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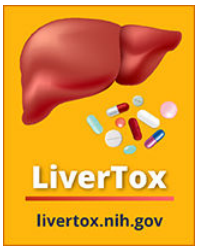

Olutasidenib

Updated: February 20, 2024.

OVERVIEW

Introduction

Olutasidenib is a small molecule inhibitor of mutated isocitrate dehydrogenase-1 (IDH1) that is used in the treatment of adults with relapsed or refractory acute myelogenous leukemia with mutated IDH1. Olutasidenib is associated with a high rate of serum aminotransferase elevations during therapy that can be severe and require early discontinuation and occasionally have led to clinically apparent acute liver injury.

Background

Olutasidenib (oh loo" ta sid' e nib) is an orally available, small molecule inhibitor of mutated isocitrate dehydrogenase-1 (IDH1) and is used to treat relapsed or refractory cases of acute myelogenous leukemia (AML) that harbor specific mutations in IDH1. Isocitrate dehydrogenase is an oxidative decarboxylase which is important in maintaining normal progenitor and stem cell differentiation. Mutation in IDH1 can lead to accumulation of a toxic intermediate (2-hydroxyglutarate; 2-HG) that blocks normal cell differentiation and promotes cancer cell growth. IDH1 mutations are found in 7% to 14% of patients with AML and in 3% to 4% with myelodysplastic syndromes. In cell culture, olutasidenib has been found to decrease 2-HG levels and restore normal cell differentiation in cancer cells with IDH1 mutations. Clinical trials of olutasidenib have demonstrated beneficial objective response rates in adult patients with AML and IDH1 mutations. Olutasidenib was approved in the United States in 2022 for adults with relapsed or refractory AML and a susceptible IDH1 mutation. Olutasidenib is available in capsules of 150 mg under the brand name Rezlidhia. The recommended dose is 150 mg twice daily until disease progression or unacceptable toxicity. Common side effects of olutasidenib include symptoms of fatigue, arthralgia, constipation, diarrhea, nausea, dyspnea, fever, rash, cough, and mucositis. Therapy is also associated with increases in serum aminotransferase levels, alkaline phosphatase, bilirubin, uric acid, and creatinine as well as deceases in serum potassium and sodium. Thrombocytopenia, neutropenia and anemia are common during olutasidenib therapy, but are most likely due to the underlying acute leukemia. Less common but potentially severe adverse events include differentiation syndrome and hepatotoxicity.

Hepatotoxicity

In the published preregistration clinical trials of olutasidenib, rates of serum ALT or AST elevations were 46% and 47% which were above 5 times the upper limit of normal (ULN) in 13% and 10%, resulting in dose modification in at least 10% of patients and discontinuation ultimately in 5% of patients. One individual treated with the combination of azacytidine and olutasidenib died of hepatic failure, and another developed a clinically apparent but self-limited episode of cholestatic hepatitis. Most hepatic effects occurred early during therapy, usually during the first or second month, but isolated instances arose as late as 5 months after starting

olutasidenib. Since its approval and general availability, at least one other case of acute hepatitis with jaundice has been reported from clinical trials of olutasidenib.

In prelicensure studies, olutasidenib therapy was also associated with "differentiation syndrome" in 9% to 16% of patients that was sometimes severe and occasionally fatal. Differentiation syndrome is the result of the sudden and rapid proliferation of myeloid cells results in release of inflammatory cytokines and symptoms of respiratory distress, accompanied by hypoxia, pulmonary infiltrates, and pleural effusions. Other manifestations include fever, renal impairment, lymphadenopathy, bone pain, peripheral edema, and weight gain. Liver dysfunction can also occur but is usually overshadowed by the more severe systemic manifestations. The onset of differentiation syndrome is generally within 2 to 8 weeks of starting therapy, and the course can be severe. Management includes prompt discontinuation of therapy and use of corticosteroids in more severe cases. Patients can be restarted on olutasidenib once the syndrome resolves. Olutasidenib has a black box warning of differentiation syndrome with specific recommendations for its prompt recognition and management. The label also warns about the risk of hepatotoxicity with recommendation to monitor liver tests during treatment and interrupt and reduce or discontinue if hepatotoxicity occurs.

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

Mechanism of Injury

Olutasidenib therapy has been clearly linked to serum enzyme elevations and to uncommon instances of clinically apparent liver injury. It is metabolized in the liver largely by CYP 3A and liver injury may be due to its metabolism to an immunogenic or toxic intermediate. Some cases may be due to differentiation syndrome, a well-known complication of olutasidenib therapy in which there is a release of proinflammatory cytokines that may cause serum aminotransferase elevations. Olutasidenib is also susceptible to drug-drug interactions with inducers or inhibitors of CYP 3A4.

