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Trastuzumab Emtansine

Updated: January 30, 2024.

OVERVIEW

Introduction

Trastuzumab emtansine (also known as ado-trastuzumab emtansine) is a humanized monoclonal antibody to the human epidermal growth factor receptor-2 (HER2) conjugated with a microtubule inhibitor which is used in the therapy of advanced, metastatic breast cancer. Trastuzumab emtansine has been linked to frequent serum enzyme elevations during therapy, to occasional instance of acute clinically apparent liver injury and, when given chronically, to nodular regenerative hyperplasia and noncirrhotic portal hypertension.

Background

Trastuzumab (tras tooz' ue mab) emtansine (em tan' seen) is a humanized monoclonal antibody to the human epidermal growth factor receptor-2 (HER2) conjugated to emtansine (DM1), a cytotoxic microtubule inhibitor, which is used in the therapy of advanced or metastatic forms of breast cancer that express HER2. The monoclonal antibody is linked by a cleavable tetrapeptide to the microtubule inhibitor which is released intracellularly after the conjugate binds to and is taken up by HER2 expressing cancer cells. Within the cancer cell, emtansine is released by lysosomal enzymes that cleave the linker molecule. The released emtansine then binds to microtubules causing cell cycle arrest and apoptotic cell death. This conjugate was shown to induce objective responses and improve survival in patients with unresectable or metastatic breast cancer who had progressed despite previous therapies, and it was approved for this indication in the United States in 2013. The antibody conjugate is available in single use vials of 100 mg per vial or 160 mg lyophilized powder under the brand name Kadcyla. The recommended dose is 3.6 mg/kg intravenously every 3 weeks until disease progression or intolerability. The antibody conjugate has a higher rate of adverse side effects than trastuzumab alone. The common adverse events include fatigue, nausea, vomiting, diarrhea, fever, myalgias, headache, constipation, serum enzyme elevations and thrombocytopenia. Less common but potential severe adverse events include hepatotoxicity, anaphylaxis, heart failure and embryo-fetal toxicity. Trastuzumab emtansine 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 large registration trials of trastuzumab emtansine for breast and other cancers, serum enzyme elevations occurred in 20% to 80% of patients and levels rose to above 5 times the upper limit of normal (ULN) in at least 5%. Some aminotransferase elevations were accompanied by serum bilirubin elevations. Subsequent to its approval and more widespread use, instances of acute liver injury including deaths from hepatic failure were reported with trastuzumab emtansine treatment, and it received a boxed warning about hepatotoxicity with

recommendations for prospective monitoring of liver tests. Some cases appeared to represent acute sinusoidal obstruction syndrome and in other cases acute, direct hepatotoxic injury.

More recently, cases of noncirrhotic portal hypertension have been described in patients on long term trastuzumab emtansine. The typical presentation is with signs and symptoms of portal hypertension after months or years of therapy and usually with only modest increases in serum aminotransferase elevations and bilirubin. Strikingly, in patients who undergo liver biopsy, cirrhosis is not present, although mild-to-moderate fibrosis is present in some. This phenotype of injury is classified as noncirrhotic portal hypertension, but the underlying liver condition is usually nodular regenerative hyperplasia with elements of sinusoidal obstruction. Hepatic imaging shows a nodular and somewhat shrunken liver and prominent splenomegaly and varices. Typically, patients improve clinically once trastuzumab emtansine is dose-reduced or discontinued, although without chemotherapy the malignancy may return and progress. Another syndrome with somewhat similar clinical features associated with long term trastuzumab emtansine therapy is a disordered, nodular liver cause by shrinkage of necrotic hepatic metastases, sometimes referred to as "pseudocirrhosis." These patients generally do not have symptoms of liver disease, and the diagnosis is made by hepatic imaging often done as a part of routine follow up of the metastatic liver disease.

Likelihood score: B (likely cause of clinically apparent liver injury).

