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Moxetumomab Pasudotox

Updated: April 12, 2019.

OVERVIEW

Introduction

Moxetumomab pasudotox is a mouse monoclonal antibody to CD22 conjugated with a toxic fragment of Pseudomonas exotoxin A which is used in the therapy of resistant forms of hairy cell leukemia. Moxetumomab pasudotox has been linked to transient serum enzyme elevations during therapy, but has not been linked to instances of clinically apparent liver injury with jaundice.

Background

Moxetumomab (mox" e toom' oh mab) pasudotox (pa soo' doe tox) is a recombinant mouse monoclonal antibody to the human CD22 cell surface marker which is highly expressed on the malignant B cells of hairy cell leukemia. The monoclonal antibody is conjugated to a fragment of a bacterial toxin, Pseudomonas exotoxin PE38 (pasudotox). When moxetumomab binds to CD22 on malignant B cells, it is internalized and the pasudotox is released by the action of lysosomal enzymes on the linker molecule that joins the monoclonal antibody and cytotoxic molecule. The intracellular exotoxin results in apoptotic cell death. This monoclonal antibody conjugate has been shown to be effective in inducing remissions in relapsed or refractory hairy cell leukemia and was given accelerated approval for this indication in the United States in 2018. Moxetumomab pasudotox is available in single dose vials of 1 mg of lyophilized powder under the brand name Lumoxiti. The recommended dose is 0.04 mg/kg by intravenous infusion over 30 minutes on days 1, 3 and 5 of each 28-day cycle. Premedication with acetaminophen, an antihistamine and H2 receptor blocker is recommended as well as careful attention to maintaining adequate hydration. Common side effects include infusion reactions, edema, nausea, fatigue, headache, fever, diarrhea, constipation and anemia. Less common but serious side effects include severe infusion reactions, hemolytic uremic syndrome, capillary leak syndrome, renal toxicity and electrolyte imbalance.

Hepatotoxicity

In publications on trials of moxetumomab pasudotox in hairy cell leukemia, serum ALT or AST elevations were frequent during therapy arising in 14% to 19% of patients, but to above 5 times the upper limit of normal (ULN) in only 3.8% to 5.5%. Serial testing for ALT and AST during moxetumomab therapy shows regular and reproducible elevations occurring with each cycle of treatment, peaking at or around day 8 and falling back to baseline by day 21. Hyperbilirubinemia was also common during moxetumomab therapy (6.3%), but there were no reported instances of clinically apparent liver injury with symptoms and jaundice that were attributed to the monoclonal-toxin conjugate. The major severe adverse reactions to moxetumomab pasudotox therapy were hemolytic uremic syndrome and capillary leak syndrome, both of which may be associated with mild-to-

moderate serum enzyme elevations, but significant liver injury with jaundice is rare. In addition, moxetumomab pasudotox has not been linked to sinusoidal obstruction syndrome, a common complication of other monoclonal-toxin conjugates.

Likelihood score: E* (unproven but suspected possible cause of clinically apparent liver injury).

Mechanism of Injury

The serum enzyme elevations that occur during moxetumomab pasudotox therapy is not known, but it is likely direct toxicity of the conjugate.

Outcome and Management

The serum enzyme elevations during moxetumomab pasudotox therapy are common but generally transient, mild and asymptomatic and rarely require dose modification or delay in therapy. Elevations of ALT or AST above 5 times the ULN should lead to more careful monitoring and suspension of further infusions, at least until levels return to normal or near normal values.

Drug Class: Antineoplastic Agents, Monoclonal Antibodies

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Moxetumomab Pasudotox – Lumoxiti®

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
Moxetumomab Pasudotox	1020748-57-5	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 12 April 2019

DeLeve LD. Gemtuzumab ozogamicin. Liver sinusoidal endothelial cells and liver injury. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2011, pp. 142-3.

(Review of agents that damage liver sinusoidal cells including gemtuzumab ozogamicin; mentions that CD33 which is present on leukemic blast cells is also present on liver sinusoidal endothelial cells; moxetumomab is not discussed, but there is no evidence linking CD22 or moxetumomab pasudotox to similar effects).

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/scripts/cder/daf/

(FDA Drug Approvals website that has product labels [package inserts], letters of approval and full FDA scientific review of the new drug application for safety and efficacy; mentions that serum ALT or AST elevations arose in 21-39% of patients treated with moxetumomab and were above 5 times ULN in 1.3-3.1%, but no patient developed acute liver injury with jaundice).

(FDA Drug Approvals website that has product labels [package inserts], letters of approval and full FDA scientific review of the new drug application for safety and efficacy; mentions that serum ALT or AST elevations arose in 21-39% of patients treated with moxetumomab and were above 5 times ULN in 1.3-3.1%, but no patient developed acute liver injury with jaundice).

Dhillon S. Moxetumomab pasudotox: first global approval. Drugs 2018; 78 (16): 1763-7. PubMed PMID: 30357593.

(Review of the current status of therapy of hairy cell leukemia and the development, structure, mechanism of action, pharmacology, clinical efficacy and safety of moxetumomab pasudotox; mentions serious adverse events of fever, sepsis, hemolytic uremic syndrome, capillary leak syndrome and renal dysfunction; no mention of ALT elevations or hepatotoxicity).

Kreitman RJ, Dearden C, Zinzani PL, Delgado J, Karlin L, Robak T, Gladstone DE, et al. Moxetumomab pasudotox in relapsed/refractory hairy cell leukemia. Leukemia 2018; 32: 1768-77. PubMed PMID: 30030507.

(Among 80 adults with relapsed or refractory hairy cell leukemia treated with moxetumomab pasudotox, durable complete responses occurred in 30% and clinical remissions in 80%, while adverse events included peripheral edema [39%], nausea [35%], fatigue [34%], headache [33%], hemolytic uremic syndrome [7.5%] and capillary leak syndrome [5%]; ALT elevations arose in 21%, but only 1.3% were above 5 times ULN and no patient had clinically apparent liver injury with jaundice).