



Ponatinib

Updated: July 25, 2014.

OVERVIEW

Introduction

Ponatinib is a tyrosine kinase receptor inhibitor that is used in the therapy of refractory chronic myelogenous leukemia (CML) positive for the Philadelphia chromosome. Ponatinib is commonly associated with transient elevations in serum aminotransferase levels during treatment, but with only rare instances of clinically apparent acute liver injury.

Background

Ponatinib (poe na' ti nib) is a broad spectrum inhibitor of the unique BCR-ABL tyrosine kinase receptor, which is the product of a fusion gene resulting from the translocation between chromosomes 9 and 22 that underlies the Philadelphia chromosome of chronic myelogenous leukemia (CML). The abnormal tyrosine kinase receptor is constitutively expressed and causes abnormal cell growth and proliferation. Inhibition of the enzyme can lead to dramatic reversal of progression of leukemia and is highly effective, although limited by the development of tumor resistance caused by mutations in the kinase. Ponatinib is actually a multi-kinase inhibitor and also has activity against scr, c-Kit and ephrin receptors, among others. Ponatinib received approval for use in the United States in 2012 and was one of 5 such specific inhibitors of BCR-ABL approved for clinical use, the others being imatinib [2001], dasatinib [2006], nilotinib [2007], and bosutinib [2012]. Ponatinib was subsequently withdrawn after identification of severe side effects of vascular thromboses, but then reapproved with a narrowing of indications and boxed warnings. Ponatinib is available in tablets of 15 and 45 mg under the brand name Inklusig. Current indications are as second line treatment of Philadelphia chromosome-positive CML in the chronic, accelerated or blast phase with the specific T315I mutation or after failure of all other BCR-ABL tyrosine kinase receptor inhibitors. The typical dose is 45 mg once daily to continue until the disease progresses or intolerable side effects arise. Common side effects include hypertension, rash, abdominal pain, nausea, constipation, arthralgias, headache, fatigue, fever and bone marrow suppression. Less common, but severe side effects include heart failure (5%), pancreatitis (6%), neuropathy (13%), ocular toxicity (3%) and arterial and venous thromboses (27%) including myocardial infarction, stroke and peripheral vascular disease.

Hepatotoxicity

In large clinical trials, elevations in serum aminotransferase levels during ponatinib therapy occurred in up to 56% of patients and were ≥ 5 times ULN in 8% of patients. While these abnormalities were reversible in most patients, they were prolonged or severe in some. Instances of clinically apparent liver disease and progressive hepatic failure and death were reported in clinical trials of ponatinib, although the clinical features of the liver injury have not been well described. The latency until onset can be rapid and most cases have had a

hepatocellular pattern of serum enzyme elevations. Because of the potential for serious hepatotoxicity, routine monitoring of liver tests is recommended during ponatinib therapy and dose modification or discontinuation recommended for ALT or AST elevations above 3 times ULN.

Reactivation of hepatitis B has been reported with imatinib and nilotinib therapy of CML, but not with ponatinib. Reactivation typically occurs in an HBsAg positive person treated with the tyrosine kinase inhibitor for 3 to 6 months, presenting with jaundice, marked serum aminotransferase elevations and an increase in HBV DNA levels. Reactivation of hepatitis B can be severe, and fatal instances have been reported after imatinib and nilotinib therapy. Screening of patients for HBsAg and anti-HBc is sometimes recommended before starting cancer chemotherapy and those with HBsAg offered prophylaxis with oral antiviral agents, such as lamivudine, tenofovir or entecavir. Whether reactivation occurs with ponatinib therapy is unknown.

Mechanism of Injury

Ponatinib is metabolized in the liver largely through the CYP 3A4 pathway and liver injury may be related to production of a toxic intermediate. Because of this pathway of metabolism, ponatinib is susceptible to drug-drug interactions when using agents that induce or inhibit CYP 3A4.

Outcome and Management

Serum aminotransferase elevations above 3 times the upper limit of normal should lead to dose reduction or temporary cessation, with resumption at a lower dose once levels return to normal. In patients with clinically apparent liver injury and jaundice, ponatinib should be discontinued permanently. Ponatinib, like imatinib and nilotinib, can cause clinically apparent liver injury and has been linked to instances of acute liver failure. There does not appear to be cross reactivity with other kinase inhibitors and switching to another BCR-ABL receptor inhibitor may be appropriate.