Mechanism of Injury

The cause of the serum enzyme elevations during trastuzumab emtansine therapy is not known, but appears to be dose related and may be a mild direct toxicity of the infusions. The mechanism of the hepatotoxicity may be direct injury to endothelial cells and vasculature, possibly by their take up of the conjugate or the released microtubule inhibitor from other cells. Several instances of liver injury in patients taking trastuzumab emtansine have been attributed to sinusoidal obstruction syndrome, and mild forms of it may explain the frequent serum enzyme and bilirubin elevations during trastuzumab emtansine therapy. In other instances the underlying condition appears to be nodular regenerative hyperplasia, which is likely the result of acute or chronic vascular injury or both.

Outcome and Management

The product label for trastuzumab emtansine recommends monitoring of liver enzymes before starting and before each dose. The serum aminotransferase elevations that arise during trastuzumab emtansine therapy are usually mild-to-moderate in severity, self-limited in course, and not associated with symptoms or jaundice. In some instances, however, the injury persists or is more severe. Elevations of serum aminotransferase levels above 5 times ULN should lead to dose interruption or modification, but persistent elevations, appearance of symptoms or jaundice or evidence of sinusoidal obstruction syndrome should lead to discontinuation. Fatal instances of acute hepatic injury have been described with trastuzumab emtansine therapy. The chronic liver injury from the monoclonal-cytotoxic conjugate is generally persistent although signs and symptoms usually regress with drug discontinuation and sometimes with dose reduction alone. These clinically apparent and severe hepatic reactions have been observed with trastuzumab emtansine, but not with trastuzumab deruxtecan or with the monoclonal antibody without a conjugate.

Drug Class: Antineoplastic Agents, Monoclonal Antibodies

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

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Trastuzumab Emtansine – Kadcyla®

DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING (Trastuzumab Emtansine)

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Trastuzumab	180288-69-1	Monoclonal Antibody	Not Available
Trastuzumab Deruxtecan	1826843-81-5	Monoclonal Antibody with Microtubular Inhibitor	SID: 381128090
Trastuzumab Emtansine	1018448-65-1	Monoclonal Antibody with Microtubular Inhibitor	SID: 135353969

ANNOTATED BIBLIOGRAPHY

References updated: 30 January 2024

Abbreviations: CT, computerized tomography; FAERS, Food and Drug Administration Adverse Event Reporting System; HER-2, human epidermal growth factor receptor 2; MR, magnetic resonance; NRH, nodular regenerative hyperplasia; TNF, tumor necrosis factor.

Zimmerman HJ. Hepatotoxic effects of oncotherapeutic and immunosuppressive agents. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 673-708.

(Expert review of hepatotoxicity published in 1999; well before the availability of most monoclonal antibody therapies).

Reuben A. Hepatotoxicity of immunosuppressive drugs. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2011, pp. 569-91.

(Review of hepatotoxicity of immunosuppressive drugs mentions that "the biological immunosuppressants are largely free from hepatotoxicity, with the exception of the TNF alpha antagonists").

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/2013/125427Orig1s000SumR.pdf

(FDA website medical review of data on safety and efficacy provided by the sponsor in support of the 2013 approval of trastuzumab emtansine as therapy of refractory metastatic HER2 positive breast cancer, mentions that ALT elevations occurred in up to 82% of patients during therapy which were above 5 times ULN in 5%, and that at least 2 instances of death from hepatic failure occurred in treated subjects).

Trastuzumab and capecitabine for metastatic breast cancer. Med Lett Drugs Ther 1998; 40 (1039): 106-8. PubMed PMID: 9814369.

(Concise review of the mechanism of action, efficacy, safety and cost of trastuzumab to be used alone or with paclitaxel for metastatic breast cancer; adverse events include infusion reactions, diarrhea and cardiac toxicity [when combined with an anthracycline]; no mention of ALT elevations or hepatotoxicity).

Cobleigh MA, Vogel CL, Tripathy D, Robert NJ, Scholl S, Fehrenbacher L, Wolter JM, et al. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. J Clin Oncol 1999; 17: 2639-48. PubMed PMID: 10561337.

