U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Lorlatinib. [Updated 2019 Apr 15].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Lorlatinib

Updated: April 15, 2019.

OVERVIEW

Introduction

Lorlatinib is a selective tyrosine kinase receptor inhibitor used in the therapy of selected cases of advanced non-small cell lung cancer. Lorlatinib is associated with transient elevations in serum aminotransferase levels during treatment but has not been linked to instances of clinically apparent acute liver injury that have been described with other similar kinase inhibitors.

Background

Lorlatinib (lor la' ti nib) is an orally available, small molecule inhibitor of the tyrosine kinase receptor of mutated anaplastic lymphoma kinase (ALK), which is the result of a chromosomal translocation found in about 5% of lung cancers. Patients with non-small cell lung cancer with the ALK mutation often respond to ALK inhibitor therapy with shrinkage of the tumor and apparent improvement in survival. However, resistance develops frequently as a result of further mutations in the cancer cells. Lorlatinib is a third generation ALK inhibitor that has activity against many of the known ALK resistance mutants. Lorlatinib received accelerated approval for use in the United States in 2018 for the treatment of refractory, advanced non-small cell lung cancer with the ALK translocation (a test for this genetic rearrangement was also approved). Lorlatinib is available in tablets of 25 and 100 mg under the brand name Lorbrena. The recommended dose is 100 mg by mouth once daily, with dose modification based upon tolerance. Side effects are common and include diarrhea, nausea, vomiting, anorexia, fatigue, diarrhea, visual disturbances, peripheral neuropathy, cognitive effects, dyspnea, weight gain, hyperlipidemia and edema. Uncommon, but potentially serious side effects include interstitial lung disease, atrial-ventricular block, QTc interval prolongation, cardiac arrhythmias and fetal-embryonal toxicity.

Hepatotoxicity

In large early clinical trials, elevations in serum aminotransferase levels occurred in up to 28% of patients treated with standard doses of lorlatinib but were above 5 times ULN in only 2% of patients and rarely led to early discontinuation of therapy. The abnormalities were typically transient, asymptomatic and not associated with jaundice. In prelicensure clinical trials there were no instances of clinically apparent liver injury. In contrast, most other ALK inhibitors have been linked to instances of acute liver injury which can be severe and even fatal. The liver injury typically arises within 4 to 12 weeks of starting therapy and presents with marked elevations in serum aminotransferase levels followed by jaundice and progressive hepatic dysfunction. While lorlatinib has not been associated with instances of severe liver injury, it has had limited clinical use.

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

Mechanism of Injury

The mechanism by which lorlatinib might cause liver injury is unknown. Lorlatinib is metabolized in the liver largely via CYP 3A4, and liver injury may be due to accumulation of a toxic or immunogenic intermediate. Lorlatinib is susceptible to drug-drug interactions, and drugs that are strong inhibitors or inducers of CYP 3A should be avoided during its use.

Outcome and Management

Routine monitoring of liver tests is recommended for patients starting lorlatinib and at intervals thereafter. Serum aminotransferase elevations above 5 times the upper limit of normal should lead to dose interruption. If changes persist, are severe, or reoccur on restarting, lorlatinib should be discontinued. Persons who develop liver injury using therapy with a specific ALK inhibitor can often be treated with other ALK inhibitors without recurrence of liver injury, but should be monitored carefully during treatment after hepatotoxicity from a related agent.

Drug Class: Antineoplastic Agents, Protein Kinase Inhibitors

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Lorlatinib – Lorbrena®

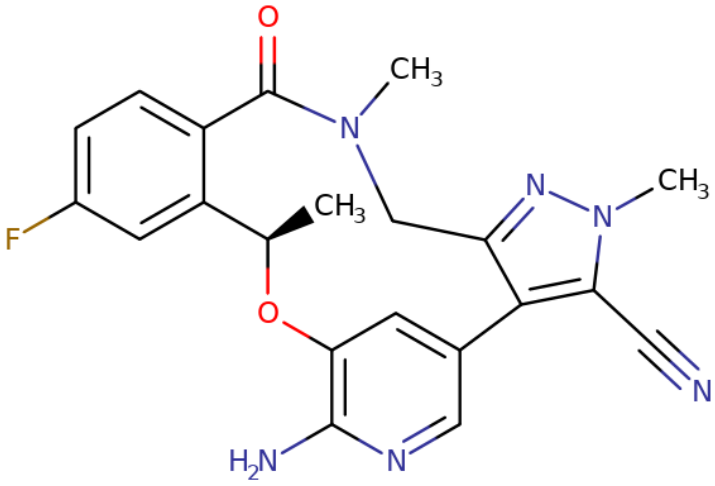
DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Lorlatinib	1454846-35-5	C21-H19-F-N6-O2	

ANNOTATED BIBLIOGRAPHY

References updated: 15 April 2019

Abbreviations used: NSCLC, non-small cell lung cancer; ALK, anaplastic lymphoma kinase.

