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Pertuzumab

Updated: April 15, 2020.

OVERVIEW

Introduction

Pertuzumab 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 refractory, advanced breast cancer. Pertuzumab has been implicated in rare instances of transient, occasionally marked serum enzyme elevations, but has not been linked to instances of clinically apparent liver injury with jaundice.

Background

Pertuzumab (per tooz' ue mab) is humanized monoclonal antibody to HER2 which is a 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. Blockage of this pathway results in cell cycle arrest and cell death. Pertuzumab binds to the dimerization site on the HER2 receptor and prevents pairing of receptors and blocks their intracellular signaling. Because the binding site for pertuzumab is different from that of trastuzumab (another monoclonal antibody to HER2), they can be used together and are believed to have additive antitumor effects. Pertuzumab in combination with trastuzumab and docetaxel has been shown to increase the rate of pathological complete responses in women with advanced HER2 positive breast cancer and it was approved for this indication in 2012. Indications were subsequently expanded to use as neoadjuvant therapy for early or advanced, metastatic breast cancer. Pertuzumab is available in multiple use vials of 420 mg under the brand name Perjeta. The typical dose is 840 mg intravenously initially, followed by 420 mg every three weeks. Common side effects include diarrhea, nausea, fatigue, rash, abdominal pain and cardiac dysfunction. Rare, but serious side effects include infusion reactions (usually with the initial dose), cardiomyopathy (especially when combined with an anthracycline), pneumonitis and fetal toxicity.

Hepatotoxicity

In large registration trials of pertuzumab for breast and other cancers, rates of serum enzyme elevations were usually not reported. In the FDA summary review the incidence of hepatic disorders was similar with pertuzumab as with placebo when added to standard breast cancer chemotherapy (9.6% vs 10.1%) as were rates of ALT elevations (3.0% vs 3.7%). Rare instances of ALT elevations above 5 times the ULN have been reported in studies of pertuzumab combined with carboplatin, docetaxel and trastuzumab or with trastuzumab emtansine. A single instance of acute liver failure was reported in a patient who received pertuzumab, trastuzumab and docetaxel in a clinical trial, but few details were given, and the injury was attributed to docetaxel. In all of these situations, the role of pertuzumab as opposed to the other antineoplastic agents being used was uncertain. Since

its approval and wider scale use, there have been no reports of clinically apparent, acute liver injury with jaundice attributed to pertuzumab.

Likelihood score: E (unlikely cause of clinically apparent acute liver injury).

Mechanism of Injury

Pertuzumab is a human monoclonal antibody and is unlikely to have intrinsic hepatotoxicity, but it may interact with endothelial growth factor receptors present on normal cells and cause injury by its direct cellular effects on epithelial growth factor pathways.

Outcome and Management

The liver injury attributed to pertuzumab has not been well characterized and there is no information on possible cross sensitivity to the injury among different monoclonal antibodies or therapies directed at epidermal growth factor receptors. Pertuzumab is usually used in combination with trastuzumab and other antineoplastic agents which are generally considered more likely causes of liver injury.

Drug Class: Antineoplastic Agents, Monoclonal Antibodies

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Pertuzumab – Perjeta®

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
Pertuzumab	380610-27-5	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 15 April 2020

Abbreviations: TNF, tumor necrosis factor; HER-2, human epidermal growth factor receptor 2.

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 tumor necrosis factor [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).

Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/125409Orig1s000MedR.pdf

(FDA website with product label and medical review of pertuzumab concludes that "overall, pertuzumab does not appear to be significantly hepatotoxic").

Gianni L, Lladó A, Bianchi G, Cortes J, Kellokumpu-Lehtinen PL, Cameron DA, Miles D, et al. Open-label, phase II, multicenter, randomized study of the efficacy and safety of two dose levels of Pertuzumab, a human epidermal growth factor receptor 2 dimerization inhibitor, in patients with human epidermal growth factor receptor 2-negative metastatic breast cancer. J Clin Oncol. 2010;28:1131–7. PubMed PMID: 20124183.

(Among 78 women with metastatic breast cancer [HER2 negative] treated with one of 2 doses of pertuzumab every 3 weeks, response rates were minimal and side effects were common, including diarrhea [51%], nausea [27%], fatigue [24%], rash [21%], abdominal pain [156%] and cardiac dysfunction [11%]; no mention of ALT elevations or hepatotoxicity).

Gianni L, Pienkowski T, Im YH, Roman L, Tseng LM, Liu MC, Lluch A, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol. 2012;13:25–32. PubMed PMID: 22153890.

