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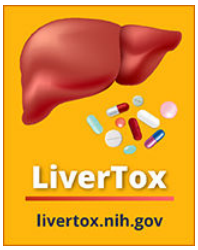

Gemtuzumab Ozogamicin

Updated: November 30, 2023.

OVERVIEW

Introduction

Gemtuzumab ozogamicin is a humanized monoclonal antibody conjugate that is used in the therapy of acute myelogenous leukemia. Gemtuzumab ozogamicin has been linked to transient serum enzyme elevations during therapy and not uncommon instances of acute sinusoidal obstruction syndrome, which can be severe and even fatal.

Background

Gemtuzumab (jem tooz' ue mab) ozogamicin (oh" zoe ga mye' sin) is a humanized monoclonal IgG4 antibody to the human CD33 cell surface marker that is highly expressed on acute myelogenous leukemia cells. The monoclonal antibody is conjugated using a linker sequence to a cytotoxic molecule, ozogamicin (N-acetyl gamma calicheamicin). When gemtuzumab binds to CD33, it is internalized and the ozogamicin is released by the action of lysosomal enzymes on the linker molecule that joins the monoclonal antibody to the cytotoxic molecule. The intracellular ozogamicin binds to cellular DNA and causes double-stranded DNA breaks resulting in apoptotic cell death. This monoclonal antibody conjugate was shown to be effective in inducing remissions in refractory, CD33 positive acute myelogenous leukemia in patients over the age of 60 years and was given accelerated approval for this indication in the United States in 2000. A subsequent randomized controlled trial, however, showed that the mortality rate was higher with gemtuzumab ozogamicin than with conventional therapy and the monoclonal antibody conjugate was withdrawn from use in 2010. Further studies suggested that a modified dosing schedule (total of 9 mg/m^2 given over days 1 and 4 or days 1, 4 and 7) was effective in prolonging event-free survival in patients with acute myelogenous leukemia and had a lower rate of severe hepatic injury than regimens using the 9 mg/m^2 dose given over one day. Accordingly, gemtuzumab ozogamicin was approved and reintroduced as a therapy of CD33 positive acute myelogenous leukemia in 2017. Current indications are for both adults and children with de novo or refractory/relapsed acute myelogenous leukemia. Gemtuzumab ozogamicin is available in powder for reconstitution in single dose vials of 4.5 mg under the brand name Mylotarg. Gemtuzumab ozogamicin can be given by itself or in combination with daunorubicin and cytarabine. The typical recommended dose regimen for induction is 3 mg/m^2 on days 1, 4 and 7 by intravenous infusion over 2 hours, but recommended dosing varies by indication, whether for induction or maintenance treatment, and by whether it is given alone or in combination with other antineoplastic agents. Common side effects include infusion reactions with fever, nausea, chills, hypotension and shortness of breath and subsequent adverse events of hemorrhage, infection, fever, nausea and vomiting, constipation, anorexia, fatigue, headache, rash, mucositis, neutropenia and thrombocytopenia. Less common, but serious side effects include anaphylactic reactions, severe neutropenia, infections, hemorrhage, and acute hepatic failure. Gemtuzumab ozogamicin

should be administered only by physicians and health care providers with training and expertise in cancer chemotherapy and management of its potential adverse effects.

Hepatotoxicity

In initial publications on trials of gemtuzumab ozogamicin, up to half of patients had serum ALT or AST elevations during therapy that were greater than 5 times the upper limit of normal (ULN) in 10% to 16%. Hyperbilirubinemia was also common during gemtuzumab therapy. More importantly, a variable proportion (ranging from 2% to 35%) of patients developed clinically apparent sinusoidal obstruction syndrome (SOS). 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 by progressive rise in serum bilirubin, aminotransferase and alkaline phosphatase levels. Recent studies using lower and fractionated regimens of administration of gemtuzumab ozogamicin have reported rates of sinusoidal obstruction syndrome of 1% to 5% compared to <1% with standard chemotherapy. In general, SOS that is severe enough to cause clinical symptoms and signs has an extremely poor prognosis, with a mortality rate as high as 70%, most patients dying of multiorgan failure. Risk factors for developing SOS after gemtuzumab ozogamicin therapy include allogenic hematopoietic cell transplantation, use of other antineoplastic agents, and presence of preexisting liver disease. There are no proven means of prevention or treatment of SOS due to gemtuzumab ozogamicin, although pretreatment with ursodiol and acute management with defibrotide are often employed.

