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Ixazomib

Updated: June 1, 2017.

OVERVIEW

Introduction

Ixazomib is a small molecule proteasome inhibitor that is used in combination with other antineoplastic agents to treat refractory multiple myeloma. Ixazomib is associated with a low rate of serum enzyme elevations during treatment and to rare instances of clinically apparent, acute liver injury.

Background

Ixazomib (ix az' oh mib) is an orally available, small molecule inhibitor of the 26S proteasome, the intracellular complex that degrades proteins involved in cell signaling and cell cycle regulation. Blocking proteasome activity prevents activation of factors involved in cell growth and resistance to chemotherapy induced apoptosis, thereby leading to cancer cell death. Preclinical studies in vitro and in vivo suggested that ixazomib had activity against several hematologic malignancies. Clinical trials of the addition of ixazomib to lenalidomide and dexamethasone in patients with multiple myeloma showed improvements in progression free survival. Ixazomib given in combination with lenalidomide and dexamethasone received approval for use in the United States in 2015 for therapy of refractory multiple myeloma. Ixazomib is available in capsules of 2.3, 3 and 4 mg under the brand name Ninlaro. The recommended starting dose is 4 mg orally on days 1, 8 and 15 of 28-day cycles of lenalidomide and dexamethasone. A lower daily dose (3 mg) is recommended for patients with renal or hepatic impairment. Common side effects include nausea, diarrhea, constipation, anorexia, fatigue, peripheral edema, thrombocytopenia, neutropenia, anemia peripheral neuropathy, rash and fever. Uncommon, but potentially severe side effects include peripheral neuropathy, bone marrow suppression, thrombocytopenia, severe diarrhea and dehydration and embryo-fetal toxicity.

Hepatotoxicity

In large clinical trials of ixazomib combined with lenalidomide and dexamethasone, elevations in serum aminotransferase levels were common, occurring in ~10% of patients. However, values greater than 5 times the upper limit of normal (ULN) were rare, occurring in <1% of recipients. Cases of clinically apparent liver injury including acute liver failure have been reported in patients receiving ixazomib, however in many instances multiple concomitant medications were being taken and the specific role of ixazomib in causing the liver injury was not always clear. The clinical features of cases of liver injury attributed to ixazomib have not been defined in any detail. Hepatotoxicity is listed as a warning in the product label for ixazomib and monitoring of serum enzymes during treatment is recommended.

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

Mechanism of Injury

The mechanism of liver injury accounting for serum enzyme elevations and hepatic toxicity during ixazomib therapy is not known, but may be a direct effect of inhibition of hepatic proteasome activity. Ixazomib is metabolized in the liver largely through the CYP 3A4 pathway and liver injury may be related to production of a toxic intermediate. Ixazomib is susceptible to drug-drug interactions with agents that are strong inhibitors or inducers hepatic CYP 3A activity.

Outcome and Management

Serum aminotransferase elevations above 5 times the upper limit of normal (if confirmed) should lead to dose reduction or temporary cessation. Clinically apparent liver injury should prompt immediate interruption of ixazomib therapy. Cases of hepatic failure attributed to ixazomib have been described, but no instance of chronic hepatitis or vanishing bile duct syndrome. The product label for ixazomib recommends monitoring of "hepatic enzymes" during treatment. There is little information on cross reactivity in risk for hepatic injury between ixazomib and other cancer chemotherapeutic agents including the tyrosine kinase inhibitors and other proteasome inhibitors such as carfilzomib and bortezomib but, because of the differences in chemical structure, there is little reason to suggest that there might be.

Drug Class: Antineoplastic Agents, Protein Kinase Inhibitors

Related Drugs: Bortezomib, Carfilzomib, Lenalidomide

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Ixazomib – Ninlaro®

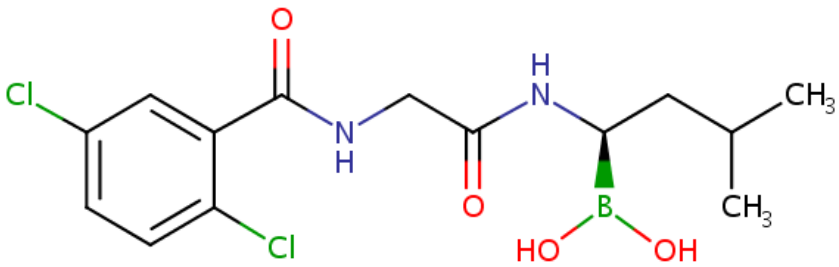
DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Ixazomib	1072833-77-2	C14-H19-B-Cl2-N2-O4	

ANNOTATED BIBLIOGRAPHY

References updated: 01 June 2017

Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999.

(Review of hepatotoxicity published in 1999 before the availability of proteasome inhibitors such as ixazomib or bortezomib).