(Among 417 women with HER2 positive breast cancer treated with 1 of 4 regimens of pertuzumab, docetaxel and trastuzumab, highest rates of response and side effects occurred with triple therapy, including one death from fulminant hepatitis after a 4th cycle; no mention of rates of ALT elevations).

Baselga J, Cortés J, Kim SB, Im SA, Hegg R, Im YH, Roman L, et al; CLEOPATRA Study Group. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med. 2012;366:109–19. PubMed PMID: 22149875.

(Among 808 women with metastatic breast cancer [HER2 positive] treated with trastuzumab and docetaxel, the addition of pertuzumab increased progression free survival from 12.4 to 18.5 months and increased side effects of diarrhea [46% to 67%] and febrile neutropenia [8% to 14%]; no mention of hepatotoxicity).

Pertuzumab (Perjecta) for HER2-positive metastatic breast cancer. Med Lett Drugs Ther. 2012;54(1395):59–60. PubMed PMID: 22825690.

(Concise review of mechanism of action, efficacy and safety of pertuzumab as therapy of metastatic breast cancer [HER2 positive] shortly after its approval for this use in the US; no mention of ALT elevations or hepatotoxicity).

Pertuzumab (Perjeta) for preoperative use in HER2-positive breast cancer. Med Lett Drugs Ther. 2013;55(1431):98–9. PubMed PMID: 24322664.

(Concise review of mechanism of action, efficacy and safety of pertuzumab as neoadjuvant [preoperative] therapy for HER2 positive breast cancer mentions cardiomyopathy, anaphylaxis and embryotoxicity, but not hepatotoxicity or ALT elevations).

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%).

Gianni L, Pienkowski T, Im YH, Tseng LM, Liu MC, Lluch A, Starosławska E, et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. Lancet Oncol. 2016;17:791–800. PubMed PMID: 27179402.

(Among 417 women with locally advanced HER2 positive breast cancer treated with neoadjuvant regimens using trastuzumab, pertuzumab and docetaxel in various combinations, adverse event rates were similar [95-100%] and serious adverse events included febrile neutropenia and diarrhea; no mention of ALT elevations or hepatotoxicity).

von Minckwitz G, Procter M, de Azambuja E, Zardavas D, Benyunes M, Viale G, Suter T, et al; APHINITY Steering Committee and Investigators. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. N Engl J Med. 2017;377:122–31. PubMed PMID: 28581356.

(Among 4805 women with operable HER2 positive breast cancer given standard adjuvant therapy and trastuzumab with either pertuzumab or placebo, disease recurrence was lower with pertuzumab [7.1% vs 8.7%], while adverse event rates were similar except for diarrhea [71% vs 45%] and rash [26% vs 20%]; no mention of ALT elevations or hepatotoxicity).

Hurvitz SA, Martin M, Symmans WF, Jung KH, Huang CS, Thompson AM, Harbeck N, et al. Neoadjuvant trastuzumab, pertuzumab, and chemotherapy versus trastuzumab emtansine plus pertuzumab in patients with HER2-positive breast cancer (KRISTINE): a randomised, open-label, multicentre, phase 3 trial. Lancet Oncol. 2018;19:115–26. PubMed PMID: 29175149.

(Among 444 patients with advanced HER2 positive breast cancer given neoadjuvant therapy with trastuzumab emtansine with pertuzumab vs trastuzumab, pertuzumab and docetaxel with carboplatin, response rates were lower with trastuzumab emtansine but so were adverse event rates with ALT elevations in 10% vs 21% that were above 5 times ULN in 2% vs 1%).

Woodward N, De Boer RH, Redfern A, White M, Young J, Truman M, Beith J. Results from the first multicenter, open-label, phase IIIb study investigating the combination of pertuzumab with subcutaneous trastuzumab and a taxane in patients with HER2-positive metastatic breast cancer (SAPPHIRE). Clin Breast Cancer. 2019;19:216–24. PubMed PMID: 30922805.

(Among 50 women with metastatic HER2 positive breast cancer treated with the combination of pertuzumab, trastuzumab and taxane, adverse events included diarrhea, fatigue, neuropathy, alopecia, rash and nausea; no mention of ALT elevations or hepatotoxicity).

Swain SM, Miles D, Kim SB, Im YH, Im SA, Semiglazov V, Ciruelos E, et al; CLEOPATRA study group. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. Lancet Oncol. 2020;21:519–30. PubMed PMID: 32171426.

(Long term follow up of randomized controlled trial of trastuzumab with docetaxel with or without pertuzumab for advance HER2 positive breast cancer [Baselga 2012] demonstrated continued superior overall survival in comparison to placebo [median of 57 vs 41 months]; adverse event rates were similar except for diarrhea and rash; no mention of ALT elevations or hepatotoxicity).