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Ivosidenib

Updated: October 20, 2018.

OVERVIEW

Introduction

Ivosidenib is an orally available small molecule inhibitor of isocitrate dehydrogenase 2 which is used as an antineoplastic agent in the treatment of selected cases of acute myeloid leukemia (AML). Ivosidenib is associated with a moderate rate of serum aminotransferase elevations during therapy and is suspected to be the cause of rare instances of clinically apparent acute liver injury.

Background

Ivosidenib (eye" voe sid' i nib) is a small molecule inhibitor of isocitrate dehydrogenase-1 (IDH1), an enzyme rearranged and mutated in some forms of leukemia and lymphoma. The mutated IDH promotes unregulated cell growth and proliferation and is overexpressed in some leukemias. Ivosidenib has been found to inhibit mutated IDH1 and in several clinical trials was found to induce objective responses in a proportion of patients with refractory AML with detectable IDH1 mutations. Ivosidenib received accelerated approval for use refractory or relapsed AML with mutated IDH1 in the United States in 2018. A specific small molecule inhibitor of IDH2, enasidenib, was approved as therapy of AML with mutations in IDH2 in 2017. These two IDH inhibitors appear to have similar efficacy against their respective mutated enzyme as well as similar adverse effects. Ivosidenib is available in tablets of 250 mg under the brand name Tibsovo. The dose is 500 mg once daily, continued until progressive disease or intolerable toxicity occurs. Side effects are common and can include fatigue, arthralgia, fever, diarrhea, nausea, abdominal pain, dyspnea, cough, peripheral edema, mucositis and rash. Uncommon, but potentially severe side effects include differentiation syndrome, QTc prolongation, Guillian Barre' syndrome, and embryo-fetal toxicity.

Hepatotoxicity

Elevations in serum aminotransferase levels are common during ivosidenib therapy occurring in 15% to 20% of patients, but rising above 5 times the upper limit of the normal range in only 1% to 2%. Ivosidenib has had limited clinical use but has not been linked to instances of acute liver injury with symptoms or jaundice. Because of the limited clinical experience with the use of IDH inhibitors, their potential for causing liver injury is not well defined.

In prelicensure studies, ivosidenib therapy was associated with "differentiation syndrome" in 5% of patients, which was sometimes severe and life-threatening. Differentiation syndrome is marked by rapid proliferation of myeloid cells and symptoms of respiratory distress, accompanied by hypoxia, pulmonary infiltrates and pleural effusions. Other manifestations include renal impairment, fever, lymphadenopathy, bone pain, peripheral edema and weight gain. Liver dysfunction can also occur but is generally 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 stopping ivosidenib and use of corticosteroids and hydroxyurea in more severe cases. Patients can be restarted on ivosidenib once the syndrome resolves.

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

Mechanism of Injury

The possible cause of the liver injury due to ivosidenib is not known. Ivosidenib is metabolized in the liver largely by the cytochrome P450 system (largely CYP 3A4) and is susceptible to drug-drug interactions with inhibitors or inducers of the microsomal enzyme system.

Outcome and Management

Ivosidenib therapy has been associated with transient serum aminotransferase elevations during therapy but has not been linked to instances of acute liver injury with jaundice or symptoms. Serum aminotransferase elevations above 5 times the upper limit of normal (if confirmed) should lead to temporary discontinuation, which should be permanent if laboratory values do not improve significantly or resolve within a few weeks or if symptoms or jaundice arise.

