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Futibatinib

Updated: November 30, 2022.

OVERVIEW

Introduction

Futibatinib is a FGF receptor 2 kinase inhibitor that is used in the treatment of unresectable, locally advanced or metastatic intrahepatic cholangiocarcinoma. Futibatinib is associated with transient and usually mild elevations in serum aminotransferase during therapy, but has not been convincingly linked to cases of clinically apparent liver injury.

Background

Futibatinib (fue" ti ba' ti nib) is an orally available, specific inhibitor of the fibroblast growth factor (FGF) receptor 1, 2 and 3 kinases that is used in the therapy of advanced or metastatic cholangiocarcinoma. Aberrant FGF receptor signaling is associated with several cancer types in which amplifications, translocations, fusings, and other activating point mutations of FGF receptors are found. These FGF receptor mutations and fusions cause uncontrolled cell growth and tumorigenesis, and are particularly common in intrahepatic cholangiocarcinomas. In cell culture and animal models, Inhibition of the mutant overexpressed receptor causes regression of cell proliferation and promotes cell death. Open label trials of futibatinib in patients with advanced or metastatic cholangiocarcinoma demonstrated a favorable overall durable response rate which led to its accelerated approval for use in the United States in 2022. Current indications are limited to adults with previously treated, unresectable, locally advanced, or metastatic intrahepatic cholangiocarcinoma with FGF receptor 2 gene fusions or other rearrangements. It is under continuing evaluation for its long term safety and efficacy as therapy of cholangiocarcinoma and for its possible efficacy in other forms of cancer associated with FGF receptor gene mutations. Futibatinib is available in tablets of 4 mg under the brand name Lytgobi. The recommended dose is 20 mg (5 tablets) once daily indefinitely or until there is disease progression or unacceptable toxicity. Common side effects include hyperphosphatemia (an effect of inhibition of FGF signaling) as well as symptoms of fatigue, nausea, diarrhea, anorexia, abdominal pain, anemia, thrombocytopenia, musculoskeletal pain, alopecia, nail toxicity, and hand-foot syndrome. Severe adverse events include neutropenic fever, sepsis, ocular toxicity, severe hyperphosphatemia and embryo-fetal toxicity.

Hepatotoxicity

In the open label clinical trials of futibatinib, adverse events were common and led to dose interruptions in 66%, dose reductions in 58%, and drug discontinuation in 5% of patients but only a small proportion of these were due to serum aminotransferase elevations. In preregistration trials in 103 patients with cholangiocarcinoma, ALT elevations arose in 50% and to above 5 times ULN in 7%. The elevations were typically self-limited and resolved rapidly with or without dose adjustments. No patients developed clinically apparent liver injury or

jaundice. Publications on the efficacy and safety of futibatinib rarely mentioned serum ALT elevations or hepatotoxicity. Since its approval, there have been no reports clinically apparent liver injury attributed to futibatinib. However, the total clinical experience with its use has been limited and the frequency of serum aminotransferase elevations during therapy suggest that clinically significant liver injury may occur.

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

Mechanism of Injury

The causes of serum enzyme elevations or liver injury from futibatinib therapy are not known. Some of the adverse effects of futibatinib are due to its effects on FGF signaling (hyperphosphatemia) and others may be due to off-target effects on other kinases (such as RET). Futibatinib is metabolized in the liver largely through the CYP 3A4 pathway and liver injury might be caused by production of a toxic or immunogenic intermediate. Because it is a substrate for CYP 3A4, futibatinib is susceptible to drug-drug interactions with agents that inhibit or induce this specific hepatic microsomal activity.

Outcome and Management

Futibatinib is associated with a moderate rate of serum aminotransferase elevations that are generally transient and not associated with symptoms or jaundice. While regular monitoring of liver tests is not recommended for futibatinib therapy, elevations if confirmed should lead to follow up monitoring. Serum aminotransferase elevations above 5 times the upper limit of normal (if confirmed) or any elevations accompanied by jaundice or symptoms should lead to dose reduction or temporary cessation until they resolve or another cause is identified. There is no evidence to suggest a cross reactivity in risk for adverse events, hypersensitivity or hepatic injury between futibatinib and other protein kinase inhibitors including other FGF receptor inhibitors such as erdafitinib, infigratinib and pemigatinib.

Drug Class: Antineoplastic Agents, Protein Kinase Inhibitors

Other FGF Receptor Kinase Inhibitors: Erdafitinib, Infigratinib, Pemigatinib

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Futibatinib – Lytgobi®

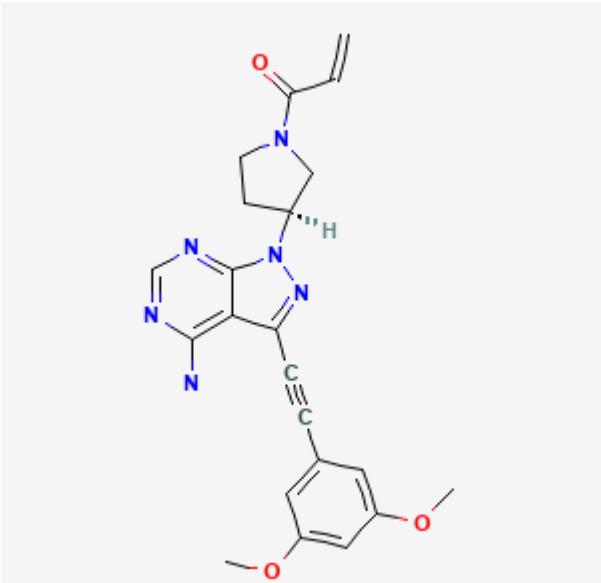
DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Futibatinib	1448169-71-8	C22-H22-N6-O3	

ANNOTATED BIBLIOGRAPHY

References updated: 30 November 2022

Abbreviations: FGF, fibroblast growth factor; HER2, human epidermal growth factor 2 receptor.