(Among 222 women with HER2 overexpressing, refractory metastatic breast cancer who were treated with trastuzumab once weekly, one developed an anaphylactoid reaction and 20 [9%] had grade 3, and 7 [3%] grade 4 hepatic adverse events [mostly ALT or Alk P elevations], usually in those with progressive disease involving the hepatobiliary system; no mention of clinically apparent liver injury with jaundice).

Smith IE. Efficacy and safety of Herceptin in women with metastatic breast cancer: results from pivotal clinical studies. Anticancer Drugs 2001; 12 Suppl 4 : S3-10. PubMed PMID: 11989525.

(Analysis of safety data from 930 patients in clinical trials and from over 30,000 in postmarketing surveillance indicated that trastuzumab is usually well tolerated, the most common side effect being infusion reactions, mainly with the first dose, serious reactions occurring in 0.3% of patients; trastuzumab may also have cardiac toxicity).

Vogel CL, Cobleigh MA, Tripathy D, Gutheil JC, Harris LN, Fehrenbacher L, Slamon DJ, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Clin Oncol 2002; 20: 719-26. PubMed PMID: 11821453.

(Among 114 women with metastatic breast cancer treated with two doses of trastuzumab "severe laboratory abnormalities were uncommon"; no mention of ALT elevations or hepatotoxicity).

Jones RL, Smith IE. Efficacy and safety of trastuzumab. Expert Opin Drug Saf 2004; 3: 317-27. PubMed PMID: 15268649.

(Review of efficacy and safety of trastuzumab mentions that it is generally well tolerated, with specific discussion of infusion reactions, cardiac and pulmonary toxicity; no mention of ALT elevations or hepatotoxicity).

Capitain O, Lortholary A, Abadie-Lacourtoisie S. [Cytolytic hepatitis and esomeprazole during chemotherapy]. Presse Med 2005; 34: 1235-6. French. PubMed PMID: 16230965.

(41 year old woman with breast cancer developed fatigue on the fifth day of the second course of trastuzumab and paclitaxel and one day after taking one dose of esomeprazole [bilirubin normal, ALT 14 times ULN, Alk P 1.5 times ULN], resolving within 8 days and not recurring with subsequent courses of the chemotherapy).

Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE Jr, Davidson NE, Tan-Chiu E, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 2005; 353: 1673-84. PubMed PMID: 16236738.

(Among 3351 women with breast cancer enrolled in two controlled trials of standard chemotherapy with or without trastuzumab, with an average follow up of 2.0 years, survival and disease free survival were superior with trastuzumab; no mention of hepatotoxicity or ALT elevations).

Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, Gianni L, et al.; Herceptin Adjuvant (HERA) Trial Study Team. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 2005; 353: 1659-72. PubMed PMID: 16236737.

(Among 5081 women with breast cancer randomized to receive trastuzumab [for 1 or 2 years] or observation, both disease free and overall survival were greater in trastuzumab treated patients; toxicity included rare cases of congestive heart failure and death, but no mention of hepatotoxicity or ALT elevations).

Smith I, Procter M, Gelber RD, Guillaume S, Feyereislova A, Dowsett M, Goldhirsch A, et al.; HERA study team. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. Lancet 2007; 369 (9555): 29-36. PubMed PMID: 17208639.

(Further follow up of trial of observation vs 1 or 2 years of trastuzumab in 5102 women with breast cancer receiving conventional chemotherapy found more serious and fatal adverse events in the trastuzumab treated patients, but none were attributed to liver injury).

Muñoz A, Carrera S, Ferreiro J, de Lobera AR, Mañé JM, López-Vivanco G. Reversible liver toxicity with adjuvant trastuzumab for localized breast cancer. Ann Oncol 2007; 18: 2045-6. PubMed PMID: 18083694.

(31 year old woman with breast cancer developed marked ALT elevations [1403 U/L] after first infusion of trastuzumab [8 mg/kg], which resolved within 4 weeks and did not recur with subsequent lower dose regimens, although minor ALT continued to occur thereafter).

