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Necitumumab

Updated: May 29, 2017.

OVERVIEW

Introduction

Necitumumab is a human monoclonal antibody to the epidermal growth factor (EGF) receptor and is an anti-angiogenesis agent used in the therapy of advanced non-small cell lung cancer. Necitumumab has not been linked to serum enzyme elevations during therapy or to idiosyncratic acute liver injury.

Background

Necitumumab (ne" si toom' ue mab) is a recombinant human monoclonal IgG1 antibody to the epidermal growth factor (EGF) receptor. The engagement of EGF with its receptors results in activation of cellular pathways that promote cell growth and angiogenesis. EGF receptors are often overexpressed in cancer cells, particularly squamous non-small cell lung cancer. Inhibition of EGF receptor signaling decreases cell growth and proliferation and 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, necitumumab was shown to extend recurrence-free survival in several forms of advanced cancer. Necitumumab was approved in the United States in 2015 for use in metastatic squamous, non-small cell lung cancer as a part of combination therapy with gemcitabine and cisplatin. Necitumumab is available in solution in single use vials of 800 mg in 50 mL (16 mg/mL) under the brand name Portrazza. The typical dose is 800 mg given intravenously over at least 60 minutes on days 1 and 8 of each 3-week cycle. It is typically given in combination with other antineoplastic agents, most commonly with gemcitabine and cisplatin. Common adverse events include rash and hypomagnesemia, but when combined with other agents, diarrhea, fatigue, anorexia, epistasis, neutropenia, and stomatitis are frequent. Uncommon, but potentially severe adverse events include arterial and venous thromboembolic events, cardiopulmonary arrest, marked hypomagnesemia, severe infusion reactions and embryofetal toxicity.

Hepatotoxicity

In large clinical trials, serum aminotransferase elevations were no more frequent in patients receiving necitumumab than placebo in combination with gemcitabine and cisplatin (35% vs 31%) and were rarely above 5 times the upper limit of normal (0.6% vs 1%). In these studies, there were no liver related serious adverse events or drug discontinuations for serum enzyme elevations. Subsequent to its approval and more general use, necitumumab has not been implicated in published cases of clinically apparent liver injury. Necitumumab is generally given with other potent antineoplastic agents and it is often difficult to attribute serum enzyme elevations or more clinically significant liver injury to one specific agent being used. Nevertheless, significant liver injury from necitumumab is probably uncommon.

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

Mechanism of Injury

The mechanism by which necitumumab might cause liver injury is unknown. Necitumumab is a monoclonal antibody and, like other proteins, is metabolized into amino acids and is unlikely to have intrinsic toxicity. Inhibition of EGF signaling does not seem to materially affect liver function.

Drug Class: Antineoplastic Agents, Monoclonal Antibodies

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Necitumumab – Portrazza®

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
Necitumumab	906805-06-9	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 29 May 2017

Abbreviations used: NSCLC, non-small cell lung cancer.

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 necitumumab).

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).

Thatcher N, Hirsch FR, Luft AV, Szczesna A, Ciuleanu TE, Dediu M, Ramlau R, et al.; SQUIRE Investigators. Necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line therapy in patients with stage IV squamous non-small-cell lung cancer (SQUIRE): an open-label, randomised, controlled phase 3 trial. Lancet Oncol 2015; 16: 763-74. PubMed PMID: 26045340.

(Among 1093 patients with advanced squamous NSCLC treated with gemcitabine and cisplatin, overall survival was improved by addition of necitumumab [median 11.5 vs 9.9 months] as were serious adverse events [48% vs 38%], common side effects attributable to necitumumab being rash and hypomagnesemia; ALT and AST elevations occurred with equal frequency [35% vs 31% and 29% vs 25%] and were rarely above 5 times ULN [≤1%]).

Paz-Ares L, Mezger J, Ciuleanu TE, Fischer JR, von Pawel J, Provencio M, Kazarnowicz A, et al.; INSPIRE investigators. Necitumumab plus pemetrexed and cisplatin as first-line therapy in patients with stage IV non-squamous non-small-cell lung cancer (INSPIRE): an open-label, randomised, controlled phase 3 study. Lancet Oncol 2015; 16: 328-37. PubMed PMID: 25701171.

(Among 633 patients with non-squamous NSCLC treated with pemetrexed and cisplatin with or without necitumumab, there were no differences in overall survival rates [median 11.3 vs 11.5 months], but severe adverse events were more frequent with necitumumab [51% vs 41%] including higher rates of severe rash [18% vs <1%], hypomagnesemia [8% vs 2%] and venous thromboembolic events [8% vs 4%]; no mention of ALT elevations or hepatotoxicity).

Garnock-Jones KP. Necitumumab: First global approval. Drugs 2016; 76: 283-9. PubMed PMID: 26729188.

(Review of the development, pharmacology, mechanism of action, clinical efficacy and safety of necitumumab; does not mention ALT elevations or hepatotoxicity).

Elez E, Hendlisz A, Delaunoit T, Sastre J, Cervantes A, Varea R, Chao G, et al. Phase II study of necitumumab plus modified FOLFOX6 as first-line treatment in patients with locally advanced or metastatic colorectal cancer. Br J Cancer 2016; 114: 372-80. PubMed PMID: 26766738.

(Among 44 patients with advanced colorectal cancer treated with necitumumab, oxaliplatin, folinic acid and fluorouracil, objective responses occurred in 64% and adverse events included rash in 90% and neutropenia in 82%; no mention of ALT elevations or hepatotoxicity).

Paz-Ares L, Socinski MA, Shahidi J, Hozak RR, Soldatenkova V, Kurek R, Varella-Garcia M, et al. Correlation of EGFR-expression with safety and efficacy outcomes in SQUIRE: a randomized, multicenter, open-label, phase III study of gemcitabine-cisplatin plus necitumumab versus gemcitabine-cisplatin alone in the first-line treatment of patients with stage IV squamous non-small-cell lung cancer. Ann Oncol 2016; 27: 1573-9. PubMed PMID: 27207107.

(Among 982 patients with advanced squamous NSCLC enrolled in a controlled trial of necitumumab [Thatcher 2015] whose tumor could be evaluated, EGF protein expression was associated with a survival benefit with necitumumab; no mention of ALT elevations or hepatotoxicity).