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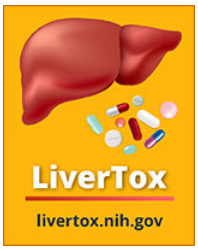
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/



Gilteritinib

Updated: January 20, 2019.

OVERVIEW

Introduction

Gilteritinib is an orally available small molecule inhibitor of FMS-like tyrosine kinase 3 (FLT3) which is used as an antineoplastic agent in the treatment of acute myeloid leukemia with FLT3 mutations. Gilteritinib is associated with a moderate rate of serum aminotransferase elevations during therapy and is suspected to cause rare instances of clinically apparent acute liver injury.

Background

Gilteritinib (gil" te ri' ti nib) is a potent small molecule inhibitor of FLT3 (FMS-like tyrosine kinase 3), a tyrosine kinase receptor that is mutated in to up one-third of patients with acute myeloid leukemia (AML). The mutated FLT3 activates an intracellular signaling cascade of RAS-MEK-PI3K-AKT-STAT-5, promoting unregulated cell growth and proliferation. Gilteritinib has been found to inhibit mutated FLT3 and in several clinical trials was found to induce objective responses in a proportion of patients with refractory AML with detectable FLT3 mutations. Gilteritinib received accelerated approval for this indication in the United States in 2018 and is available in tablets of 40 mg under the brand name Xospata. The recommended dose is 120 mg once daily, continued until progressive disease or intolerable toxicity occurs. Side effects are common and can include fatigue, myalgia, arthralgia, fever, diarrhea, nausea, abdominal pain, dizziness, headache, hypotension, cough and stomatitis. Uncommon, but potentially severe side effects include posterior reversible encephalopathy syndrome, febrile neutropenia and sepsis, QTc prolongation, pancreatitis, and embryo-fetal toxicity.

Hepatotoxicity

Elevations in serum aminotransferase levels are common during gilteritinib therapy occurring in 78% of patients and rising above 5 times the upper limit of the normal range in 12%. Gilteritinib 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 FLT3 inhibitors, their potential for causing liver injury is not well defined.

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

Mechanism of Injury

The possible cause of the liver injury due to gilteritinib is not known. Gilteritinib 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

Gilteritinib 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

Gilteritinib – Xospata®

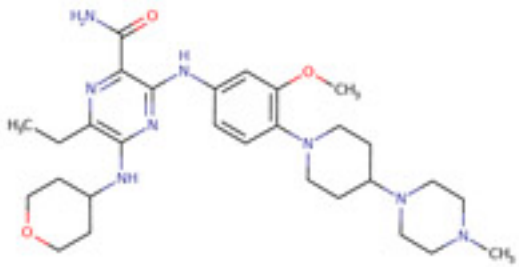
DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Gilteritinib	1254053-43-4	C29-H44-N8-O3	

ANNOTATED BIBLIOGRAPHY

References updated: 20 January 2019

Abbreviations: FLT3, FMS-like tyrosine kinase-3; AML, acute myelogenous 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 gilteritinib).

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; mentions that ALT elevations occurred in 78% of patients receiving gilteritinib, and levels were above 5 times ULN in 12%).

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Perl AE, Altman JK, Cortes J, Smith C, Litzow M, Baer MR, Claxton D, et al. Selective inhibition of FLT3 by gilteritinib in relapsed or refractory acute myeloid leukaemia: a multicentre, first-in-human, open-label, phase 1-2 study. Lancet Oncol 2017; 18: 1061-75. PubMed PMID: 28645776.

(Among 252 adults with refractory or relapsed AML treated with different doses of gilteritinib, responses occurred in 40% and complete remission in 8%; while adverse events were frequent including febrile neutropenia, sepsis and pneumonia, and while ALT elevations arose in 18% of recipients which were above 5 times ULN in 5%, there were no instances of clinically apparent liver injury).

Fathi AT, Chen YB. The role of FLT3 inhibitors in the treatment of FLT3-mutated acute myeloid leukemia. Eur J Haematol 2017; 98: 330-6. PubMed PMID: 28000291.

(Review of the role of mutated FLT3 in AML and efficacy of drugs with activity against FLT3 in AML, including sorafenib, quizartinib, crenolanib and gilteritinib).