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Pemigatinib

Updated: November 30, 2022.

OVERVIEW

Introduction

Pemigatinib is a fibroblast growth factor (FGF) receptor kinase inhibitor that is used to treat unresectable, locally advanced or metastatic intrahepatic cholangiocarcinoma, as well as myeloid or lymphoid neoplasms with FGFR rearrangements. Pemigatinib is associated with transient and usually mild-to-moderate elevations in serum aminotransferase levels during therapy, but has not been convincingly linked to cases of clinically apparent liver injury with jaundice.

Background

Pemigatinib (pem" i ga' ti nib) is an orally available, small molecule inhibitor of the fibroblast growth factor (FGF) receptors 1, 2 and 3. Pemigatinib is used as therapy of advanced or metastatic cancers that harbor amplications, translocations, fusing or other activating point mutations of FGF receptors. Cholangiocarcinomas often harbor mutations in the FGF receptor 2 that cause the receptor to be activated and promote uncontrolled growth and tumorigenesis. Inhibition of the mutant receptor causes regression of cell proliferation and promotes cell death, effects that can be shown in cell culture and in animal models using cancer cells with FGF receptor activating mutations. After trials of pemigatinib in patients with refractory, advanced cholangiocarcinoma demonstrated a moderate rate of durable clinical responses, it received accelerated approval for use in the United States in 2020. Current indications are limited to adults with previously treated, unresectable, locally advanced, or metastatic cholangiocarcinoma and myeloid or lymphoid neoplasms with FGF receptor gene fusions and other rearrangements. Pemigatinib is available in tablets of 4.5, 9.0 and 13.5 mg under the brand name Pemazyre. The recommended dose for cholangiocarcinoma is 13.5 mg once daily for the first 14 days of 21 day cycles. For other neoplasms, the recommended dose is 13.5 mg per day continuously until disease progression or unacceptable toxicity. Adverse events are common and often include hyperphosphatemia (an effect of inhibition of FGF signaling), as well as symptoms of fatigue, nausea, diarrhea, constipation, dysgeusia, anorexia, abdominal pain, musculoskeletal pain, dizziness, alopecia, dryness of the eyes, mouth, and skin, blurred vision, nail toxicity, and hand-foot syndrome. Severe adverse events include ocular toxicity, severe hyperphosphatemia and embryo-fetal toxicity.

Hepatotoxicity

In preregistration clinical trials of pemigatinib, ALT elevations arose in 43% to 50% of patients and were above 5 times ULN in 4% to 12%. Elevations in serum bilirubin were also common, but usually in the context of cholangiocarcinoma with partial or complete biliary obstruction. There were no cases of clinically apparent liver injury with jaundice and no deaths from liver failure attributable to pemigatinib therapy. The elevations were

typically self-limited and resolved rapidly with or without dose adjustments. Since its approval, there have been no reports clinically apparent liver injury attributed to pemigatinib. 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 pemigatinib therapy are not known. Some of the adverse effects of pemigatinib are due to its effects on FGF signaling (hyperphosphatemia) and others may be due to off-target effects on other kinases. Pemigatinib is metabolized in the liver largely by CYP 3A4, and liver injury might be caused by production of a toxic or immunogenic intermediate. Because it is a substrate for CYP 3A4, pemigatinib is susceptible to drug-drug interactions with agents that inhibit or induce this specific hepatic drug-metabolizing microsomal activity.

