, Rytting M, York S, et al. Inotuzumab ozogamicin, an anti-CD22-calecheamicin conjugate, for refractory and relapsed acute lymphocytic leukaemia: a phase 2 study. Lancet Oncol 2012; 13: 403-11. PubMed PMID: 22357140.

(Among 49 patients with refractory or relapsed ALL treated with inotuzumab, 57% had an objective response and adverse events included fever [59%], ALT elevations [57%: all but 1 being less than 5 times ULN], hyperbilirubinemia [26%], hypotension [26%] and SOS in 5 of 22 [23%] who subsequently underwent HCT, 1 case being fatal).

Wagner-Johnston ND, Goy A, Rodriguez MA, Ehmann WC, Hamlin PA, Radford J, Thieblemont C, et al. A phase 2 study of inotuzumab ozogamicin and rituximab, followed by autologous stem cell transplant in patients with relapsed/refractory diffuse large B-cell lymphoma. Leuk Lymphoma 2015; 56: 2863-9. PubMed PMID: 25707288.

(Among 63 patients with relapsed or refractory large B cell lymphoma treated with inotuzumab and rituximab, the objective response rate was 29% and adverse events were common including AST elevations in 43%; 4 of 18 patients [22%] who subsequently underwent HCT developed significant hepatotoxicity, 2 with suspected SOS).

Kantarjian HM, DeAngelo DJ, Stelljes M, Martinelli G, Liedtke M, Stock W, Gökbuget N, et al. Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. N Engl J Med 2016; 375: 740-53. PubMed PMID: 27292104.

(Among 326 patients with refractory or relapsed ALL treated with inotuzumab ozogamicin or standard intensive chemotherapy, complete remissions were more frequent with inotuzumab [81% vs 29%] and medial overall survival was greater [7.7 vs 6.7 months], and while adverse events were frequent in both groups, SOS occurred in 11% [including 2 fatal cases following HCT] with inotuzumab vs 1% with standard therapy).

Kantarjian HM, Vandendries E, Advani AS. Inotuzumab ozogamicin for acute lymphoblastic leukemia. N Engl J Med 2016; 375: 2100-2101. PubMed PMID: 27959720.

(Further follow up of patients in a controlled trial [Kantarjian 2016] mentions that 15 of 71 patients [21%] who underwent HCT after receipt of inotuzumab for ALL developed SOS, and that there was no correlation between time after receipt of the agent and frequency of SOS).

Goy A, Forero A, Wagner-Johnston N, Christopher Ehmann W, Tsai M, Hatake K, Ananthakrishnan R, et al. A phase 2 study of inotuzumab ozogamicin in patients with indolent B-cell non-Hodgkin lymphoma refractory to rituximab alone, rituximab and chemotherapy, or radioimmunotherapy. Br J Haematol 2016; 174: 571-81. PubMed PMID: 27101934.

(Among 81 patients with refractory non-Hodgkin lymphoma treated with inotuzumab ozogamicin, the objective response rate was 67% and adverse events were common including thrombocytopenia [74%], neutropenia [56%], anemia [15%], ALT elevations [20%: only 1 rising above 5 times ULN] and hyperbilirubinemia [15%]).

Kantarjian HM, DeAngelo DJ, Advani AS, Stelljes M, Kebriaei P, Cassaday RD, Merchant AA, et al. Hepatic adverse event profile of inotuzumab ozogamicin in adult patients with relapsed or refractory acute lymphoblastic leukaemia: results from the open-label, randomised, phase 3 INO-VATE study. Lancet Haematol 2017; 4: e387-e398. PubMed PMID: 28687420.

(Secondary analysis of liver related adverse events in a large controlled trial of inotuzumab vs placebo [Kantarjian 2016], with follow up data on all 326 patients enrolled, reported elevations in ALT in 15% vs 13%, AST in 23% vs 11%, Alk P in 13% vs 7%, bilirubin in 21% vs 17% and SOS in 13% [n=22, 5 fatal] vs <1% with SOS occurring without intervening HCT in 5 [3%] vs none).