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 tyrosine kinase receptor inhibitors).

DeLeve LD. Kinase inhibitors. Gefitinib. Cancer chemotherapy. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, p. 556.

(Review of hepatotoxicity of cancer chemotherapeutic agents; crizotinib is listed as causing moderate-to-severe aminotransferase elevations in 4-7% of patients and as having caused fatal hepatotoxicity in some instances, but there is no mention of lorlatinib).

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).

(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).

Shaw AT, Engelman JA. ALK in lung cancer: past, present, and future. J Clin Oncol 2013; 31: 1105-11. PubMed PMID: 23401436.

(Review of the history of discovery of ALK mutations and development of crizotinib as therapy of NSCLC patients with this mutation; no discussion of lorlatinib or of hepatotoxicity or ALT elevations).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 49 cases [6%] were attributed to antineoplastic agents, including 9 due to kinase inhibitors such as imatinib and lapatinib, but none were attributed to any of the small molecule ALK inhibitors).

Shaw AT, Friboulet L, Leshchiner I, Gainor JF, Bergqvist S, Brooun A, Burke BJ, et al. Resensitization to crizotinib by the lorlatinib ALK resistance mutation L1198F. N Engl J Med 2016; 374: 54-61. PubMed PMID: 26698910.

(52 year old woman with metastatic, ALK-mutation positive NSCLC was treated successfully with crizotinib but then developed resistant tumor that did not respond to ceritinib, but did to lorlatinib, only to later develop a lorlatinib resistant mutation that was predicted to be sensitive to crizotinib and responded dramatically to its reintroduction, both response and resistance being predicted by the sequential ALK mutations).

Shaw AT, Felip E, Bauer TM, Besse B, Navarro A, Postel-Vinay S, Gainor JF, et al. Lorlatinib in non-small-cell lung cancer with ALK or ROS1 rearrangement: an international, multicentre, open-label, single-arm first-in-man phase 1 trial. Lancet Oncol 2017; 18: 1590-9. PubMed PMID: 29074098.

(Among 54 patients with NSCLC treated with lorlatinib in different dose regimens, the objective response rate was 42-50% and adverse events included hypercholesterolemia [72%], edema [39%], peripheral neuropathy [39%], cognitive effects [24%] and AST elevations [13%]).

Betton M, Gounant V, Sannier A, Hanouna G, Goujon JM, Brosseau S, Zalcman G, et al. Minimal change disease induced by lorlatinib. J Thorac Oncol 2018; 13: e154-e156. PubMed PMID: 30049381.

(64 year old woman with NSCLC treated with lorlatinib developed leg edema and proteinuria one month after starting, renal biopsy showing minimal change glomerulonephritis, which resolved on stopping and recurred on restarting).

Chabrol A, Mayenga M, Hamid AM, Friard S, Salvator H, Doubre H, Fraboulet S, et al. Lorlatinib - induced pulmonary arterial hypertension. Lung Cancer 2018; 120: 60-1. PubMed PMID: 29748016.

(Two women, ages 55 and 64 years, developed dyspnea 1 and 2 months after starting lorlatinib for NSCLC and right heart catherization showed pulmonary arterial hypertension and decreased cardiac index, both improving upon stopping the ALK inhibitor therapy).

Solomon BJ, Besse B, Bauer TM, Felip E, Soo RA, Camidge DR, Chiari R, et al. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study. Lancet Oncol 2018; 19: 1654-67. PubMed PMID: 30413378.

(Among 276 patients with NSCLC and ALK or ROS1 mutations, objective response rates varied from 32% to 67% and adverse events were frequent including hypercholesterolemia [81%], edema [43%], peripheral neuropathy

[30%], cognitive effects [18%] and ALT elevations [9%], which were above 5 times ULN in only 1% and were not associated with jaundice or symptoms of liver injury).

Waqar SN, Morgensztern D. Lorlatinib: a new-generation drug for ALK-positive NSCLC. Lancet Oncol 2018; 19: 1555-7. PubMed PMID: 30413381.

(Commentary on Solomon [2018] mentions that lorlatinib has shown promise in treatment-naïve as well as experienced patients with NSCLC and ALK mutations).

Ryser CO, Diebold J, Gautschi O. Treatment of anaplastic lymphoma kinase-positive non-small cell lung cancer: update and perspectives. Curr Opin Oncol 2019; 31: 8-12. PubMed PMID: 30394941.

(Review of the management of NSCLC with ALK mutations using first [crizotinib], second [alectinib, ceritinib, brigatinib] and third generation [lorlatinib] ALK inhibitors; mentions hepatotoxicity of crizotinib and ceritinib).

Syed YY. Lorlatinib: first global approval. Drugs 2019; 79: 93-8. PubMed PMID: 30604291.

(Review of the mechanism of action, history of development, pharmacology, clinical efficacy and safety of lorlatinib shortly after its approval in the US; mentions that 10% of patients had AST elevations during therapy but none required discontinuation or led to serious hepatic adverse events).