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Olaratumab

Updated: May 29, 2017.

OVERVIEW

Introduction

Olaratumab is a human monoclonal antibody to the platelet-derived growth factor (PDGF) receptor alpha and an antineoplastic agent used in the therapy of advanced soft tissue sarcoma. Olaratumab has not been linked to serum enzyme elevations during therapy or to idiosyncratic acute liver injury.

Background

Olaratumab (oh" lar at' ue mab) is a recombinant human monoclonal IgG1 antibody to the platelet-derived growth factor receptor alpha. Signaling through PDGF receptors promotes cell proliferation and angiogenesis. Inhibition of the PDGF signaling decreases formation of new blood vessels, which plays an important role in growth and spread of cancer cells. When used in combination with other antineoplastic agents, olaratumab has been shown to extend recurrence-free survival in several forms of advanced cancer. Olaratumab was approved in the United States in 2016 for use in combination with doxorubicin for refractory, advanced soft tissue sarcoma. Olaratumab is available in solution in single use vials of 500 mg in 50 mL or 190 mg in 19 mL (10 mg/mL) under the brand name Lartruvo. The typical dose is 15 mg/kg intravenously over 60 minutes on days 1 and 8 of each 21-day cycle. Premedication with diphenhydramine and dexamethasone is recommended with the initial dose. Olaratumab is administered with doxorubicin and this combination has significant adverse side effects, including nausea and vomiting, diarrhea, fatigue, anorexia, abdominal pain, alopecia, peripheral neuropathy, neutropenia, and stomatitis. Uncommon, but potentially severe adverse events include severe infusion reactions, hypersensitivity reactions, and embryofetal toxicity.

Hepatotoxicity

In preregistration clinical trials, serum aminotransferase elevations were no more frequent in patients receiving olaratumab and doxorubicin than in those receiving doxorubicin alone (17.5% vs 16.1%), and no patient developed elevations above 5 times ULN or required dose modification or discontinuation for liver test abnormalities. Hepatotoxicity was not listed as a cause of serious adverse events or a reason for discontinuation of olaratumab. Subsequent to its approval and more general use, olaratumab has not been implicated in published cases of clinically apparent liver injury. Olaratumab is generally given with other potent antineoplastic agents and it is often difficult to attribute serum enzyme elevations or clinically apparent liver injury to a specific agent being used.

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

Mechanism of Injury

The possible mechanism of liver injury caused by olaratumab is not known. It is a recombinant protein and unlikely to be inherently hepatoxic. Proteins are metabolized to small polypeptides and amino acids in many cells including hepatocytes and do not alter the activity of drug metabolizing enzymes or hepatic transporter molecules. Blocking of PDGF signaling does not seem to harm liver cells or alter hepatic function.

Drug Class: Antineoplastic Agents, Monoclonal Antibodies

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Olaratumab – Lartruvo®

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
Olaratumab	1024603-93-7	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 29 May 2017

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 agents; mentions rituximab and problems of reactivation of hepatitis B, but also states that "the biological immunosuppressants are largely free from hepatotoxicity, with the exception of the TNF alpha antagonists"; no specific discussion of olaratumab).

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).

Chiorean EG, Sweeney C, Youssoufian H, Qin A, Dontabhaktuni A, Loizos N, Nippgen J, et al. A phase I study of olaratumab, an anti-platelet-derived growth factor receptor alpha (PDGFRα) monoclonal antibody, in patients with advanced solid tumors. Cancer Chemother Pharmacol 2014; 73: 595-604. PubMed PMID: 24452395.

(Among 19 patients with advanced solid tumors treated with one of 5 regimens of olaratumab, there were no objective responses and the most common adverse events were fatigue, constipation, diarrhea and fever; no mention of ALT elevations or hepatotoxicity).

Doi T, Ma Y, Dontabhaktuni A, Nippgen C, Nippgen J, Ohtsu A. Phase I study of olaratumab in Japanese patients with advanced solid tumors. Cancer Sci 2014; 105: 862-9. PubMed PMID: 24816152.

(Among 16 patients with various advanced tumors treated with olaratumab [10, 15 or 20 mg/kg], adverse events included proteinuria in 25% and AST elevations in 12%, but none required dose modification or discontinuation).

Tap WD, Jones RL, Van Tine BA, Chmielowski B, Elias AD, Adkins D, Agulnik M, et al. Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial. Lancet 2016; 388 (10043): 488-97. PubMed PMID: 27291997.

(Among 133 patients treated with doxorubicin, addition of olaratumab [15 mg/kg] on days 1 and 8 of 21-day cycles increased the objective response rate [18% vs 12%] and overall survival [median 26.5 vs 14.7 months]; adverse events were more frequent with addition of olaratumab and included neutropenia [38% vs 35%], mucositis [53% vs 35%], nausea [73% vs 52%], vomiting [45% vs 18%], and diarrhea [34% vs 23%]; no mention of ALT elevations or hepatotoxicity).

van der Graaf WT. Olaratumab in soft-tissue sarcomas. Lancet 2016; 388 (10043): 442-4. PubMed PMID: 27291995.

(Editorial accompanying Tap [2016] discussing the promise of PDGF pathway inhibition for soft tissue sarcoma).

Wagner AJ, Kindler H, Gelderblom H, Schöffski P, Bauer S, Hohenberger P, Kopp HG, et al. A phase II study of a human anti-PDGFRα monoclonal antibody (olaratumab, IMC-3G3) in previously treated patients with unresectable and/or metastatic gastrointestinal stromal tumors. Ann Oncol 2017; 28 (3): 541-6.

(Among 21 patients with refractory metastatic gastrointestinal stromal tumors treated with olaratumab [20 mg/kg every 2 weeks], no objective responses were seen and side effects included fatigue [38%], nausea [19%], peripheral edema [14%] and single instances of syncope and hypertension; no mention of ALT elevations or hepatotoxicity).

Klug LR, Heinrich MC. PDGFRA antibody for soft tissue sarcoma. Cell 2017; 168: 555. PubMed PMID: 28187274.

(Commentary on PDGF signaling and the possible role of its inhibition in treatment of soft tissue sarcoma).