Likelihood score: A (well known cause of clinically significant liver injury, typically the result of sinusoidal obstruction syndrome).

Mechanism of Injury

The cause of the serum enzyme elevations during gemtuzumab ozogamicin therapy is not known, but it is likely due to direct toxicity of the conjugated ozogamicin. The propensity of gemtuzumab ozogamicin to cause sinusoidal obstruction syndrome is perhaps due to the fact that hepatic sinusoidal endothelial cells express CD33 on the cell surface and the antibody conjugate may be taken up by these cells, resulting in their damage and release of apoptotic fragments into sinusoids causing pro-inflammatory and pro-fibrotic reactions and sinusoidal obstruction.

Outcome and Management

The product label of gemtuzumab includes a boxed warning of hepatic injury and sinusoidal obstruction syndrome and recommends monitoring of serum enzymes and bilirubin before each dose as well as clinical monitoring for signs and symptoms of sinusoid obstruction syndrome during therapy. The serum aminotransferase elevations that occur during low dose, fractionated gemtuzumab ozogamicin therapy are usually transient, mild and asymptomatic and do not require dose modification or delay in therapy. Serum aminotransferase elevations above 5 times the upper limit of normal or elevations in serum bilirubin should lead to more careful monitoring and suspension of further infusions, at least until levels return to normal or near normal levels. If patients develop symptoms, signs, or laboratory evidence of sinusoidal obstruction syndrome, therapy should be discontinued and patients carefully monitored.

Drug Class: Antineoplastic Agents, Monoclonal Antibodies

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

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Gemtuzumab Ozogamicin – Mylotarg®

DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Gemtuzumab Ozogamicin	356547-88-1	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 30 November 2023

Abbreviations used: AML, acute myelogenous leukemia; OD, odds ratio; SOS, sinusoidal obstruction syndrome; HCT, hematopoietic cell transplantation.

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).

Chabner BA, Barnes J, Neal J, Olson E, Mujagiv H, Sequist L, Wilson W, et al. Targeted therapies: tyrosine kinase inhibitors, monoclonal antibodies, and cytokines. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1731-53.

(Textbook of pharmacology and therapeutics).

Gemtuzumab for relapsed acute myeloid leukemia. Med Lett Drugs Ther 2000; 42: 67-8. PubMed PMID: 10908423.

(Concise review of the mechanism of action, efficacy and safety of gemtuzumab in acute myeloid leukemia [AML]; mentions that it has been associated with hyperbilirubinemia, serum enzyme elevations and one case of hepatic failure).

Neumeister P, Eibl M, Zinke-Cerwenka W, Scarpatetti M, Sill H, Linkesch W. Hepatic veno-occlusive disease in two patients with relapsed acute myeloid leukemia treated with anti-CD33 calicheamicin (CMA-676) immunoconjugate. Ann Hematol 2001; 80: 119-20. PubMed PMID: 11261323.

(2 patients with sinusoidal obstruction syndrome [SOS] after an initial dose of gemtuzumab ozogamicin; a 50 year old man with refractory AML developed jaundice 2 weeks after a single infusion [bilirubin 27 mg/dL], with hepatomegaly and ascites dying 2 weeks later; and, a 45 year old woman with refractory AML developed jaundice 8 days after initial infusion [bilirubin 32 mg/dL], with ascites, renal failure and death 4 weeks later).

Bross PF, Beitz J, Chen G, Chen XH, Duffy E, Kieffer L, Roy S, et al. Approval summary: gemtuzumab ozogamicin in relapsed acute myeloid leukemia. Clin Cancer Res 2001; 7: 1490-6. PubMed PMID: 11410481.

