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Elotuzumab

Updated: March 25, 2017.

OVERVIEW

Introduction

Elotuzumab is a humanized monoclonal antibody to cell surface receptor SLAMF7 which is used in combination with other antineoplastic agents in the therapy of multiple myeloma. Elotuzumab 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.

Background

Elotuzumab (el" oh tooz' ue mab) is humanized IgG1 monoclonal antibody to the cell surface receptor signaling lymphocyte activation molecule family member 7 (SLAMF7), which is a transmembrane glycoprotein that is frequently overexpressed on multiple myeloma cells and is found normally on natural killer (NK) cells. The monoclonal antibody binds to the cell surface receptor and triggers cell apoptosis of cancer cells and activation of NK cells which may increase its antineoplastic activity. In preregistration trials, the addition of elotuzumab to lenalidomide and dexamethasone led to an increase in overall response rates and prolongation of progression-free survival. Elotuzumab was given accelerated approval for use in the United States in 2015. Current indications are as therapy of refractory multiple myeloma administered in combination with lenalidomide (or bortezomib) and dexamethasone or as monotherapy in patients who have failed at least three previous regimens. Elotuzumab is available as a powder for reconstitution in single use vials of 300 or 400 mg under the brand name Empliciti. The recommended dose is 10 mg/kg intravenously every week for 2 cycles and every 2 weeks thereafter until disease progression or unacceptable toxicities occur. Premedication with dexamethasone, diphenhydramine, ranitidine and acetaminophen is recommended. Side effects are common and can include infusion reactions, fatigue, diarrhea, constipation, anorexia, fever, cough, nasopharyngitis, peripheral neuropathy and pneumonia. Uncommon, but potentially severe adverse reactions include severe infusion reactions, bacterial infections and secondary malignancies.

Hepatotoxicity

In preregistration trials of elotuzumab for multiple myeloma, serum enzyme elevations were frequent, but were similar in patients receiving lenalidomide and dexamethasone with elotuzumab as in those on lenalidomide and dexamethasone alone, any ALT elevation occurring in 55% vs 51% and ALT elevations above 5 times the upper limit of normal in 4.4% vs 4.1%. The Food and Drug Administration analysis of submitted results described one case of suspected injury due to elotuzumab with jaundice and serum ALT elevations and a liver biopsy demonstrating possible drug induced liver injury. On the basis of this report, the product label for elotuzumab

warned of possible rare instances of hepatotoxicity. Since approval and more wide scale use of elotuzumab, there have been no further published reports of its hepatotoxicity.

Likelihood score: D (possible rare cause of clinically apparent liver injury).

Mechanism of Injury

The cause of liver injury during elotuzumab therapy is not known and separation of the possible role of elotuzumab versus lenalidomide or other antineoplastic agents given concurrently is difficult. Nevertheless, the monoclonal antibody may cause liver injury through its indirect effects on inhibition of SLAMF7 signaling in the liver or activation of NK cells.

Outcome and Management

The liver injury attributed to elotuzumab has usually been self-limited and not associated with symptoms or jaundice. Patients who develop persistent serum enzyme elevations above 5 times the upper limit of normal should have therapy withheld until values decline. Patients who develop symptoms of liver injury or jaundice with serum enzyme elevations should have therapy discontinued. There is no information on possible cross sensitivity to the injury among different monoclonal antibodies.

Drug Class: Antineoplastic Agents, Monoclonal Antibodies

CASE REPORT

Case 1. Acute liver injury arising during elotuzumab, lenalidomide and dexamethasone therapy of multiple myeloma.

[Modified from: FDA analysis]

A 54 year old man with relapsed multiple myeloma, previously treated with bortezomib, melphalan and dexamethasone followed by autologous hemopoietic stem cell transplant, developed jaundice approximately 7 months after enrolling in an experimental trial of elotuzumab combined with lenalidomide and dexamethasone. He had a previous history of nonalcoholic fatty liver disease and pretreatment laboratory tests demonstrated elevations in ALT (134 U/L) and AST (101 U/L), with normal alkaline phosphatase and bilirubin levels (Table). Further elevations in aminotransferases occurred 6 months into therapy which worsened and were associated with jaundice a few weeks later. All therapy was stopped and he underwent evaluation which showed no evidence of infection with hepatitis A, B, C or E, while abdominal imaging showed fatty liver without changes suggestive of biliary obstruction. Serum bilirubin levels rose to 8.1 mg/dL and a liver biopsy showed changes of chronic hepatitis with cirrhosis and decrease in bile ducts. After several weeks, laboratory test results began to improve and returned to close to baseline levels by 6 weeks after onset.

Key Points

Medication:	Elotuzumab with lenalidomide and dexamethasone
Pattern:	Hepatocellular (R=7.6)
Severity:	3+ (jaundice, hospitalization)
Latency:	30 weeks
Recovery:	6 weeks
Other medications:	Metformin, oxycodone, penicillin, valaciclovir, leucovorin, levothyroxine, sulfamethoxazole, trimethoprim, sertraline, perindopril, lormetazepam, repaglinide, insulin, aspirin, quinine, fenofibrate and omeprazole

Key Points

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
Elotuzumab, Lenalidomide and Dexamethasone					
0	Pre	134	94	0.8	Started chemotherapy
28	Pre	82	95	0.8	Started 2nd cycle
196	Pre	90	146	0.9	
210	0	527	173	2.0	
216	15	713		8.1.	
234	33	77	184	2.8	
253	52	46	151	1.8	Liver biopsy
Normal Values		**<50**	**<120**	**<1.2**	