Drug Class: [Antineoplastic Agents, Protein Kinase Inhibitors](#)

Other Drugs in the Subclass, Chronic Myeloid Leukemia Agents: [Bosutinib](#), [Dasatinib](#), [Imatinib](#), [Nilotinib](#), [Omacetaxine](#)

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Ponatinib – Inklusig®

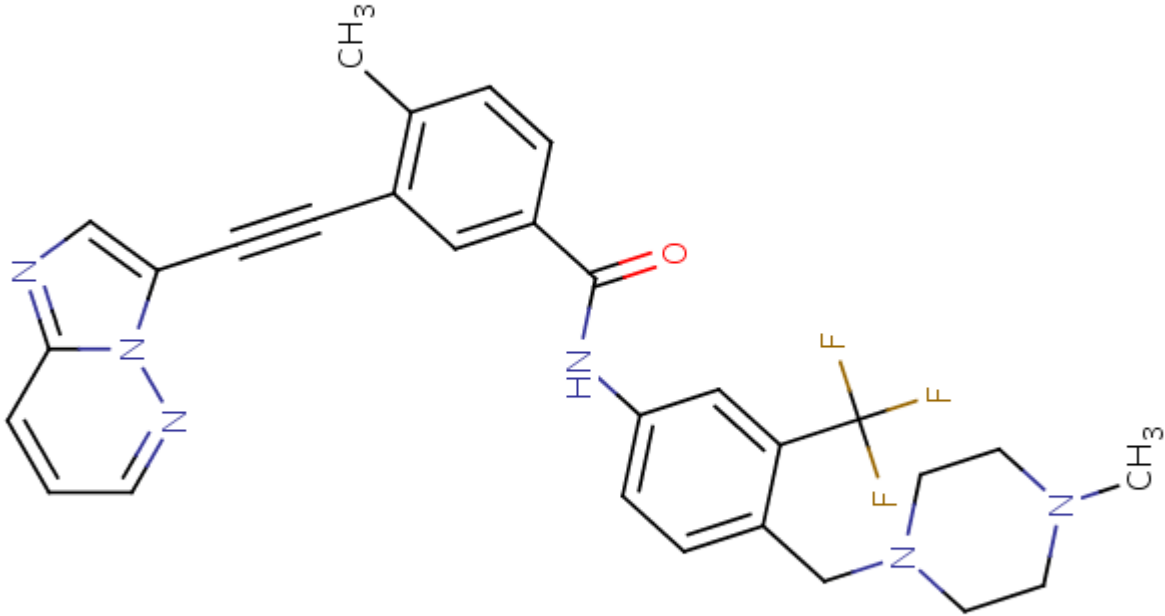
DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Ponatinib	943319-70-8	C ₂₉ H ₂₇ F ₃ N ₆ O	 <p>The chemical structure of Ponatinib is a complex molecule. It features a central benzimidazole ring system. Attached to this is a propargyl group (an ethynyl group, -C≡C-), which is further connected to a 4-methylphenyl ring (a benzene ring with a methyl group, -CH₃, at the para position). This 4-methylphenyl ring is linked via a carbonyl group (-C(=O)-) to a secondary amine (-NH-). The secondary amine is connected to a 2-(2,2,2-trifluoroethyl)phenyl ring (a benzene ring with a -CH₂-CF₃ group at the ortho position). Finally, the 2-(2,2,2-trifluoroethyl)phenyl ring is connected via a methylene group (-CH₂-) to a piperazine ring, which is substituted with a methyl group (-CH₃) on one of its nitrogen atoms.</p>

ANNOTATED BIBLIOGRAPHY

References updated: 25 July 2014

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 and ponatinib).

DeLeve LD. Cancer chemotherapy. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 541-67.

(Review of hepatotoxicity of cancer chemotherapeutic agents; imatinib, gefitinib, erlotinib and crizotinib are discussed, but not ponatinib).

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).