Srinivasan S, Parsa V, Liu CY, Fontana JA. Trastuzumab-induced hepatotoxicity. Ann Pharmacother 2008; 42: 1497-501. PubMed PMID: 18780811.

(54 year old woman with breast cancer on paclitaxel and trastuzumab developed progressive increases in ALT, starting with first dose and resulting in discontinuation after 8th cycle, falling to normal thereafter).

Burris HA 3rd, Rugo HS, Vukelja SJ, Vogel CL, Borson RA, Limentani S, Tan-Chiu E, et al. Phase II study of the antibody drug conjugate trastuzumab-DM1 for the treatment of human epidermal growth factor receptor 2 (HER2)-positive breast cancer after prior HER2-directed therapy. J Clin Oncol 2011; 29: 398-405. PubMed PMID: 21172893.

(Among 112 patients with advanced breast cancer despite previous therapy who were treated with trastuzumab emtansine for an average of 4 months, common side effects were fatigue, nausea and headache; rates of ALT elevations were not provided, but one patient stopped therapy early because of "thrombocytopenia and hepatotoxicity").

Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, Pegram M, et al.; EMILIA Study Group. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med 2012; 367: 1783-91. PubMed PMID: 23020162.

(Among 991 women with HER2 expressing breast cancer who had failed previous therapy who received either trastuzumab emtansine or lapatinib with capecitabine, overall survival was improved with the antibody conjugate, but ALT levels were elevated in 17%, AST in 22%, and platelets decreased in 28% of patients; 3 patients stopped therapy early because of aminotransferase elevations, but no patient had both bilirubin and marked ALT elevations and there were no liver related deaths).

Krop IE, LoRusso P, Miller KD, Modi S, Yardley D, Rodriguez G, Guardino E, et al. A phase II study of trastuzumab emtansine in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer who were previously treated with trastuzumab, lapatinib, an anthracycline, a taxane, and capecitabine. J Clin Oncol 2012; 30: 3234-41. PubMed PMID: 22649126.

(Among 110 patients with advanced, refractory breast cancer treated with trastuzumab emtansine for an average of 17 months, ALT elevations occurred in 14% and one patient died from "abnormal hepatic function").

Vucicevic D, Carey EJ, Karlin NJ. Trastuzumab-induced hepatotoxicity: a case report. Breast Care (Basel) 2013; 8: 146-8. PubMed PMID: 24419371.

(60 year old woman was found to have serum enzyme elevations without symptoms 41 days after finishing 6 months [8 cycles] of trastuzumab and while receiving trastuzumab exemestane [bilirubin 1.0 mg/dL, ALT 91 rising to 523 U/L, Alk P 100 rising to 231 U/L, INR 0.94], resolving incompletely 4 months later).

Ado-trastuzumab emtansine (Kadcyla) for HER2-positive metastatic breast cancer. Med Lett Drugs Ther 2013; 55 (1425): 75-6. PubMed PMID: 24662957.

(Concise summary of mechanism of action, efficacy, safety and costs of trastuzumab emtansine, a conjugate of trastuzumab with a microtubule inhibitor, mentions that increased aminotransferase levels occurred in more than 25% of patients and serious, sometimes fatal, liver toxicity has been reported).

Force J, Saxena R, Schneider BP, Storniolo AM, Sledge GW Jr, Chalasani N, Vuppalanchi R. Nodular regenerative hyperplasia after treatment with trastuzumab emtansine. J Clin Oncol 2016; 34 (3): e9-12. PubMed PMID: 24778392.

(Two women, ages 66 and 50 years, with metastatic breast cancer presented with evidence of portal hypertension [ascites, varices, low platelet counts] 16 months after starting cyclic therapy with trastuzumab emtansine [bilirubin normal, ALT 48 and ~120 U/L, Alk P 400 U/L and not given], biopsy showing nodular regenerative hyperplasia and both patients improving when the agent was stopped).

Miller KD, Diéras V, Harbeck N, Andre F, Mahtani RL, Gianni L, Albain KS, et al. Phase IIa trial of trastuzumab emtansine with pertuzumab for patients with human epidermal growth factor receptor 2-positive, locally advanced, or metastatic breast cancer. J Clin Oncol 2014; 32: 1437-44. PubMed PMID: 24733796.

