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NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Trastuzumab. [Updated 2024 Jan 30].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Trastuzumab

Updated: January 30, 2024.

OVERVIEW

Introduction

Trastuzumab is a humanized monoclonal antibody to the human epidermal growth factor receptor 2 (HER2) which is used in combination with other antineoplastic agents in the therapy of breast and gastric cancer. Trastuzumab has been implicated in causing instances of transient serum enzyme elevations, but has only rarely been linked to instances of clinically apparent liver injury with jaundice. In contrast, the recently developed conjugates of trastuzumab with the microtubule inhibitor emtansine or the topoisomerase inhibitor deruxtecan, which are used as an antineoplastic agents for advanced resistant breast cancer, has been linked to frequent serum enzyme elevations during therapy. Trastuzumab emtansine has been linked to instances of acute clinically apparent liver injury that can be severe and even fatal and, when given chronically, to non-cirrhotic portal hypertension.

Background

Trastuzumab (tras tooz' ue mab) is a humanized monoclonal antibody to HER2 which is a human epidermal growth factor receptor that is overexpressed in 20% to 25% of breast cancers and a smaller proportion of other cancers such as gastric, lung, ovarian and pancreatic. The interaction of epidermal growth factor (EGF) with HER2 results in rapid cell growth and proliferation via intracellular pathways. Binding of trastuzumab to HER2 blocks this cell signaling pathway and causes growth arrest. Trastuzumab was shown to decrease recurrences and prolong survival in patients with breast cancer that were HER2 positive. Trastuzumab was approved for use in the United States in 1998 and current indications include breast and gastric cancers that express HER2. Trastuzumab is available in single use vials of 150 mg lyophilized powder generically under the brand name Herceptin. The typical dose is 2 to 8 mg/kg intravenously weekly or every three weeks, the dose and duration of therapy varying with different indications. Common side effects include fatigue, nausea and vomiting, diarrhea, infusion reactions, rash, headache, fever, cough, dyspnea, neutropenia, infections, thrombocytopenia, and anemia. Rare, but serious side effects include severe infusion reactions (usually with the initial dose), cardiomyopathy (especially when combined with an anthracycline), pneumonitis, tumor lysis syndrome and fetal toxicity. Trastuzumab should be prescribed and administered only by health care workers with expertise and experience in cancer chemotherapy and management of its adverse events.

Trastuzumab emtansine (em tan' seen) and **transtuzumab deruxtecan** (de rux" tee can) are conjugates of trastuzumab with toxic molecules, which are released after binding and uptake by HER2 expressing cells and are used in the therapy of metastatic breast, gastric, or lung cancers that express HER2. The two conjugates have separate toxicities and their likelihood of causing hepatotoxicity varies, perhaps due to the different toxin

conjugates rather than the monoclonal antibody. These monoclonal antibody conjugates are discussed separately in different chapters in LiverTox.

Hepatotoxicity

In large registration trials of trastuzumab for advanced or metastatic breast and other cancers, rates of serum enzyme elevations and instances of clinically apparent liver injury are rarely mentioned. In one large study, ALT elevations arose in 3% of patients treated but there were no instances of clinically apparent liver disease. The package insert for trastuzumab does not provide information of the rate of serum ALT or AST elevations or report cases of liver injury. Since its approval and widescale use, there have been at least 4 published case reports of serum ALT elevations occurring after 1 to 8 cycles of trastuzumab therapy. One case was symptomatic but none were accompanied by jaundice or hyperbilirubinemia. Immune allergic features and autoantibodies were not present. The abnormalities improved on stopping therapy and in one case recurred in a similar pattern on re-exposure. Abnormalities of liver enzymes during trastuzumab therapy are often attributed to progressive disease or hepatic effects of other medications being given with the monoclonal antibody. Thus, trastuzumab can probably cause clinically significant liver injury but it is uncommon, mild and usually self-limited in course, resolving with discontinuation.

Likelihood score: C (probable rare cause of clinically apparent liver injury).

Mechanism of Injury

The cause of the serum enzyme elevations during trastuzumab therapy is not known, but may be due to the direct effect of inhibiting human epidermal growth factor signaling in liver. While the liver injury may be dose related and may be a mild direct toxicity of the infusions, other possibilities are that it is caused by the antineoplastic agents that are used with trastuzumab such as doxorubicin, cyclophosphamide, paclitaxel, docetaxel, carboplatin, or 5-fluorouracil.

Outcome and Management

The liver injury attributed to trastuzumab has invariably been self-limited and not associated with symptoms or jaundice. There is no information on possible cross sensitivity to the injury among different monoclonal antibodies or therapies directed at epidermal growth factor receptors. In some instances, trastuzumab has been tolerated at lower doses after recovery with minimal ALT elevations.

Drug Class: Antineoplastic Agents, Monoclonal Antibodies

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Trastuzumab – Herceptin®

DRUG CLASS

Antineoplastic Agents

Trastuzumab Conjugates: Trastuzumab Emtansine, Trastuzumab Deruxtecan

COMPLETE LABELING (Trastuzumab)

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

ANNOTATED BIBLIOGRAPHY

References updated: 30 January 2024

Abbreviations: CT, computerized tomography; 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).

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; 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 metastatic breast cancer who were treated with trastuzumab once weekly, one developed an anaphylactoid reaction and 5 [3%] had ALT elevations above 5 times the ULN, but most liver enzyme abnormalities were associated with progressive disease, and there were no deaths from liver failure).

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 over 30,000 from postmarketing surveillance indicates 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, survival and disease free 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, resistant 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 ado-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 ado-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 chemotherapy 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 therapy with 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: 191-5. 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 develop viral 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 2.5 and 4.5 years of trastuzumab emtansine therapy, in both of whom liver biopsy showed sinusoidal obstruction syndrome and disordered hepatic plates).

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 angiomas 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).

Nodehi RS, Kalantari B, Raafat J, Ansarinejad N, Moazed V, Mortazavizadeh SMR, Hosseinzadeh M, et al. A randomized, double-blind, phase III, non-inferiority clinical trial comparing the efficacy and safety of TA4415V (a proposed Trastuzumab biosimilar) and Herceptin (Trastuzumab reference product) in HER2-positive early-stage breast Cancer patients. BMC Pharmacol Toxicol. 2022;23:57. PubMed PMID: 35902898.

(Among 92 patients with early stage HER2 positive breast cancer treated with conventional chemotherapy followed by adjuvant trastuzumab or a biological equivalent, the objective response rate was 83% and 89% and adverse event rates were similar; no mention of hepatotoxicity or ALT elevations).

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]).