(Review of the preclinical and clinical trials of gemtuzumab ozogamicin for refractory AML that formed the basis of its accelerated approval by the FDA, mentions that 45 of 142 patients developed severe liver test abnormalities, 12 of whom had elevations in both bilirubin and ALT).

Giles FJ, Kantarjian HM, Kornblau SM, Thomas DA, Garcia-Manero G, Waddelow TA, David CL, et al. Mylotarg (gemtuzumab ozogamicin) therapy is associated with hepatic venoocclusive disease in patients who have not received stem cell transplantation. Cancer 2001; 92: 406-13. PubMed PMID: 11466696.

(Among 119 patients with AML treated with gemtuzumab ozogamicin, 14 [12%] developed SOS with abrupt onset of weight gain, abdominal distension and pain [bilirubin 2.2-33.6 mg/dL, peak ALT 43-1789 U/L], being a major cause of death in 5, and probably contributory in 3 and possibly in 4 more patients).

Tack DK, Letendre L, Kamath PS, Tefferi A. Development of hepatic veno-occlusive disease after Mylotarg infusion for relapsed acute myeloid leukemia. Bone Marrow Transplant 2001; 28: 895-7. PubMed PMID: 11781652.

(67 year old woman with refractory AML after hematopoietic cell transplantation [HCT] developed SOS arising 6 days after intravenous gemtuzumab ozogamicin, with ascites and jaundice [peak bilirubin 15.8 mg/dL]).

Gordon LI. Gemtuzumab Ozogamicin (Mylotarg) and hepatic veno-occlusive disease: take two acetaminophen, and. Bone Marrow Transplant 2001; 28: 811-2. PubMed PMID: 11781639.

(Editorial in response to Tack [2001] reviewing the pathogenesis of SOS and the possible role of free radicals and potential for acetaminophen to contribute to the injury).

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 AML treated with gemtuzumab ozogamicin, liver injury suggestive of SOS developed in 11, 7 of whom died of hepatic failure 8 to 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).

Giles F, Garcia-Manero G, Cortes J, Thomas D, Kantarjian H, Estey E. Ursodiol does not prevent hepatic venoocclusive disease associated with Mylotarg therapy. Haematologica 2002; 87: 1114-6. PubMed PMID: 12368170.

(Among 85 patients with refractory AML or myelodysplastic syndromes treated with gemtuzumab ozogamicin and given ursodiol starting the day before infusion and continuing for 21 days, ten [12%] developed SOS, a rate similar to that reported before use of ursodiol [Giles 2001]).

O'Boyle KP, Murigeppa A, Jain D, Dauber L, Dutcher JP, Wiernik PH. Probable veno-occlusive disease after treatment with gemtuzumab ozogamicin in a patient with acute myeloid leukemia and a history of liver transplantation for familial hemochromatosis. Med Oncol 2003; 20: 379-84. PubMed PMID: 14716035.

(69 year old man with a history of liver transplantation and AML developed rising AST and bilirubin levels 7 days and died 13 days after an infusion of gemtuzumab ozogamicin).

Nabhan C, Rundhaugen L, Jatoi M, Riley MB, Boehlke L, Peterson LC, Tallman MS. Gemtuzumab ozogamicin (Mylotarg^{TM}) is infrequently associated with sinusoidal obstructive syndrome/veno-occlusive disease. Ann Oncol 2004; 15: 1231-6. PubMed PMID: 15277263.

(Among 47 patients with AML treated with gemtuzumab as a single agent, 23 [48%] had elevation of liver tests, but only one [2%] developed clinically apparent SOS).

Amadori S, Suciu S, Willemze R, Mandelli F, Selleslag D, Stauder R, Ho A, et al.; EORTC leukemia group; GIMEMA leukemia group. Sequential administration of gemtuzumab ozogamicin and conventional chemotherapy as first line therapy in elderly patients with acute myeloid leukemia: a phase II study (AML-15) of the EORTC and GIMEMA leukemia groups. Haematologica 2004; 89: 950-6. PubMed PMID: 15339678.

