U.S. National Library of Medicine
National Center for Biotechnology Information

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 2015 Jun 12].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Trastuzumab

Updated: June 12, 2015.

OVERVIEW

Introduction

Trastuzumab is a humanized monoclonal antibody to the HER2 receptor which is used in combination with other antineoplastic agents in the therapy of breast and gastric cancer. Trastuzumab has been implicated in rare instances of transient, marked serum enzyme elevations, but has not been linked to instances of clinically apparent liver injury with jaundice. In contrast, the recently developed conjugate of trastuzumab with the microtubule inhibitor emtansine, which is used as an antineoplastic agent for advanced resistant breast cancer, has been linked to frequent serum enzyme elevations during therapy and, when given chronically, to nodular regenerative hyperplasia.

Background

Trastuzumab (tras tooz' ue mab) is humanized monoclonal antibody to HER2 which is a human growth factor receptor that is overexpressed in 20% to 25% of breast cancers. The interaction of epidermal growth factor (EGF) with HER2 results in rapid cell growth and proliferation via intracellular pathways that include MAP and PI3 kinase. Binding of trastuzumab to the HER2 receptor blocks this cell signaling pathway and causes growth arrest. Trastuzumab was shown to decrease recurrences and prolong survival in women 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 multiple use vials under the brand name Herceptin. The typical dose is 2 to 8 mg/kg intravenously every week, the dose and duration of therapy varying with different indications. Common side effects include fatigue, nausea and vomiting, diarrhea, infusion reactions, rash, headache, neutropenia, infections and anemia. Rare, but serious side effects include infusion reactions (usually with the initial dose), cardiomyopathy (especially when combined with an anthracycline), pneumonitis and fetal toxicity.

Ado-trastuzumab emtansine (em tan' seen) is a conjugate of trastuzumab with emtansine (DM1), a microtubule inhibitor derived from maytansine that is taken up with trastuzumab into HER2 expressing cancer cells and degraded in lysosomes resulting in release of DM1, which binds to tubulin and disrupts microtubular networks resulting in cell cycle arrest and cell death. This conjugate, when combined with other antineoplastic agents, has shown increased efficacy in advanced, metastatic breast cancer. Ado-trastuzumab emtansine was approved for use in previously treated, advanced breast cancer in the United States in 2013, and experience with its use has been limited. The antibody conjugate is available in single use vials 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 more common adverse

events include fatigue, nausea, myalgias, headache, constipation, serum enzyme elevations and thrombocytopenia.

Hepatotoxicity

In large registration trials of trastuzumab for breast and other cancers, rates of serum enzyme elevations were rarely reported and there were no instances of clinically apparent liver injury. Since its approval and wide scale use, there have been several isolated reports of serum ALT elevations occurring after 1 to 8 cycles of trastuzumab therapy. The abnormalities have been elevations of ALT and AST with no or minimal increase in alkaline phosphatase levels and no symptoms or bilirubin elevations. The abnormalities were invariably self-limited and, in at least one instance, did not recur with use of lower doses of trastuzumab. There have been no published reports of clinically apparent, acute liver injury with jaundice attributed to trastuzumab.

In contrast, in large registration trials ado-trastuzumab emtansine was linked to serum enzyme elevation or bilirubin elevations in up to 24% of patients. Furthermore instances of acute liver injury including deaths from hepatic failure were reported, although details of the timing and pattern of injury were not provided. A recent report of nodular regenerative hyperplasia in two women with breast cancer who were treated for 16 months with ado-trastuzumab emtansine suggests that it can cause vascular injury to the liver and with chronic therapy can lead to nodular regeneration. Patients present with symptoms or signs of portal hypertension with modest, typically nonspecific elevations in serum aminotransferases and alkaline phosphatase and decrease in platelet count. Jaundice did not occur. Imaging studies demonstrated a nodular liver and evidence of portal hypertension (splenomegaly, varices). Both patients improved once the antineoplastic agent was withdrawn. Typically nodular regenerative hyperplasia improves upon withdrawal of the causative agent, but it can result in hepatic failure if not identified and the drug is continued.

Mechanism of Injury

The cause of the serum enzyme elevations during trastuzumab therapy is not known, but appears to be dose related and may be a mild direct toxicity of the infusions. The hepatotoxicity of ado- trastuzumab emtansine has not been fully defined, but is probably due to injury to endothelial cells and vasculature, possibly by the microtubule inhibitor conjugate. While sinusoidal obstruction syndrome has not been described, mild forms of it may explain the frequent serum enzyme and bilirubin elevations during ado-trastuzumab emtansine therapy.

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. Patients who develop evidence of portal hypertension or nodular regeneration during ado-trastuzumab emtansine therapy should have the drug discontinued.

Drug Class: Antineoplastic Agents, Monoclonal Antibodies

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Trastuzumab – Herceptin®

Box continues on next page...

Box continued from previous page.

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
Trastuzumab	**180288-69-1**	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 12 June 2015

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").

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).

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 anti-HER2 monoclonal antibody 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 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 recurrent 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 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).