(Among 64 women with HER2 positive metastatic breast cancer [HER2 positive] treated with the combination of pertuzumab and trastuzumab emtansine [every 3 weeks], common side effects were fatigue [61%], nausea [50%] and diarrhea [39%] and "hepatic dysfunction" in 38% with ALT levels above 5 times ULN in 9%).

Ishizuna K, Ninomiya J, Ogawa T, Tsuji E. Hepatotoxicity induced by trastuzumab used for breast cancer adjuvant therapy: a case report. J Med Case Rep 2014; 8: 417. PubMed PMID: 25491149.

(60 year old Japanese woman with breast cancer developed liver test abnormalities after a second cycle of trastuzumab [bilirubin normal, ALT 246 U/L, Alk P 553 U/L] which recurred one year later after readministration of a single infusion [bilirubin normal, ALT 102 U/L, Alk P 377 U/L], resolving within 2 months of stopping).

Spano JP, Beuzeboc P, Coeffic D, Arnould L, Lortholary A, Andre F, Ferrero JM. Long term HER2+ metastatic breast cancer survivors treated by trastuzumab: Results from the French cohort study LHORA. Breast 2015; 24: 376-83. PubMed PMID: 25913287.

(Among 160 women with breast cancer treated with trastuzumab [for a median of 5.3 years], long term adverse events included cardiac failure and cardiomyopathy; no mention of ALT elevations or hepatotoxicity).

Ghabril M, Vuppalanchi R. Drug-induced nodular regenerative hyperplasia. Semin Liver Dis 2014; 34: 240-5. PubMed PMID: 24879987.

(Review of the clinical presentation, etiology, course and management of nodular regenerative hyperplasia which is often due to medications including trastuzumab emtansine).

Diéras V, Harbeck N, Budd GT, Greenson JK, Guardino AE, Samant M, Chernyukhin N, Smitt MC, Krop IE. Trastuzumab emtansine in human epidermal growth factor receptor 2-positive metastatic breast cancer: an integrated safety analysis. J Clin Oncol 2014; 32: 2750-7. PubMed PMID: 25024070.

(Among 884 patients with HER2 positive breast cancer treated with trastuzumab emtansine in 6 controlled trials, common adverse events were fatigue [46%], nausea [43%], thrombocytopenia [32%], headache [29%], constipation [27%] and ALT elevations [16%], typically during the first few months, rising to above 5 times ULN in 3.1%, resulting in drug discontinuation in 0.5% and death in 2 patients).

Mandaliya H, Baghi P, Prawira A, George MK. A rare case of paclitaxel and/or trastuzumab induced acute hepatic necrosis. Case Rep Oncol Med 2015; 2015: 825603. PubMed PMID: 26605100.

(62 year old woman with HER2 positive breast cancer developed acute respiratory failure within 12 hours of first dose of paclitaxel and trastuzumab, liver test results "were inconclusive" and she died 36 hours later: "surprisingly, autopsy showed acute hepatic/liver necrosis").

Bishop AJ, Ensor J, Moulder SL, Shaitelman SF, Edson MA, Whitman GJ, Bishnoi S, et al. Prognosis for patients with metastatic breast cancer who achieve a no-evidence-of-disease status after systemic or local therapy. Cancer 2015; 121: 4324-32. PubMed PMID: 26348887.

(Among 570 patients with metastatic breast cancer seen between 2003 and 2005 at a single referral center, overall 5 year survival was 24%, but was higher in those who achieved "no evidence of disease" status [78% vs 13%] and those who received trastuzumab, no mention of adverse events or hepatotoxicity).

Giuliani J, Bonetti A. Acute liver failure caused by metastatic breast cancer: can we expect some results from chemotherapy? Dig Dis Sci 2015; 60: 2541-3. PubMed PMID: 26088368.