(Among 57 patients with AML treated with gemtuzumab ozogamicin on days 1 and 15, severe myelosuppression was universal and SOS occurred in 3, which was fatal in 2 patients).

Perry R, Penk Kapoor N, Shah AJ, Kapoor N, Shah AJ. Gemtuzumab ozogamicin exposure and portal fibrosis. Pediatr Blood Cancer 2005; 45: 82-3. PubMed PMID: 15880448.

(An 8 year old girl and 5 year old boy with acute leukemia developed clinical evidence of SOS after several courses of gemtuzumab ozogamicin therapy, and liver biopsies showed periportal fibrosis).

Arceci RJ, Sande J, Lange B, Shannon K, Franklin J, Hutchinson R, Vik TA, et al. Safety and efficacy of gemtuzumab ozogamicin in pediatric patients with advanced CD33+ acute myeloid leukemia. Blood 2005; 106: 1183-8. PubMed PMID: 15886328.

(Among 29 children with relapsed or refractory AML treated with gemtuzumab ozogamicin, 21% developed ALT or AST elevations and one SOS).

Larson RA, Sievers EL, Stadtmauer EA, Löwenberg B, Estey EH, Dombret H, Theobald M, et al. Final report of the efficacy and safety of gemtuzumab ozogamicin (Mylotarg) in patients with CD33-positive acute myeloid leukemia in first recurrence. Cancer 2005; 104: 1442-52. PubMed PMID: 16116598.

(277 patients with relapsed AML treated with gemtuzumab ozogamicin, 28% developed ALT levels ≥5 times ULN and 29% bilirubin levels ≥3 times ULN and 0.9% SOS).

Lannoy D, Decaudin B, Grozieux de Laguérenne A, Barrier F, Pignon JM, Wetterwald M, et al. Gemtuzumab ozogamicin-induced sinusoidal obstructive syndrome treated with defibrotide: a case report. J Clin Pharm Ther 2006; 31: 389-92. PubMed PMID: 16882110.

(65 year old man with AML treated with gemtuzumab ozogamicin developed SOS 23 days after the first dose and died of multiorgan failure several weeks later despite therapy with defibrotide).

McKoy JM, Angelotta C, Bennett CL, Tallman MS, Wadleigh M, Evens AM, Kuzel TM, et al. Gemtuzumab ozogamicin-associated sinusoidal obstructive syndrome (SOS): an overview from the research on adverse drug events and reports (RADAR) project. Leuk Res 2007; 31: 599-604. PubMed PMID: 16959316.

(Analysis of the FDAs MedWatch database revealed 99 reports of SOS in adult and 6 in pediatric patients treated with gemtuzumab ozogamicin; review of clinical trials and observational studied found highest rates of SOS [14-40%] in patients who underwent HCT within 3 months of receiving gemtuzumab or who received concurrent chemotherapy with potentially hepatotoxic agents).

Maradei SC, Maiolino A, de Azevedo AM, Colares M, Bouzas LF, Nucci M. Serum ferritin as risk factor for sinusoidal obstruction syndrome of the liver in patients undergoing hematopoietic stem cell transplantation. Blood 2009; 114: 1270-5. PubMed PMID: 19401560.

(Among 427 patients undergoing HCT, 88 [21%] developed SOS of whom 57 [65%] died; risk factors being allogenic HCT [33%], receipt of imatinib [52%], busulfan [39%], and ferritin above 2000 ng/mL [34%]; only one patient received gemtuzumab).

Zwaan CM, Reinhardt D, Zimmerman M, Hasle H, Stary J, Stark B, Dworzak M, et al.; International BFM Study Group on Paediatric AML. Salvage treatment for children with refractory first or second relapse of acute myeloid leukaemia with gemtuzumab ozogamicin: results of a phase II study. Br J Haematol 2010; 148: 768-76. PubMed PMID: 19995399.

(Among 30 children with refractory or relapsing AML treated with gemtuzumab ozogamicin, "treatment was generally well tolerated", only 19 [63%] had ALT or AST elevations which were ≥5 times ULN in 2 [7%], and none developed SOS).