Dang NH, Ogura M, Castaigne S, Fayad LE, Jerkeman M, Radford J, Pezzutto A, et al. Randomized, phase 3 trial of inotuzumab ozogamicin plus rituximab versus chemotherapy plus rituximab for relapsed/refractory aggressive B-cell non-Hodgkin lymphoma. Br J Haematol 2018; 182 (4): 583-6. PubMed PMID: 28677896.

(Among 332 patients with non-Hodgkin lymphoma treated with rituximab combined with inotuzumab ozogamicin or with standard chemotherapy, overall survival was similar in the two groups while adverse events were more frequent with inotuzumab including elevations in ALT [17% vs 8%], Alk P [13% vs 5%], bilirubin [8% vs 2%] and SOS [2% vs none]).

Lamb YN. Inotuzumab ozogamicin: first global approval. Drugs 2017; 77: 1603-10. PubMed PMID: 28819740.

(Review of the history of development, mechanism of action, pharmacology, clinical efficacy and safety of inotuzumab ozogamicin shortly after its approval in the US; mentions that cases of SOS were more frequent with inotuzumab than standard therapy [13% vs 1%], some cases arising years after its administration, often after HCT).

Kantarjian H, Ravandi F, Short NJ, Huang X, Jain N, Sasaki K, Daver N, et al. Inotuzumab ozogamicin in combination with low-intensity chemotherapy for older patients with Philadelphia chromosome-negative acute lymphoblastic leukaemia: a single-arm, phase 2 study. Lancet Oncol 2018; 19: 240-8. PubMed PMID: 29352703.

(Among 52 elderly patients [60 years or older] with newly diagnosed ALL treated with inotuzumab ozogamicin and low intensity standard chemotherapy, almost all patients had an objective response, and all had hepatic adverse events including SOS in 4 patients [8%], 2 of which were fatal, 1 occurring after HCT).

Jabbour E, Ravandi F, Kebriaei P, Huang X, Short NJ, Thomas D, Sasaki K, et al. Salvage chemoimmunotherapy with inotuzumab ozogamicin combined with mini-hyper-CVD for patients with relapsed or refractory Philadelphia chromosome-negative acute lymphoblastic leukemia: a phase 2 clinical trial. JAMA Oncol 2018; 4: 230-4. PubMed PMID: 28859185.

(Among 59 patients with relapsed or refractory ALL treated with inotuzumab and lower dose standard chemotherapy, the overall objective response rate was 78%, while 95% had at least one hepatic adverse event and 9 [15%] developed SOS, all of whom had received HCT either before or after inotuzumab therapy).

Inotuzumab ozogamicin (Besponsa)--an antibody-drug conjugate for ALL. Med Lett Drugs Ther 2018; 60 (1547): e90-e91. PubMed PMID: 29913470.

(Concise review of the mechanism of action, clinical efficacy, safety and costs of inotuzumab ozogamicin, shortly after its approval as therapy of refractory or relapsed, B-cell precursor ALL in adults, mentions that SOS occurred in 18 of 79 patients [23%] treated with inotuzumab who subsequently underwent HCT, the mortality rate of which was 28%).

McDonald GB, Freston JW, Boyer JL, DeLeve LD. Liver complications following treatment of hematologic malignancy with anti-CD22-calicheamicin (inotuzumab ozogamicin). Hepatology. 2019;69:831-844. PubMed PMID: 30120894.

(Expert analysis of liver injury in two large controlled trials of trastuzumab ozogamicin vs standard care in 628 adults with ALL identified SoS in 1.5% vs none and drug induced liver injury in 8% vs 1%).

Corbacioglu S, Jabbour EJ, Mohty M. Risk factors for development of and progression of hepatic veno-occlusive disease/sinusoidal obstruction syndrome. Biol Blood Marrow Transplant. 2019;25:1271-1280. PubMed PMID: 30797942.

(Systematic review of the risk factors for development of SOS after HCT identified gemtuzumab ozogamicin and inotuzumab ozogamicin as having hazard risk odds ratios of 20 and 22).