(35 year old woman with HER2 positive breast cancer developed evidence of metastatic replacement of the liver [bilirubin 5.0 mg/dL, ALT 236 U/L, GGT 449 U/L] and improvement with combination chemotherapy including trastuzumab, liver tests returning to normal but then died with progressive disease 9 months later, indicating that this symptom is not as grim as previously reported using more modern chemotherapeutic regimens).

Sharp A, Johnston SR. Dose-reduced trastuzumab emtansine: active and safe in acute hepatic dysfunction. Case Rep Oncol 2015; 8: 113-21. PubMed PMID: 25873876.

(59 year old woman with HER2 positive breast cancer, refractory after multiple chemotherapy regimens, developed jaundice associated with a 7 cm liver mass [bilirubin ~8.2 mg/dL, ALT ~1000 U/L, Alk P ~650 U/L], which responded to trastuzumab emtansine with resolution of jaundice, improvement in liver enzymes, and shrinkage of the mass).

Gelmon KA, Boyle FM, Kaufman B, Huntsman DG, Manikhas A, Di Leo A, Martin M, et al. Lapatinib or trastuzumab plus taxane therapy for human epidermal growth factor receptor 2-positive advanced breast cancer: final results of NCIC CTG MA.31. J Clin Oncol 2015; 33: 1574-83. PubMed PMID: 25779558.

(Among 652 patients with HER2 positive advanced breast cancer treated with lapatinib or trastuzumab combined with a taxane, progression free survival was better with trastuzumab, while symptoms of rash, diarrhea and febrile neutropenia were more common with lapatinib, decrease in left ventricular function arose in 2.3% of trastuzumab vs 0% of lapatinib recipients, and "hepatic dysfunction" occurred in <1% of both groups).

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, only four cases were attributed to a monoclonal antibody [3 to infliximab and 1 to adalimumab]; no cases were attributed to trastuzumab).

Yan H, Endo Y, Shen Y, Rotstein D, Dokmanovic M, Mohan N, Mukhopadhyay P, et al. Ado-trastuzumab emtansine targets hepatocytes via human epidermal growth factor receptor 2 to induce hepatotoxicity. Mol Cancer Ther 2016; 15: 480-90. PubMed PMID: 26712117.

(In cultured human and mouse hepatocytes and in mouse models, trastuzumab emtansine can cause hepatocellular injury after binding to cell surface HER2 receptors and uptake into hepatocytes).

Bunchorntavakul C, Reddy KR. Drug hepatotoxicity: newer agents. Clin Liver Dis 2017; 21: 115-34. PubMed PMID: 27842767.

(Review of literature on hepatotoxicity of newly approved agents mentions that trastuzumab can cause ALT elevations in 7-12% of patients and rarely acute hepatitis but has not been linked to reactivation of HBV, while trastuzumab emtansine causes ALT elevations in 17-22% of patients and has been linked to cases of hepatitis, acute liver failure, portal hypertension and nodular regenerative hyperplasia [NRH], but not to reactivation of HBV).

Liu Y, Li ZY, Li X, Wang JN, Huang QA, Huang Y. Liver toxicity of chemotherapy and targeted therapy for breast cancer patients with hepatitis virus infection. Breast 2017; 35: 191-195. PubMed PMID: 28800545.

(Among 835 patients with breast cancer receiving targeted therapy, rates of ALT elevations were slightly higher in the 52 with HBsAg [35%] and the 21 with anti-HCV [43%] than controls [28%] as were rates of chemotherapy disruption for liver test abnormalities [9.6% and 9.5% vs 5%], but no patient developed viral reactivation, although the proportion of those with HBsAg who were receiving antiviral prophylaxis was not provided).

Liu Y, Li ZY, Wang JN, Li X, Huang QA, Huang Y. Effects of hepatitis C virus infection on the safety of chemotherapy for breast cancer patients. Breast Cancer Res Treat 2017; 164: 379-83. PubMed PMID: 28447238.

(Among 835 patients with breast cancer receiving target therapy, rates of "hepatitis" were slightly higher in the 21 with anti-HCV in serum [23%] than in controls [14%] as were rates of chemotherapy disruption for liver test abnormalities [9.5% vs 5%], but no patient had reactivation as define by a 1 log increase in HCV RNA levels).