Chevallier P, Prebet T, Turlure P, Hunault M, Vigouroux S, Harousseau JL, Blaise D, et al. Prior treatment with gemtuzumab ozogamicin and the risk of veno-occlusive disease after allogeneic haematopoietic stem cell transplantation. Bone Marrow Transplant 2010; 45: 165-70. PubMed PMID: 19584826.

(Among 44 adults with AML treated gemtuzumab ozogamicin followed by HCT, 3 [7%] developed SOS).

Löwenberg B, Beck J, Graux C, van Putten W, Schouten HC, Verdonck LF, Ferrant A, et al.; Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON); German Austrian AML Study Group (AMLSG); Swiss Group for Clinical Cancer Research Collaborative Group (SAKK). Gemtuzumab ozogamicin as postremission treatment in AML at 60 years of age or more: results of a multicenter phase 3 study. Blood 2010; 115: 2586-91. PubMed PMID: 20103782.

(Randomized trial of gemtuzumab ozogamicin vs placebo in patients with AML after remission, found overall survival was not improved by the monoclonal conjugate [17% vs 16% at 5 years] and 17% had moderate-to-severe hepatic side effects, one patient dying of SOS during the first course of therapy).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010; 52: 2065-76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury, including 2 attributed to antineoplastic agents, 1 due to melphalan and 1 to gemtuzumab ozogamicin).

Maniecki MB, Hasle H, Bendix K, Møller HJ. Is hepatotoxicity in patients treated with gemtuzumab ozogamicin due to specific targeting of hepatocytes? Leuk Res 2011; 35: e84-6. PubMed PMID: 21329979.

(Immunohistochemical staining of liver tissue showed that both hepatocytes and macrophages [Kupffer cells] express CD33).

Malfuson JV, Konopacki J, Thepenier C, Eddou H, Foissaud V, de Revel T. Fractionated doses of gemtuzumab ozogamicin combined with 3 + 7 induction chemotherapy as salvage treatment for young patients with acute myeloid leukemia in first relapse. Ann Hematol 2012; 91: 1871-7. PubMed PMID: 22820971.

(Among 14 patients with relapsed AML treated with fractionated doses of gemtuzumab ozogamicin [3 mg/m2 given on days 1, 4 and 7:], 11 had a response and underwent HCT, of whom 4 subsequently developed nonfatal SOS, all resolving with conservative management).

Castaigne S, Pautas C, Terré C, Raffoux E, Bordessoule D, Bastie JN, Legrand O, et al.; Acute Leukemia French Association. Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study. Lancet 2012; 379 (9825): 1508-16. PubMed PMID: 22482940.

(Among 280 patients with previously untreated AML given standard chemotherapy with or without gemtuzumab ozogamicin, grade 3 hepatic adverse events occurred in 6% of standard vs 13% of gemtuzumab treated subjects and SOS occurred in 3 subjects, being fatal in 2).

Iacobucci I, Lonetti A, Candoni A, Sazzini M, Papayannidis C, Formica S, Ottaviani E, et al. Profiling of drug-metabolizing enzymes/transporters in CD33+ acute myeloid leukemia patients treated with gemtuzumab-ozogamicin and fludarabine, cytarabine and idarubicin. Pharmacogenomics J 2013; 13: 335-41. PubMed PMID: 22584460.

(Analysis of 1931 single nucleotide variants in 225 drug metabolizing enzyme or transporter genes in 95 patients with AML undergoing chemotherapy with gemtuzumab ozogamicin combined with other agents identified several variants associated with a higher or lower risk of hepatotoxicity).

Amadori S, Suciu S, Stasi R, Salih HR, Selleslag D, Muus P, De Fabritiis P, et al. Sequential combination of gemtuzumab ozogamicin and standard chemotherapy in older patients with newly diagnosed acute myeloid leukemia: results of a randomized phase III trial by the EORTC and GIMEMA consortium (AML-17). J Clin Oncol 2013; 31: 4424-30. PubMed PMID: 24127442.