Outcome and Management

Olutasidenib has been clearly linked to serum aminotransferase elevations and clinically significant liver injury. For this reason, frequent monitoring of liver tests is recommended in the product label with testing at baseline, at least once weekly for the first two months, once every other week for the third month, once during the fourth month, and every other month thereafter for the duration of therapy. Serum aminotransferase elevations above 5 times ULN should lead to dose reduction or temporary cessation. ALT or AST elevations above 20 times ULN or any elevations accompanied by jaundice or symptoms should lead to discontinuation. There does not appear to be cross reactivity in risk for hepatic injury among the various IDH inhibitors but few instances have been studied.

Drug Class: Antineoplastic Agents, Protein Kinase Inhibitors

Other IDH1 and IDH2 Inhibitors: Enasidenib, Ivosidenib

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Olutasidenib – Rezlidhia®

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
Olutasidenib	1887014-12-1	C18-H15-Cl-N4-O2	SID: 376005569

ANNOTATED BIBLIOGRAPHY

References updated: 20 February 2024

Abbreviations: AML, acute myelogenous leukemia; IDH1, isocitrate dehydrogenase-1.

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 small molecule enzyme inhibitors such as olutasidenib).

DeLeve LD. Erlotinib. Cancer chemotherapy. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 556.

(Review of hepatotoxicity of cancer chemotherapeutic agents discusses several tyrosine kinase enzyme inhibitors including imatinib, gefitinib, erlotinib and crizotinib, but not the isocitrate dehydrogenase inhibitors such as olutasidenib).

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).

FDA. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/215814Orig1s000MultidisciplineR.pdf

(Integrated FDA review of the data on safety and efficacy of olutasidenib that formed the basis of its approval as therapy of adult with relapsed or refractory acute myelogenous leukemia, mentions that ALT elevations arose in 46% of patients, were above 5 times ULN in 11%, and that among 425 patients treated in two studies of olutasidenib, there were 19 cases of suspected drug induced liver injury, two of which were considered convincingly related to the drug, one of which was fatal).

Watts JM, Baer MR, Yang J, Prebet T, Lee S, Schiller GJ, Dinner SN, et al. Olutasidenib alone or with azacitidine in IDH1-mutated acute myeloid leukaemia and myelodysplastic syndrome: phase 1 results of a phase 1/2 trial. Lancet Haematol. 2023;10:e46-e58. PubMed PMID: 36370742.

(Among 78 patients with AML or a myelodysplastic syndrome who were treated with olutasidenib with or without azacytidine, the objective response rate varied by indication and drug regimen from 25% to 77%, and adverse events were largely thrombocytopenia, febrile neutropenia and anemia; liver test abnormalities above 5 times the ULN arose in 10 patients [13%], led to discontinuation in 2 [3%], but ultimately resolved in all).

de la Fuente MI, Colman H, Rosenthal M, Van Tine BA, Levacic D, Walbert T, Gan HK, et al. Olutasidenib (FT-2102) in patients with relapsed or refractory IDH1-mutant glioma: A multicenter, open-label, phase Ib/II trial. Neuro Oncol. 2023;25:146-156. PubMed PMID: 35639513.

(Among 26 patients with relapsed or refractory brain gliomas harboring IDH1 mutations treated with olutasidenib [150 mg twice daily], only 2 had an objective response, but all [100%] had adverse events that included ALT elevations in 8 [31%] of which 3 [12%] were above 5 times ULN, and one of which resulted in a symptomatic and icteric acute hepatitis).

Kang C. Olutasidenib: first approval. Drugs. 2023;83:341-346. PubMed PMID: 36848032.

(Summary of the mechanism of action, history of development, pharmacokinetics, efficacy, and safety of olutasidenib shortly after its approval in the US, mentions that ALT elevations arose is 23-31% of patients).

Olutasidenib (Rezlidhia) for acute myeloid leukemia. Med Lett Drugs Ther. 2023;65:e58-e59. PubMed PMID: 37020343.

(Concise summary of the mechanism of action, clinical efficacy, safety, and costs of olutasidenib shortly after its approval for use in AML in the US, mentions that hepatotoxicity can occur and that routine monitoring of liver function tests is recommended before starting and regularly for the duration of treatment).