



Enasidenib

Updated: October 20, 2018.

OVERVIEW

Introduction

Enasidenib is an orally available small molecule inhibitor of isocitrate dehydrogenase and antineoplastic agent that is used in the therapy of selected cases of acute myeloid leukemia (AML). Enasidenib is associated with a moderate rate of serum aminotransferase elevations during therapy and rare instances of clinically apparent acute liver injury.

Background

Enasidenib (en" a sid' e nib) is a small molecule inhibitor of isocitrate dehydrogenase-2 (IDH2), an enzyme rearranged and mutated in some forms of leukemia and lymphoma. The mutated IDH2 causes epigenetic alterations that result in a block in myeloid cell differentiation. Enasidenib has been found to inhibit mutated IDH2 and in several clinical trials was found to induce objective responses in a high proportion of patients with refractory AML who harbored mutant IDH2. Enasidenib received accelerated approval for use in refractory or relapsed AML with IDH2 mutations in 2017. Enasidenib is available in tablets of 50 and 100 mg under the brand name IDHIFA. The recommended initial dose is 100 mg once daily, continued until progressive disease or intolerable toxicity occurs. Side effects are common and frequently severe (77%), leading to dose interruptions (43%) or discontinuations (17%). Common adverse events include diarrhea, nausea and vomiting, abdominal pain, fatigue and anorexia. Less common but potentially severe side effects include differentiation syndrome, tumor lysis syndrome and embryo-fetal toxicity.

Hepatotoxicity

Elevations in serum aminotransferase levels are common during enasidenib therapy, occurring in over half of patients but rising above 5 times the ULN in only 1% to 2%. In addition, enasidenib is an inhibitor of UGT1A1 and is associated with increases in serum indirect bilirubin in 83% of patients which rise to levels of 5 to 10 mg/dL in 15% to 20% of subjects. These elevations are not accompanied by serum enzyme elevations and represent indirect (unconjugated) hyperbilirubinemia without liver injury as occurs in patients with Gilbert syndrome. In pooled analysis of prelicensure clinical studies in 345 subjects, there were no cases of clinically apparent liver injury or deaths from liver disease. There has been limited clinical experience with the use of IDH inhibitors, so that their potential for causing liver injury is not well defined.

In prelicensure studies, enasidenib therapy was associated with "differentiation syndrome" in 14% of patients which was sometimes severe and was fatal in at least two instances. 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 enasidenib and use of corticosteroids in more severe cases. Patients can be restarted on enasidenib once the syndrome resolves.

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

Mechanism of Injury

The cause of the liver injury due to enasidenib is not known. Enasidenib 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. Enasidenib is also metabolized by UGT1A1 and competes with bilirubin for conjugation accounting for the frequency of benign hyperbilirubinemia in treated patients.

Outcome and Management

Enasidenib frequently causes mild-to-moderate transient elevations in serum aminotransferase levels without symptoms or jaundice. Liver injury may also accompany acute differentiation syndrome induced by enasidenib, but therapy has not been linked to isolated, clinically apparent liver injury or acute liver failure. Serum aminotransferase elevations above 5 times the upper limit of normal (if confirmed) should lead to dose adjustment or 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

Enasidenib – IDHIFA®

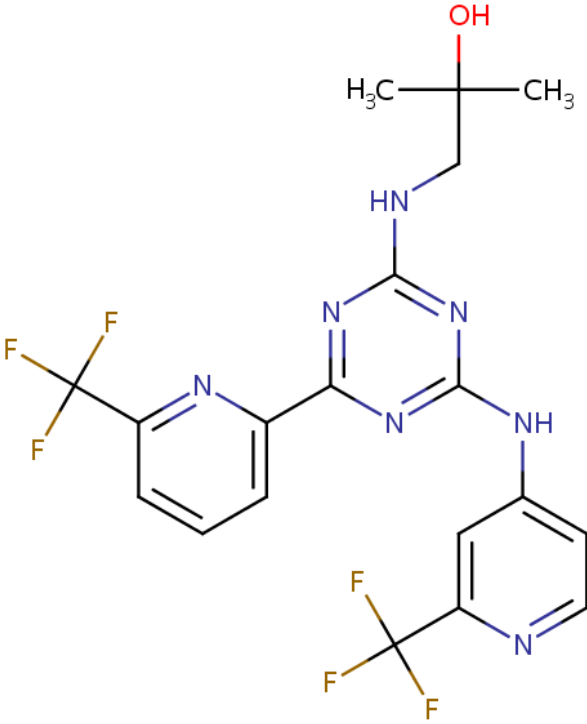
DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Enasidenib	1446502-11-9	C ₁₉ -H ₁₇ -F ₆ -N ₇ -O	 <p>The chemical structure of Enasidenib is a complex heterocyclic molecule. It features a central 1,3,5-triazine ring. Attached to this ring are: a 2-(trifluoromethyl)pyridin-5-yl group, a 4-(trifluoromethyl)pyridin-2-ylamino group, and a 2-(2-hydroxypropan-2-ylamino)ethyl group. The trifluoromethyl groups are represented by a central carbon atom bonded to three fluorine atoms (F).</p>