(Among 472 patients with AML, addition of a course of gemtuzumab ozogamicin before standard chemotherapy resulted in no improvement in overall response rates, but was associated with higher early mortality some of which was due to SOS).

Kharfan-Dabaja MA, Hamadani M, Reljic T, Pyngolil R, Komrokji RS, Lancet JE, Fernandez HF, et al. Gemtuzumab ozogamicin for treatment of newly diagnosed acute myeloid leukaemia: a systematic review and meta-analysis. Br J Haematol 2013; 163: 315-25. PubMed PMID: 24033280.

(Systematic review and metaanalysis of 7 controlled trials of gemtuzumab ozogamicin in 3942 patients found no increase in overall survival and a higher rate of early mortality [relative risk, RR =1.6] and SOS [RR=7.7]).

Tallman MS, McDonald GB, DeLeve LD, Baer MR, Cook MN, Graepel GJ, Kollmer C. Incidence of sinusoidal obstruction syndrome following Mylotarg(gemtuzumab ozogamicin): a prospective observational study of 482 patients in routine clinical practice. Int J Hematol 2013; 97: 456-64. PubMed PMID: 23460018.

(Among 482 patients with AML treated with gemtuzumab ozogamicin in multiple clinical practices, 44 [9%] developed SOS of whom 13 [3%] died of resultant multiorgan failure).

de Witte T, Suciu S, Meert L, Halkes C, Selleslag D, Bron D, Amadori S, et al. Idarubicin and cytarabine in combination with gemtuzumab ozogamicin (IAGO) for untreated patients with high-risk MDS or AML evolved from MDS: a phase II study from the EORTC and GIMEMA Leukemia Groups (protocol 06013). Ann Hematol 2015; 94: 1981-9. PubMed PMID: 26410352.

(Among 30 patients with high risk myelodysplastic syndromes or AML treated with idarubicin, cytarabine and gemtuzumab ozogamicin [one dose, 5 mg/m^2], ALT elevations above 5 times ULN arose in 16 [53%] and one patient had nonfatal SOS).

Koren-Michowitz M, Maayan H, Apel A, Shem-Tov N, Yerushalmi R, Volchek Y, Avigdor A, et al. Salvage therapy with ARA-C and gemtuzumab ozogamicin in AML patients relapsing after stem cell transplantation. Ann Hematol 2015; 94: 375-8. PubMed PMID: 25307457.

(Among 16 patients with AML who relapsed after HCT and were treated with cytarabine and gemtuzumab ozogamicin, serum enzyme elevations occurred in 80% and were above 5 times ULN in 27%, with mild SOS occurring in 3 subjects after repeat HCT).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 49 [5.5%] were attributed to antineoplastic agents, but none were linked to use of gemtuzumab ozogamicin).

Battipaglia G, Labopin M, Candoni A, Fanin R, El Cheikh J, Blaise D, Michallet M, et al. Risk of sinusoidal obstruction syndrome in allogeneic stem cell transplantation after prior gemtuzumab ozogamicin treatment: a retrospective study from the Acute Leukemia Working Party of the EBMT. Bone Marrow Transplant 2017; 52: 592-9. PubMed PMID: 28092357.

(Among 146 adults with AML who received gemtuzumab ozogamicin and underwent HCT, 11 [8%] developed SOS which was fatal in 3 [2%]).

Jen EY, Ko CW, Lee JE, Del Valle PL, Aydanian A, Jewell C, Norsworthy KJ, et al. FDA approval: gemtuzumab ozogamicin for the treatment of adults with newly diagnosed CD33-positive acute myeloid leukemia. Clin Cancer Res. 2018;24:3242-3246. PubMed PMID: 29476018.

(Summary of the data on safety and efficacy of gemtuzumab ozogamicin as therapy of newly diagnosed CD33-positive AML based upon a randomized controlled trial in 271 patients receiving daunorubicin and cytarabine with or without gemtuzumab ozogamicin in which toxicities did not differ significantly between treatment arms, liver dysfunction arising in 4% of both).