Chalasanani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology 2008; 135: 1924-34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease in the US collected from 2004 to 2008, one case was attributed to imatinib, but none to other kinase inhibitors).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010; 52: 2065-76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury, none of which were attributed to kinase inhibitors).

Cortes JE, Kantarjian H, Shah NP, Bixby D, Mauro MJ, Flinn I, O'Hare T, et al. Ponatinib in refractory Philadelphia chromosome-positive leukemias. N Engl J Med 2012; 367: 2075-88. PubMed PMID: 23190221.

(Among 81 patients with previously treated, resistant hematologic malignancies [60 with CML] hematologic responses occurred independent of BCR-ABL mutations, and adverse events included pancreatitis [14%] and ALT elevations [10%] which were mostly mild, only one being ≥ 5 times ULN).

Goldman JM. Ponatinib for chronic myeloid leukemia. N Engl J Med 2012; 367: 2148-9. PubMed PMID: 23190226.

(Editorial in response to Cortes [2012] discussing ponatinib as a third generation tyrosine kinase inhibitor with activity against mutated forms of BCR-ABL).

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; ponatinib is listed as having the potential to cause clinically apparent liver injury and hepatic failure, for which reason it has a "boxed warning" and routine liver test screening is recommended).

Shah NP, Talpaz M, Deininger MW, Mauro MJ, Flinn IW, Bixby D, Lustgarten S, et al. Ponatinib in patients with refractory acute myeloid leukaemia: findings from a phase 1 study. Br J Haematol 2013; 162: 548-52. PubMed PMID: 23691988.

(Among 12 patients with AML and FLT3 mutations, responses to ponatinib therapy occurred in 3; no mention of hepatotoxicity).

Ponatinib (Inclusig) for CML and Ph+ ALL. Med Lett Drugs Ther 2013; 55 (1424): 71-2. PubMed PMID: 24276500.

(Concise summary of mechanism of action, efficacy, safety and costs of ponatinib of Philadelphia chromosome positive CML or ALL shortly after its approval, mentions the potential of serious hepatic toxicity).

Cortes JE, Kim DW, Pinilla-Ibarz J, le Coutre P, Paquette R, Chuah C, Nicolini FE, et al.; PACE Investigators. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. N Engl J Med 2013; 369: 1783-96. PubMed PMID: 24180494.

(Among 449 patients with CML or ALL with BCR-ABL and resistance or intolerance to other tyrosine kinase receptor inhibitors who were treated with ponatinib for an average of 12.8 months, common side effects were rash, dry skin and abdominal pain with ALT elevations in 3-12%, and values ≥ 5 times ULN in 2-3%).

Prasad V, Mailankody S. The accelerated approval of oncologic drugs: lessons from ponatinib. JAMA 2014; 311: 353-4. PubMed PMID: 24449310.

(Editorial on the accelerated approval of ponatinib and subsequent withdrawal when rates of vascular thrombosis at 2.7 years were found to be 48%).

Mayer K, Gielen GH, Willinek W, Müller MC, Wolf D. Fatal progressive cerebral ischemia in CML under third-line treatment with ponatinib. Leukemia 2014; 28: 976-7. PubMed PMID: 24170029.

(55 year old man with CML developed visual loss 3 weeks after starting ponatinib, with subsequent deterioration and death, autopsy showing brain edema and bilateral cerebral infarcts).

Deininger M. The current status of ponatinib in the treatment of chronic myeloid leukemia. Clin Adv Hematol Oncol 2014; 12: 329-31. PubMed PMID: 25003490.

Narasimhan NI, Dorer DJ, Davis J, Turner CD, Marbury TC, Sonnichsen D. Evaluation of pharmacokinetics and safety of ponatinib in subjects with chronic hepatic impairment and matched healthy subjects. Cancer Chemother Pharmacol 2014; 74: 341-8. PubMed PMID: 24934866.

(In a study of 16 patients with cirrhosis given a single dose of ponatinib, pharmacokinetic parameters were similar despite varying degrees of liver disease severity [Child class A, B and C], and laboratory tests remained stable, except for a rise in amylase and lipase in one patient who developed pancreatitis 2 days after the single dose).