Hidalgo-Blanco A, Aguirresarobe-Gil de San Vicente M, Aresti S, de Miguel E, Cabriada-Nuno JL. Pseudocirrhosis in metastatic breast cancer. Gastroenterol Hepatol 2018; 41: 111-3. PubMed PMID: 28187872.

(39 year old woman with HER2-positive breast cancer received a 1-year course of trastuzumab at the end of which she had normal ALT levels and CT appearance of the liver, but 18 months later she presented with abnormalities of both suggestive of pseudocirrhosis).

Lepelley M, Allouchery M, Long J, Boucherle D, Ranchoup Y, Le Marc'Hadour F, Villier C, Sturm N. Nodular regenerative hyperplasia induced by trastuzumab emtansine: role of emtansine? Ann Hepatol 2018; 17: 1067-71. PubMed PMID: 30600283.

(48 year old woman with HER2-negative breast cancer in 2008 had recurrence in 2012 that was HER2-positive and after 12 months of trastuzumab emtansine therapy presented with mild ALT and AST elevations and MRI showing splenomegaly and dystrophic liver, a biopsy of which showed NRH, liver abnormalities improving, but cancer progressing when chemotherapy was stopped).

Talima S, Kassem H, Kassem N. Chemotherapy and targeted therapy for breast cancer patients with hepatitis C virus infection. Breast Cancer 2019; 26: 154-63. PubMed PMID: 30191397.

(Two of 58 Egyptian women with advanced breast cancer and chronic hepatitis C developed viral reactivation during targeted chemotherapy, one on lapatinib and one trastuzumab).

Fujii Y, Doi M, Tsukiyama N, Hattori Y, Ohya K, Shiroma N, Morio K, et al. Sinusoidal obstruction syndrome post-treatment with trastuzumab emtansine (T-DM1) in advanced breast cancer. Int Cancer Conf J 2019; 9: 18-23. PubMed PMID: 31950012.

(Two women with metastatic HER2-positive breast cancer developed noncirrhotic portal hypertension after 2.5 and 4.5 years of trastuzumab emtansine therapy, and liver biopsy showed sinusoidal obstruction syndrome and disordered hepatic plates in both).

Milam P, Berger M, Ramaswamy B, Reinbolt R, Wesolowski R, Kaffenberger BH. Spider telangiectases and palmar erythema as harbingers of structural liver changes in three breast cancer patients on ado-trastuzumab emtansine. J Clin Aesthet Dermatol 2019; 12: 23-6. PubMed PMID: 31531159.

(Three women [ages 53, 60 and 63 years] with advanced breast cancer developed cutaneous stigmata of cirrhosis after 17 to 34 cycles of trastuzumab emtansine with spider angiomata and palmar erythema, minimal ALT and AST elevations, decreased platelet counts [43,000-123,000/μL], and usually with splenomegaly and nodular liver on CT or MR imaging).

Duret-Aupy N, Lagarce L, Blouet A, Kettani S, Conte C, Bourneau-Martin D, Drablier G, et al. Liver sinusoidal obstruction syndrome associated with trastuzumab emtansine treatment for breast cancer. Therapie 2019; 74: 675-7. PubMed PMID: 31023619.

(87 year old woman on trastuzumab emtansine for two years developed variceal hemorrhage, ascites and edema, with normal ALT, and CT showing no evidence of cirrhosis, but liver biopsy showing sinusoidal obstruction syndrome).

Modi S, Saura C, Yamashita T, Park YH, Kim SB, Tamura K, Andre F, et al.; DESTINY-Breast01 Investigators. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. N Engl J Med. 2020;382:610-621. PubMed PMID: 31825192.