Norsworthy KJ, Ko CW, Lee JE, Liu J, John CS, Przepiorka D, Farrell AT, Pazdur R. FDA approval summary: Mylotarg for treatment of patients with relapsed or refractory CD33-positive acute myeloid leukemia. Oncologist. 2018;23:1103-1108. PubMed PMID: 29650683.

(Summary of the data on safety and efficacy of gemtuzumab ozogamicin as therapy of relapsed or refractory CD33-positive AML which led to the FDA reapproval of this agent for this indication and de novo AML [Jen et al 2018], in trials of lower dose, fractionated regimens of gemtuzumab ozogamicin [3 mg/m^2 on days 1, 4 and 7]; among 87 patients treated with this regimen, 16% had ALT elevations but none were above 5 times ULN and there were no cases of SoS).

Short NJ, Rytting ME, Cortes JE. Acute myeloid leukaemia. Lancet. 2018;392(10147):593-606. PubMed PMID: 30078459.

(Review of the epidemiology, pathogenesis, risk stratification, diagnosis, and treatment of AML, including regimens for de novo as well as relapsed or refractory cases).

Lambert J, Pautas C, Terré C, Raffoux E, Turlure P, Caillot D, Legrand O, et al. Gemtuzumab ozogamicin for de novo acute myeloid leukemia: final efficacy and safety updates from the open-label, phase III ALFA-0701 trial. Haematologica. 2019;104:113-119. PubMed PMID: 30076173.

(Among 271 patients with de novo AML treated with daunorubicin and cytarabine with or without gemtuzumab ozogamicin, event-free survival was 17.3 vs 9.5 months and overall survival 27.5 vs 21.8 months, SOS arising in 6 [4.5%: 1 case fatal] vs none, and discontinuation for hepatobiliary adverse events arising in 8 [6.1%] vs 1 [0.7%]).

Ali S, Dunmore HM, Karres D, Hay JL, Salmonsson T, Gisselbrecht C, Sarac SB, et al. The EMA review of Mylotarg (gemtuzumab ozogamicin) for the treatment of acute myeloid leukemia. Oncologist. 2019;24:e171-e179. PubMed PMID: 30898889.

(Summary of the data on safety and efficacy of gemtuzumab ozogamicin for treatment of AML by the European Medicines Agency [EMA] showing an improvement in event-free survival in a randomized controlled trial and a metaanalysis of 52 trials; most frequent adverse reactions leading to discontinuation were thrombocytopenia, SOS, hemorrhage, and infection, SOS arising in 6 of 131 patients [4.6%], two of whom died and resulting in a higher 30-day mortality [3.8% vs 2.2%] and higher discontinuation rates [31% vs 7%] with gemtuzumab).

Roeker LE, Kim HT, Glotzbecker B, Nageshwar P, Nikiforow S, Koreth J, Armand P, et al. Early clinical predictors of hepatic veno-occlusive disease/sinusoidal obstruction syndrome after myeloablative stem cell transplantation. Biol Blood Marrow Transplant. 2019;25:137-144. PubMed PMID: 30081073.

(Among 1853 patients undergoing myeloablative HCT at a single referral center between 1996 and 2015, 205 [11%] developed SOS, the rate decreasing over time from a peak of 18.5% in 2006-2007 to 3% in 2014-2015).

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.

(Review of publications on risk factors for SOS after allogeneic HCT found a strong association with prior treatment with gemtuzumab ozogamicin [odds ratio =20], but recent studies indicate that the incidence of SOS has decreased with use of lower-dose fractionated regimens).

Schlenk RF, Paschka P, Krzykalla J, Weber D, Kapp-Schwoerer S, Gaidzik VI, Leis C, et al. Gemtuzumab ozogamicin in *NPM1*-mutated acute myeloid leukemia: early results from the prospective randomized AMLSG 09-09 phase III study. J Clin Oncol. 2020;38:623-632. PubMed PMID: 31851556.