Kantarjian HM, DeAngelo DJ, Stelljes M, Liedtke M, Stock W, Gökbuget N, O'Brien SM, et al. Inotuzumab ozogamicin versus standard of care in relapsed or refractory acute lymphoblastic leukemia: final report and long-term survival follow-up from the randomized, phase 3 INO-VATE study. Cancer. 2019;125: 2474-2487. PubMed PMID: 30920645.

(Among 326 adults with refractory or relapsed ALL treated with inotuzumab ozogamicin or standard chemotherapy and followed for 2 years or more, the complete remission rate was 74% vs 31%, and the 2-year overall survival rate was 23% vs 10%, although SOS occurred in 14% vs 2%).

Agrawal V, Pourhassan H, Tsai NC, Ngo D, Koller P, Malki MMA, Salhotra A, et al. Post-transplantation sinusoidal obstruction syndrome in adult patients with B cell acute lymphoblastic leukemia treated with pretransplantation inotuzumab. Transplant Cell Ther. 2023;29:314-320. PubMed PMID: 36682470.

(Among 47 adults with refractory or relapsed ALL who received inotuzumab ozogamicin and subsequently underwent HCT, 12 [26%] developed SOS which was severe in 9 and fatal in 4).

Lee J, Yoon JH, Kwag D, Lee JH, Kim TY, Min GJ, Park SS, et al. Hepatic venoocclusive disease/sinusoidal obstruction syndrome with normal portal vein flow mimicking aggravated chronic hepatic GVHD following inotuzumab ozogamicin salvage therapy: a case report of pathologic-radiologic discrepancy. Ther Adv Hematol. 2021;12:20406207211066176. PubMed PMID: 34987745.

(49 year old woman with relapse of ALL 2 years after a successful HCT and with chronic graft-vs-host [GvH] disease was treated with inotuzumab ozogamicin and developed progressive hepatic failure that led to a liver transplant, the explant showing SOS rather than GvH disease).

Sabatino D, Henneman A, Ahmad S, Jou E, Goldberg B. Evaluation of the efficacy of ursodiol for prevention of hepatotoxicity in patients receiving gemtuzumab ozogamicin and inotuzumab ozogamicin. J Oncol Pharm Pract. 2023;29:840-845. PubMed PMID: 35293248.

(In a retrospective analysis of patients who received gemtuzumab or inotuzumab ozogamicin with [n=14] or without ursodiol [n=35] prophylaxis, the rate of SOS was less with ursodiol [14% vs 43%], but after controlling for risk factors the difference was not statistically significant).

Fischer D, Toenges R, Kiil K, Michalik S, Thalhammer A, Bug G, Gökbuget N, Lang F. Liver failure after treatment with inotuzumab and polychemotherapy including PEG-asparaginase in a patient with relapsed Philadelphia chromosome-negative acute lymphoblastic leukemia. Ann Hematol. 2024;103(2):489-498. PubMed PMID: 37999763.

(58 year old woman with relapsed ALL after HCT was treated with inotuzumab ozogamicin followed by methotrexate and pegaspargase and developed fatal acute liver failure 2 weeks later, autopsy showing steatosis and cholestasis typical of asparaginase induced injury, but no evidence of SOS).

Sun C, Yang X, Tang L, Chen J. A pharmacovigilance study on drug-induced liver injury associated with antibody-drug conjugates (ADCs) based on the food and drug administration adverse event reporting system. Expert Opin Drug Saf. 2023:1-12. PubMed PMID: 37898875.

(Analysis of the FDA reporting system [FAERS] for cases of drug induced liver injury submitted between 2004 and 2022, found 17,784 reports, 504 [3%] attributed to antibody-drug conjugates, 202 from the US, the implicated agents being gemtuzumab ozogamicin [n=98], brentuximab vedotin [n=37], trastuzumab emtansine [n=25], enfortumab vedotin [n=16], inotuzumab ozogamicin [n=15], transtuzumab deruxtecan [n=8], and polatuzumab vedotin [3]).