Drug Class: Antineoplastic Agents, Protein Kinase Inhibitors

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Ivosidenib – Tibsovo®

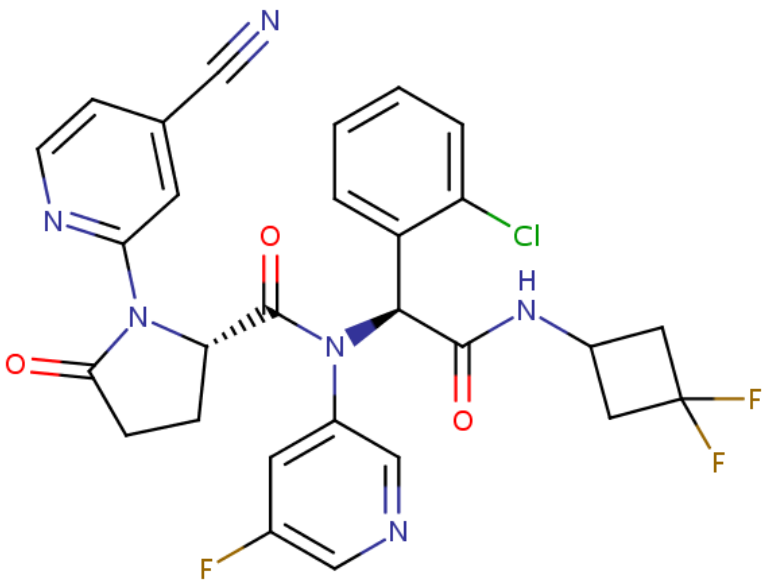
DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Ivosidenib	1448347-49-6	C28-H22-Cl-F3-N6-O3	

ANNOTATED BIBLIOGRAPHY

References updated: 20 October 2018

Abbreviation: IHD, Isocitrate dehydrogenase

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 kinase inhibitors).

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 published in 2013 before the availability of ivosidenib and enasidenib).

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).

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).

Birendra KC, DiNardo CD. Evidence for clinical differentiation and differentiation syndrome in patients with acute myeloid leukemia and IDH1 mutations treated with the targeted mutant IDH1 inhibitor, AG-120. Clin Lymphoma Myeloma Leuk 2016; 16: 460-5. PubMed PMID: 27245312.

(Three patients with AML and mutant IHD1, who were treated with ivosidenib, developed clinically apparent differentiation syndrome during the first two cycles of therapy manifested by neutrophil-predominant leukocytosis, fever, cough, shortness of breath, pulmonary failure, pleural and pericardial effusions; treated successfully with corticosteroids and hydroxyurea which allowed subsequent courses of ivosidenib; no mention of ALT elevations or hepatic involvement).

Upadhyay VA, Brunner AM, Fathi AT. Isocitrate dehydrogenase (IDH) inhibition as treatment of myeloid malignancies: Progress and future directions. Pharmacol Ther 2017; 177: 123-8. PubMed PMID: 28315358.

(Review of the role of mutations in IDH-1 and -2 in oncogenesis which act as "oncometabolites" causing accumulation of 2-hydroxyglutarate which inhibits histone demethylases causing epigenetic changes in cellular differentiation genes; factors that make these mutation enzymes promising targets for anticancer therapeutics).

DiNardo CD, Stein EM, de Botton S, Roboz GJ, Altman JK, Mims AS, Swords R, et al. Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML. N Engl J Med 2018; 378: 2386-98. PubMed PMID: 29860938.

(Among 258 patients with relapsed or refractory, IDH1 mutant AML who were treated with ivosidenib, the overall response rate was 42% and adverse events included diarrhea [21%], leukocytosis [30%], febrile neutropenia [29%], fatigue [26%], dyspnea [25%], QTc prolongation [25%], peripheral edema [22%], anemia [22%], cough [21%] and differentiation syndrome [5%, none fatal], while ALT elevations occurred in 27% of patients, but values were above 5 times ULN in less than 1%).

Fathi AT, DiNardo CD, Kline I, Kenvin L, Gupta I, Attar EC, Stein EM, de Botton S; AG221-C-001 Study Investigators. Differentiation syndrome associated with enasidenib, a selective inhibitor of mutant isocitrate dehydrogenase 2: analysis of a phase 1/2 study. JAMA Oncol 2018; 4: 1106-10. PubMed PMID: 29346478.

(Among 281 patients with AML treated with enasidenib [50-650 mg daily] in open label trials, 33 [12%] were judged to have developed differentiation syndrome marked by dyspnea, fever, lung infiltrates and hypoxia with onset after 7-129 days [median 30 days], usually responding to corticosteroid therapy, half requiring dose interruption, none dying acutely, and all able to restart enasidenib after its resolution).