(Among 581 adults with AML and NPMI mutations treated with idarubicin, cytarabine, etoposide and all-trans retinoic acid with or without gemtuzumab ozogamicin, event-free survival and cumulative mortality were similar in the two treatment arms and, while early death rates were higher, late relapse rates were lower with gemtuzumab ozogamicin).

Ho VT, Martin AS, Pérez WS, Steinert P, Zhang MJ, Chirnomas D, Hoang CJ, et al. Prior gemtuzumab ozogamicin exposure in adults with acute myeloid leukemia does not increase hepatic veno-occlusive disease risk after allogeneic hematopoietic cell transplantation: a center for international blood and marrow transplant analysis. Biol Blood Marrow Transplant. 2020;26:884-892. PubMed PMID: 31891815.

(Among 137 patients with a history of gemtuzumab ozogamicin exposure vs 548 non-exposed controls, 5 year survival rates after HCT were similar, SOS was diagnosed in 4% vs 3%, was severe in 3% vs 1% and fatal in 3% vs less than 1%).

Joubert N, Beck A, Dumontet C, Denevault-Sabourin C. Antibody-drug conjugates: the last decade. Pharmaceuticals (Basel). 2020;13:245. PubMed PMID: 32937862.

(Review of the development, structure, efficacy, adverse event rates and approval of vector based chemotherapy using selective delivery by a monoclonal antibody and cancer cell injury by a conjugated cellular toxin [payload] including 9 that are FDA approved and 6 others in pivotal trials).

Ladha A, Mannis G, Muffly L. Hepatic veno-occlusive disease in allogeneic stem cell transplant recipients with prior exposure to gemtuzumab ozogamicin or inotuzumab ozogamicin. Leuk Lymphoma. 2021;62:257-263. PubMed PMID: 32988266.

(Review of the incidence of SOS after HCT in patients with prior exposure to gemtuzumab ozogamicin or inotuzumab ozogamicin).

Duncan C, St Martin A, Pérez WS, Steinert P, Zhang MJ, Chirnomas D, Hoang CJ, et al. Veno-occlusive disease risk in pediatric patients with acute myeloid leukemia treated with gemtuzumab ozogamicin before allogeneic hematopoietic cell transplantation. Pediatr Blood Cancer. 2021;68:e29067. PubMed PMID: 33871892.

(Among 496 children with AML who underwent myeloablative allogeneic HCT between 2008-2011 with [n=148] or without [n=348] prior exposure to gemtuzumab ozogamicin, 5 year survival rates were 51% vs 55%, SOS arose in 16% vs 10%, which was severe in 8% vs 3% and fatal in 3 [2%] vs 1 [<1%] patients).

Kloehn J, Brodt G, Ernst J, Gruhn B. Analysis of risk factors for hepatic sinusoidal obstruction syndrome following allogeneic hematopoietic stem cell transplantation in pediatric patients. J Cancer Res Clin Oncol. 2022;148:1447-1455. PubMed PMID: 34255148.

(Among 105 children undergoing allogeneic HCT over a 12 year period at a single referral center in Germany, 15 [14%] developed SOS which was fatal in 3; risk factors for SOS being prior gemtuzumab exposure [OR=11], high serum ferritin levels, and elevated INR).

Döhner H, Weber D, Krzykalla J, Fiedler W, Kühn MWM, Schroeder T, Mayer K, et al.; German–Austrian AML Study Group. Intensive chemotherapy with or without gemtuzumab ozogamicin in patients with NPM1-mutated acute myeloid leukaemia (AMLSG 09-09): a randomised, open-label, multicentre, phase 3 trial. Lancet Haematol. 2023;10:e495-e509. PubMed PMID: 37187198.

(Among 588 adults with NPMI-mutated AML treated with idarubicin, cytarabine, etoposide and all-trans retinoic acid with or without gemtuzumab ozogamicin, there were no differences in short and long term survival rates or in hepatoxicity rates [1% in both arms], with one death from hepatotoxicity in the gemtuzumab ozogamicin group).

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 Oct 29:1-12. Epub ahead of print. 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]).