Outcome and Management

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

Drug Class: Antineoplastic Agents, Protein Kinase Inhibitors

Other FGF Receptor Kinase Inhibitors: Erdafitinib, Futibatinib, Infigratinib

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Pemigatinib – Pemazyre®

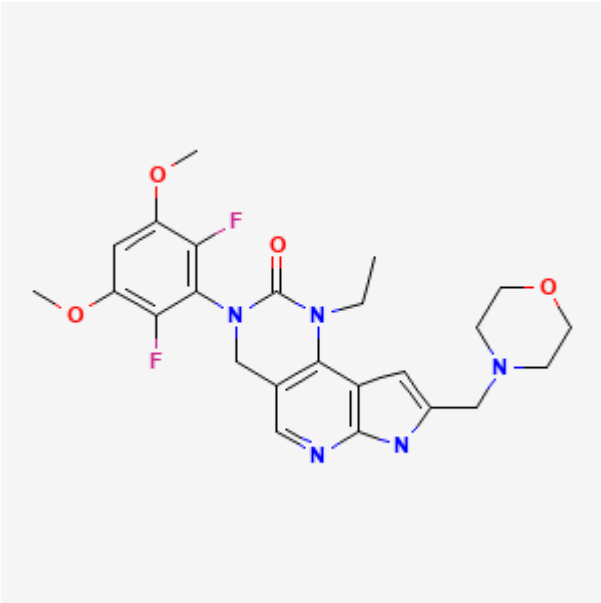
DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Pemigatinib	1513857-77-6	C24-H27-F2-N5-O4	

ANNOTATED BIBLIOGRAPHY

References updated: 30 November 2022

Abbreviations: FGF, fibroblast growth factor.

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 small molecule FGF receptor 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 discusses several tyrosine kinase inhibitors including imatinib, gefitinib, erlotinib and crizotinib, but not pemigatinib).

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/2020/213736Orig1s000MultidisciplineR.pdf

(FDA website with product labels, letters and multidisciplinary review of the applications for pemigatinib mentions that adverse events were common, led to drug discontinuation in 9%, interruptions in 43% [some due to ALT elevations], dose reductions in 14%, and ALT elevations in 43-50% of treated subjects which were above 5 times ULN in 4-12%, but all were self-limited and there were no drug related serious hepatic adverse events or instances of clinically apparent liver injury with jaundice).

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 pemigatinib).

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).

Pemigatinib (Pemazyre) for cholangiocarcinoma. Med Lett Drugs Ther. 2018;60(1546):e208–e209. PubMed PMID: 33451178.

(Concise review of the mechanism of action, pharmacokinetics, clinically efficacy, safety and costs of pemigatinib shortly after it was approved for use in cholangiocarcinoma, adverse events being common but no mention of hepatotoxicity or serum ALT elevations).

Liu PCC, Koblish H, Wu L, Bowman K, Diamond S, DiMatteo D, Zhang Y, et al. INCB054828 (pemigatinib), a potent and selective inhibitor of fibroblast growth factor receptors 1, 2, and 3, displays activity against genetically defined tumor models. PLoS One. 2020;15:e0231877. PubMed PMID: 32315352.

(Review of the FGF cell pathway, effects of inhibiting the FGF receptor and the implications of such inhibition for cancer chemotherapy).

Abou-Alfa GK, Sahai V, Hollebecque A, Vaccaro G, Melisi D, Al-Rajabi R, Paulson AS, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. Lancet Oncol. 2020;21:671–684. PubMed PMID: 32203698.

(Among 146 adults with locally advanced or metastatic cholangiocarcinoma treated with pemigatinib, objective responses arose in 36% of patients with FGF receptors aberrations but in none of those without, adverse events were common and included hyperphosphatemia [55%], nausea, fatigue and nail changes; ALT elevations arose in only 2% of treated patients).

Hoy SM. Pemigatinib: first approval. Drugs. 2020;80:923–929. PubMed PMID: 32472305.

(Review of the chemical structure, mechanism of action, clinical efficacy and costs of pemigatinib which is a specific inhibitor of FGF receptors 1, 2 and 3, but also has activity against other targets perhaps accounting for some of its adverse effects).

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 10-20% of cholangiocarcinomas).

Yang X, Yang X, Zhao H. Pemigatinib-related calcification in the liver. Am J Gastroenterol. 2022 Nov 4. Epub ahead of print.

(54 year old man with refractory cholangiocarcinoma achieved a remission after 3 months of treatment with pemigatinib, but 8 months later was found to have calcifications in the liver around the tumor 8, probably the result of hyperphosphatemia).