(Among 184 patients with unresectable or metastatic refractory HER2 positive breast cancer treated with trastuzumab deruxtecan the objective response rate was 61% and overall adverse event rate was 99.5%, most commonly with nausea, fatigue, alopecia, vomiting, constipation, decreased appetite, and 14% of patients developed interstitial lung disease, 5% a prolonged QT interval, 2.7% infusion reactions, and ALT elevations in 12% which were above 5 times ULN in 2%; no mention of clinically apparent liver injury).

Battisti NML, Rogerson F, Lee K, Shepherd S, Mohammed K, Turner N, McGrath S, et al. Safety and efficacy of T-DM1 in patients with advanced HER2-positive breast cancer The Royal Marsden experience. Cancer Treat Res Commun. 2020;24:100188. PubMed PMID: 32619830.

(Among 128 patients with advanced, refractory HER2-positive breast cancer who were treated with trastuzumab emtansine at a single UK referral center from 2014 to 2019, the median overall survival rate was 20.4 months and adverse events were frequent including "deranged liver function" in 69%, "liver toxicity" in 20%, resulting in dose modification in 6%, and discontinuation in 2%).

Emens LA, Esteva FJ, Beresford M, Saura C, De Laurentiis M, Kim SB, Im SA, et al. Trastuzumab emtansine plus atezolizumab versus trastuzumab emtansine plus placebo in previously treated, HER2-positive advanced breast cancer (KATE2): a phase 2, multicentre, randomised, double-blind trial. Lancet Oncol. 2020;21:1283-1295. PubMed PMID: 33002436.

(Among 202 patients with advance, refractory HER2-positive breast cancer treated with trastuzumab emtansine with or without atezolizumab [anti-PD-L1], the median progression free survival was similar in the two groups [8.2 vs 6.8 months], while serious adverse events were more frequent with atezolizumab [33% vs 9%] including ALT elevations above 5 times ULN [5% vs 3%]).

Garrido I, Magalhães A, Lopes J, Macedo G. Trastuzumab Emtansine-Induced Nodular Regenerative Hyperplasia: Is Dose Reduction Enough as a Preventable Measure? Dig Dis. 2022;40:787-792. PubMed PMID: 35078201.

(52 year old woman with HER2-positive, metastatic lung cancer was treated with trastuzumab emtansine and had an objective clinical response, but rapidly developed persistently abnormal liver tests which worsened [peak ALT 110 U/L, Alk P 474 U/L, bilirubin 1.7 mg/dL] with fall of platelet count to 74,000/mcL, with liver biopsy showing NRH, but a decrease in dose [3.6 to 1.8 mg/kg every 3 weeks] was followed by fall of liver tests and stabilization of platelet count with maintained clinical response).

Cortés J, Kim SB, Chung WP, Im SA, Park YH, Hegg R, Kim MH, et al.; DESTINY-Breast03 Trial Investigators. Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer. N Engl J Med. 2022; 386: 1143-1154. PubMed PMID: 35320644.

(Among 524 patients with refractory, advanced or metastatic HER2-positive breast cancer treated with trastuzumab deruxtecan or trastuzumab emtansine, progression free survival at 1 year was 76% vs 34% and adverse event rates 98% vs 87%, with deruxtecan having higher rates of neutropenia and anemia but lower rates of ALT elevations [19.5% vs 27%] which were above 5 times ULN in 1.6% vs 4.6%).

Ma P, Tian H, Shi Q, Liu R, Zhang Y, Qi X, Chen Y. High risks adverse events associated with trastuzumab emtansine and trastuzumab deruxtecan for the treatment of HER2-positive/mutated malignancies: a pharmacovigilance study based on the FAERS database. Expert Opin Drug Saf. 2023;22:685-696. PubMed PMID: 37068935.

(Analysis of the FDA Adverse Event Reporting System [FARES] from 2004 to 2022 identified 2113 reports for trastuzumab emtansine [Tm] and 1269 for trastuzumab deruxtecan [Td], and while liver test abnormalities were reported with both, Tm had high report rates of hepatic cirrhosis [n=35], portal hypertension [24], and nodular regenerative hyperplasia [17], while Td had none for these diagnoses).

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], trastuzumab deruxtecan [n=8], and polatuzumab vedotin [3]).