Zimmerman HJ. 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 inhibitors such as futibatinib).

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 inhibitors including imatinib, gefitinib, erlotinib and crizotinib, but not futibatinib).

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/2022/214801Orig1s000MultidisciplineR.pdf

(FDA website with product labels, letters and multidisciplinary review of the applications for futibatinib mentions that adverse events were common, led to drug discontinuation in 5% [none liver related], interruptions in 66% [10% liver related] and dose reductions in 58% [5% liver related], and ALT elevations arose in 50% of 103 treated subjects which were above 5 times ULN in 7%, but all were self-limited and there were no serious hepatic adverse events or instances of clinically apparent liver injury with jaundice).

Spraggs CF, Xu CF, Hunt CM. Genetic characterization to improve interpretation and clinical management of hepatotoxicity caused by tyrosine kinase inhibitors. Pharmacogenomics. 2013;14:541–54. PubMed PMID: 23556451.

(Review of genetic associations of serum ALT and bilirubin elevations during therapy with tyrosine kinase inhibitors focusing on lapatinib and pazopanib; futibatinib is not discussed).

Shah RR, Morganroth J, Shah DR. Hepatotoxicity of tyrosine kinase inhibitors: clinical and regulatory perspectives. Drug Saf. 2013;36:491–503. PubMed PMID: 23620168.

(Review of the hepatotoxicity of 18 tyrosine kinase inhibitors approved for use in cancer in the US as of 2013, before the availability of futibatinib which is not discussed).

Arai Y, Totoki Y, Hosoda F, Shirota T, Hama N, Nakamura H, Ojima H, et al. Fibroblast growth factor receptor tyrosine kinase fusions define a unique molecular subtype of cholangiocarcinoma. Hepatology. 2014;59:1427–34. PubMed PMID: 24122810.

(Whole transcriptome sequencing from 8 cholangiocarcinomas identified two FGF receptor fusion genes and screening of different human cancer tissues found FGF receptor fusions in 9 of 102 cholangiocarcinomas [all intrahepatic] but only 1 of 149 colorectal, 1 of 96 hepatocellular, and none of 212 gastric cancers; expression of the fusion kinases in cell cultures led to anchorage independent growth and tumorigenesis when implanted in mice).

Bahleda R, Meric-Bernstam F, Goyal L, Tran B, He Y, Yamamiya I, Benhadji KA, et al. Phase I, first-in-human study of futibatinib, a highly selective, irreversible FGFR1-4 inhibitor in patients with advanced solid tumors. Ann Oncol. 2020;31:1405–1412. PubMed PMID: 32622884.

(Among 86 patients with various solid tumors harboring aberrations in FGF and FGF receptor genes treated with different futibatinib dose regimens, partial responses arose in patients with cholangiocarcinoma, glioblastoma, colorectal and breast cancer, and adverse events were frequent including hyperphosphatemia [59%], constipation [34%], diarrhea [37%], nausea [29%], and ALT elevations [19%], but there were no hepatic severe adverse events or treatment related deaths).

Krook MA, Reeser JW, Ernst G, Barker H, Wilberding M, Li G, Chen HZ, et al. Fibroblast growth factor receptors in cancer: genetic alterations, diagnostics, therapeutic targets and mechanisms of resistance. Br J Cancer. 2021;124:880–892. PubMed PMID: 33268819.

(Review of the association of FGF receptors and cancer chemotherapeutic agents, activating mutations being found in 5-10% of cancers overall, but in 10% to 20% of cholangiocarcinomas).

Rizzo A, Ricci AD, Brandi G. Futibatinib, an investigational agent for the treatment of intrahepatic cholangiocarcinoma: evidence to date and future perspectives. Expert Opin Investig Drugs. 2021;30:317–324.

(Review of futibatinib a kinase inhibitor of FGF receptors which are commonly aberrant in cholangiocarcinoma [6-25%] and thus a strong candidate for FGF receptor kinase inhibitor therapy).

Meric-Bernstam F, Bahleda R, Hierro C, Sanson M, Bridgewater J, Arkenau HT, Tran B, et al. Futibatinib, an irreversible FGFR1-4 inhibitor, in patients with advanced solid tumors harboring FGF/FGFR aberrations: a phase I dose-expansion study. Cancer Discov. 2022;12:402–415. PubMed PMID: 34551969.

(Among 197 adults with various advanced solid tumors treated with futibatinib, the overall response rate was 13.7% with partial responses in various cancers including cholangiocarcinoma, gastric, urothelial, CNS, head-neck and breast cancer and the safety profile was "manageable" with ALT elevations in 64% [10% above 5 times ULN], hyperphosphatemia in 81%, diarrhea in 33%, constipation in 32%, nausea in 28%, fatigue in 25%, and hand-foot syndrome in 13%).