ANNOTATED BIBLIOGRAPHY

References updated: 20 October 2018

Abbreviations: IDH2, isocitrate dehydrogenase-2; AML, acute myeloid leukemia.

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 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).

Kim ES. Enasidenib: First global approval. *Drugs* 2017; 77: 1705-11. PubMed PMID: 28879540.

(Review of the mechanism of action, pharmacology, clinically efficacy and safety of enasidenib, a "first-in-class" small molecule inhibitor of IDH2, shortly after its approval for use in AML in the US; mentions that elevations in bilirubin occur in 81% of patients, nausea in 50%, diarrhea 43%, anorexia 34%, vomiting 34%, differentiation syndrome 14% and tumor lysis syndrome 6%; no mention of ALT elevations or hepatotoxicity).

Stein EM, DiNardo CD, Pollyea DA, Fathi AT, Roboz GJ, Altman JK, Stone RM, et al. Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia. *Blood* 2017; 130: 722-31. PubMed PMID: 28588020.

(Dose finding and pilot study of enasidenib in 239 patients with mutant IDH2 positive AML, the complete remission rate was 19% and severe adverse events included hyperbilirubinemia [12%], differentiation syndrome [6%] and tumor lysis syndrome [3%]; no mention of ALT elevations or hepatotoxicity).

Amatangelo MD, Quek L, Shih A, Stein EM, Roshal M, David MD, Marteyn B, et al. Enasidenib induces acute myeloid leukemia cell differentiation to promote clinical response. *Blood* 2017; 130: 732-41. PubMed PMID: 28588019.

(Companion manuscript to Stein [2017] measured mutant IDH2 burden in patients receiving enasidenib showing increases in differentiation of myeloid cells and declines in mutant IDH2 positive cells in recipients of acalabrutinib).

Yen K, Travins J, Wang F, David MD, Artin E, Straley K, Padyana A, et al. AG-221, a first-in-class therapy targeting acute myeloid leukemia harboring oncogenic IDH2 mutations. *Cancer Discov* 2017; 7: 478-93. PubMed PMID: 28193778.

(Description of the discovery of a specific inhibitor of IDH2 [AG-221: enasidenib] using high throughput screening and demonstration of its activity in decreasing the mutant IDH2 induced block in cellular differentiation in human AML cells leading differentiation rather than necrosis of malignant blasts).

Fathi AT, DiNardo CD, Kline I, Kenvin L, Gupta I, Attar EC, Stein EM, et al.; 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 to 650 mg daily] in open label trials, 33 [12%] were judged to have 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 were able to restart enasidenib after its resolution).

Patel SA. Enasidenib-induced differentiation syndrome in IDH2-mutant acute myeloid leukemia. *JAMA Oncol* 2018; 4: 1110-1. PubMed PMID: 29346477.

(Commentary on Fathi [2018] stressing the need to promptly recognize differentiation syndrome and manage it correctly).

In brief: Two new drugs for AML. *Med Lett Drugs Ther* 2018; 60 (1543): e56. PubMed PMID: 29635267.

(Brief summary of the mechanism of action, clinical efficacy and safety of enasidenib shortly after its approval for use in the US; mentions indirect hyperbilirubinemia without apparent liver toxicity occurring in 38% and differentiation syndrome in 10% of patients [2 of which were fatal] in a pooled analysis of prelicensure clinical trials).