Comment

These results were analyzed by FDA staff during the review of results from a phase III study of lenalidomide and dexamethasone (a standard second line therapy of multiple myeloma) with or without elotuzumab. Some degree of serum enzyme elevations was common, occurring in more than half of patients, but this individual developed the combination of jaundice with ALT elevations that were above 5 times ULN with only minor elevations in alkaline phosphatase, a pattern referred to as "Hy's Law", in reference to Hyman J. Zimmerman who noted that the mortality rate of drug induced liver injury is above 10% if jaundice arises with a hepatocellular pattern of serum enzymes. While this case appears to be drug induced liver injury, one cannot say for sure that it was due to elotuzumab as opposed to lenalidomide (a well known cause) or one of the many other medications that he was taking. Complicating the case was the presence of evidence of nonalcoholic fatty liver disease even before the chemotherapy was started, so that the case is an example of acute injury superimposed upon chronic liver disease (acute-on-chronic). The prompt discontinuation of therapy was likely important in insuring a beneficial outcome. A liver biopsy done somewhat late in the course of the injury showed cirrhosis, chronic hepatitis and a decrease in bile ducts, a finding that would not be expected from hepatocellular injury.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Elotuzumab – Empliciti®

DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Elotuzumab	915296-00-3	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 25 March 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 drugs; mentions that "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).

Lonial S, Dimopoulos M, Palumbo A, White D, Grosicki S, Spicka I, Walter-Croneck A, et al.; ELOQUENT-2 Investigators. Elotuzumab therapy for relapsed or refractory multiple myeloma. N Engl J Med 2015; 373: 621-31. PubMed PMID: 26035255.

(Among 646 patients with refractory multiple myeloma treated with lenalidomide and dexamethasone with or without elotuzumab for an average of 2 years, progression-free survival was prolonged by addition of elotuzumab [median 19 vs 15 months], and side effects were common but similar between the two groups, except for infusion reactions [10% vs none]; no mention of ALT elevations or hepatotoxicity).

Mateos MV, Granell M, Oriol A, Martinez-Lopez J, Blade J, Hernandez MT, Martín J, et al. Elotuzumab in combination with thalidomide and low-dose dexamethasone: a phase 2 single-arm safety study in patients with relapsed/refractory multiple myeloma. Br J Haematol 2016; 175: 448-56. PubMed PMID: 27434748.

(Among 40 patients with refractory multiple myeloma treated with elotuzumab combined with thalidomide and dexamethasone, the overall response rate was 38% and adverse events were frequent, including fatigue and edema, but there were no liver related serious adverse events or deaths and no mention of ALT elevations).

Richardson PG, Jagannath S, Moreau P, Jakubowiak AJ, Raab MS, Facon T, Vij R, et al.; 1703 study investigators. Elotuzumab in combination with lenalidomide and dexamethasone in patients with relapsed multiple myeloma: final phase 2 results from the randomised, open-label, phase 1b-2 dose-escalation study. Lancet Haematol 2015; 2: e516-27. PubMed PMID: 26686406.

(Among 73 patients with relapsed multiple myeloma after 1 to 3 previous treatments who were treated with elotuzumab [10 or 20 mg/kg weekly for 8 weeks and then every other week], 61 [84%] achieved an objective response, and adverse events included diarrhea [66%], muscle spasms [62%], fatigue [56%] and bone marrow suppression, but there were no liver related severe adverse events or deaths and no mention of ALT elevations).

Markham A. Elotuzumab: first global approval. Drugs 2016; 76: 397-403. PubMed PMID: 26809244.

(Review of the mechanism of action, clinical efficacy and safety of elotuzumab after its approval for use in refractory multiple myeloma; does not mention ALT elevations or hepatotoxicity).

Three new drugs for multiple myeloma. Med Lett Drugs Ther 2016; 58 (1495): e70-1. PubMed PMID: 27192621.

(Concise review of three agents that had been recently approved for use in multiple myeloma including elotuzumab; no mention of ALT elevations or hepatotoxicity).

Gormley NJ, Ko CW, Deisseroth A, Nie L, Kaminskas E, Kormanik N, Goldberg KB, et al. FDA drug approval: elotuzumab in combination with lenalidomide and dexamethasone for the treatment of relapsed or refractory multiple myeloma. Clin Cancer Res 2017; 23 (22): 6759-63. PubMed PMID: 28249893.

(Summary of the data on safety and efficacy of elotuzumab that provided the basis for its approval; mentions that severe adverse reactions include infusion reactions, infections, secondary malignancies and hepatotoxicity).

Brioli A, Mügge LO, Hochhaus A, Von Lilienfeld-Toal M. Safety issues and management of toxicities associated with new treatments for multiple myeloma. Expert Rev Hematol 2017; 10: 193-205. PubMed PMID: 28116920.

(Review of adverse events from new treatments of multiple myeloma and their management; does not specifically discuss hepatotoxicity).

Kapoor P, Rajkumar SV. Multiple myeloma in 2016: Fresh perspectives on treatment and moments of clarity. Nat Rev Clin Oncol 2017; 14: 73-4. PubMed PMID: 28071678.

(Review of new agents for therapy of multiple myeloma, focusing upon the advantages of triple therapy).

Center for Drug Evaluation and Research. Elotuzumab. Medical/Statistical Review(s). Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/761035Orig1s000MedR.pdf

(accessed: March 31, 2017).