DeLeve LD. Cancer chemotherapy. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 552.

(Review of hepatotoxicity of cancer chemotherapeutic agents; bortezomib is listed as being implicated in causing hepatocellular injury, but ixazomib is not mentioned).

Chabner BA, Barnes J, Neal J, Olson E, Mujagic 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. 1731-54.

(Textbook of pharmacology and therapeutics).

Laubach J, Hideshima T, Richardson P, Anderson K. Clinical translation in multiple myeloma: from bench to bedside. Semin Oncol 2013; 40: 549-53. PubMed PMID: 24135399.

(Review of recent development of new agents to treat multiple myeloma including bortezomib which showed activity against myeloma cell lines and was then evaluated clinically).

Kumar SK, Berdeja JG, Niesvizky R, Lonial S, Laubach JP, Hamadani M, Stewart AK, et al. Safety and tolerability of ixazomib, an oral proteasome inhibitor, in combination with lenalidomide and dexamethasone in patients with previously untreated multiple myeloma: an open-label phase 1/2 study. Lancet Oncol 2014; 15: 1503-12. PubMed PMID: 25456369.

(Among 65 patients with refractory multiple myeloma treated with ixazomib combined with lenalidomide and dexamethasone, dose limiting toxicities were nausea, diarrhea and skin rash).

Assouline SE, Chang J, Cheson BD, Rifkin R, Hamburg S, Reyes R, Hui AM, et al. Phase 1 dose-escalation study of IV ixazomib, an investigational proteasome inhibitor, in patients with relapsed/refractory lymphoma. Blood Cancer J 2014; 4: e251. PubMed PMID: 25325301.

(Among 30 patients with refractory lymphoma treated with different doses of ixazomib significant adverse events included neutropenia, thrombocytopenia, diarrhea, lymphopenia, rash and renal failure; no mention of ALT elevations or hepatotoxicity).

Kumar SK, Bensinger WI, Zimmerman TM, Reeder CB, Berenson JR, Berg D, Hui AM, et al. Phase 1 study of weekly dosing with the investigational oral proteasome inhibitor ixazomib in relapsed/refractory multiple myeloma. Blood 2014; 124: 1047-55. PubMed PMID: 24904120.

(Among 60 patients with refractory multiple myeloma treated with 4 different doses of ixazomib, dose limiting toxicities were nausea, diarrhea and skin rash; peripheral neuropathy developed in 40% of patients, and ALT elevations in 10%, which were above 5 times ULN in only 1 patient [2%]).

Wang H, Guan F, Chen D, Dou QP, Yang H. An analysis of the safety profile of proteasome inhibitors for treating various cancers. Expert Opin Drug Saf 2014: 1-12. PubMed PMID: 25005844.

(Review of efficacy and safety of bortezomib and several second-generation proteasome inhibitors including carfilzomib, marizomib, ixazomib and oprozomib; no discussion of hepatotoxicity or serum enzyme elevations).

Smith DC, Kalebic T, Infante JR, Siu LL, Sullivan D, Vlahovic G, Kauh JS, et al. Phase 1 study of ixazomib, an investigational proteasome inhibitor, in advanced non-hematologic malignancies. Invest New Drugs 2015; 33: 652-63. PubMed PMID: 25777468.

(Among 96 patients treated with intravenous ixazomib [twice weekly] toxicities included rash, thrombocytopenia, fatigue, dehydration and renal failure; no mention of ALT elevations or hepatotoxicity).

Moreau P, Masszi T, Grzasko N, Bahlis NJ, Hansson M, Pour L, Sandhu I, et al; TOURMALINE-MM1 Study Group. Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med 2016; 374: 1621-34. PubMed PMID: 27119237.

(Among 722 patients with refractory or relapsed multiple myeloma treated with lenalidomide and dexamethasone, progression free survival was improved by addition of ixazomib while serious adverse event rates were not [47% vs 49%]; side effects more common in ixazomib recipients included rash [36% vs 23%], vomiting [23% vs 12%], severe thrombocytopenia [12% vs 7%] and peripheral neuropathy [27% vs 22%], but not "liver impairment" [7% vs 6%]).

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

(Concise summary of standard therapy for multiple myeloma and the mechanism of action, clinical efficacy, safety and costs of ixazomib, daratumumab and elotuzumab; does not mention liver related adverse events).

Schlafer D, Shah KS, Panjic EH, Lonial S. Safety of proteasome inhibitors for treatment of multiple myeloma. Expert Opin Drug Saf 2017; 16: 167-83. PubMed PMID: 27841029.

(Review of the safety of proteasome inhibitors including bortezomib, carfilzomib and ixazomib; mentions that rates of liver impairment are not increased by addition of ixazomib to lenalidomide and dexamethasone).