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Nilotinib

Updated: February 4, 2014.

OVERVIEW

Introduction

Nilotinib is a selective tyrosine kinase receptor inhibitor used in the therapy of chronic myelogenous leukemia. Nilotinib therapy is associated with transient elevations in serum aminotransferase levels and rare instances of clinically apparent acute liver injury.

Background

Nilotinib (nye loe' ti nib) is a selective inhibitor of the abnormal tyrosine kinase receptor known as bcr-abl, formed by the reciprocal translocation between chromosome 9 and 22, which creates the Philadelphia chromosome that is associated with chronic myelogenous leukemia (CML). The bcr-abl tyrosine kinase receptor is constitutively expressed in leukemic cells and causes unregulated cell growth and proliferation. Nilotinib is a specific inhibitor of bcr-abl and structurally related to imatinib. Like imatinib, nilotinib also blocks the tyrosine kinase activity of the abnormal tyrosine kinase (cKit) that is found in gastrointestinal stromal tumors (GIST) and platelet derived growth factor (PDGF), which is commonly mutated in renal cell carcinoma. Nilotinib received approval for use in the United States in 2007 for treatment of Philadelphia chromosome-positive CML resistant to or intolerant of prior treatment that included imatinib. Indications were subsequently expanded to include newly diagnosed cases of CML in the chronic phase. Nilotinib is available in capsules of 150 and 200 mg under the brand name Tasigna. The recommended initial dose is 400 mg by mouth twice daily, with dose modification based upon tolerance. Side effects are common and include fatigue, diarrhea, anorexia, skin discoloration, rash, hand-foot syndrome, edema, muscle cramps, arthralgias, headache, abdominal discomfort, anemia, cough, and pruritus. Uncommon side effects include QT interval prolongation, heart failure, pancreatitis, tumor lysis syndrome and renal failure.

Hepatotoxicity

Elevations in serum aminotransferase levels are common during nilotinib therapy, occurring in up to 70% of patients, but rising to greater than 5 times the upper limit of normal (ULN) in only 4% to 9% of recipients. These abnormalities are usually asymptomatic. If levels are markedly elevated (ALT or AST persistently greater than 5 times ULN or bilirubin more than 3 times ULN), dose adjustment or temporary discontinuation and restarting at a lower dose is recommended. In high doses, nilotinib is also associated with elevations in serum bilirubin, but these are largely in the indirect (unconjugated) fraction and are not associated with serum enzyme elevations or symptoms, resolving with dose adjustment or discontinuation. The majority of patients with marked bilirubin elevations on nilotinib therapy have underlying Gilbert Syndrome. There have been no published case reports of clinically apparent liver injury attributed to nilotinib, but it has been used in a restricted population of patients

for a relatively short period of time. The product label does mention hepatitis and jaundice as reported adverse events. Severe tumor lysis syndrome with multiorgan including hepatic failure can occur with nilotinib but is rare. In addition, most other tyrosine kinase receptor inhibitors have been linked to rare instances of clinically apparent liver injury, usually arising after 1 to 8 weeks of treatment and presenting with a hepatocellular or mixed pattern of serum enzyme elevations. Immunoallergic and autoimmune features are uncommon. The liver injury can be severe and lead to acute liver failure. Routine monthly monitoring of liver tests during therapy with tyrosine kinase receptor inhibitors is recommended.

Mechanism of Injury

The cause of the liver injury due to nilotinib is unknown. Nilotinib is metabolized in the liver largely by the cytochrome P450 system, and liver injury may be due to accumulation of a toxic intermediate or from a drug-drug interaction with other medications.

Outcome and Management

Serum aminotransferase elevations above 5 times the upper limit of normal (if confirmed) should lead to dose reduction or temporary cessation. Cross reactivity of the hepatic injury with other tyrosine kinase inhibitors is not common, but can occur. In using this medication, other potentially hepatotoxic agents should be avoided.

Drug Class: Antineoplastic Agents, Protein Kinase Inhibitors

Other Drugs in the Subclass, Chronic Myeloid Leukemia Agents: Bosutinib, Dasatinib, Imatinib, Omacetaxine, Ponatinib

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Nilotinib – Tasigna®

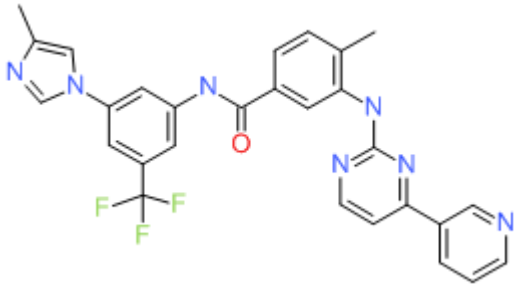
DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Nilotinib	641571-10-0	C28-H22-F3-N7-O	

ANNOTATED BIBLIOGRAPHY

References updated: 04 February 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 tyrosine kinase receptor inhibitors).

DeLeve LD. Kinase inhibitors. Cancer chemotherapy. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 556-7.

(Review of hepatotoxicity of cancer chemotherapeutic agents discusses gefitinib, erlotinib and crizotinib but not nilotinib).

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).

Kantarjian H, Giles F, Wunderle L, Bhalla K, O'Brien S, Wassmann B, Tanaka C, et al. Nilotinib in imatinib-resistant CML and Philadelphia chromosome-positive ALL. N Engl J Med 2006; 354: 2542-51. PubMed PMID: 16775235.

(Trial of escalating doses of nilotinib in 119 patients with imatinib resistant chronic myelogenous leukemia [CML]; dose limiting toxic effects included elevations of indirect serum bilirubin [n=9] and ALT [n=3]; no mention of clinically apparent liver injury).

DeRemer DL, Ustun C, Natarajan K. Nilotinib: a second-generation tyrosine kinase inhibitor for the treatment of chronic myelogenous leukemia. Clin Ther 2008; 30: 1956-75. PubMed PMID: 19108785.

(Review of mechanism of action, pharmacology, clinical efficacy and tolerability of nilotinib based upon analyses of phase II and III trials; most common toxicities were neutropenia and thrombocytopenia, rash, nausea, headache, itching and fatigue. ALT and AST elevations were "infrequent", with values >5 times ULN in 1-4% of patients; instances of hyperbilirubinemia were also observed, but were self-limiting and attributed to Gilbert Syndrome).

Perini GF, Santos FP, Funke V, Ruiz J, Neto BH, Hamerschlak N. Nilotinib post-liver transplantation for acute hepatic failure related to imatinib. Leuk Res 2009; 33: e234-5. PubMed PMID: 19632720.

(47 year old woman with CML developed jaundice and confusion after 18 months of imatinib therapy [bilirubin 20 mg/dL, ALT 828 U/L, prothrombin time 24 sec], leading to emergency liver transplantation; later treated with nilotinib without recurrence of liver injury).

Breccia M, Alimena G. Nilotinib therapy in chronic myelogenous leukemia: the strength of high selectivity on BCR/ABL. Curr Drug Targets 2009; 10: 530-6. PubMed PMID: 19519355.

(Review of development, mechanism of action, clinical efficacy and safety of nilotinib, a tyrosine kinase receptor inhibitor similar to imatinib; serum bilirubin elevations occurred in 3-16% of patients; no mention of clinically apparent liver injury).

Koren-Michowitz M, le Coutre P, Duyster J, Scheid C, Panayiotidis P, Prejzner W, Rowe JM, et al. Activity and tolerability of nilotinib: a retrospective multicenter analysis of chronic myeloid leukemia patients who are imatinib resistant or intolerant. Cancer 2010; 116: 4564-72. PubMed PMID: 20572041.

(88 patients with CML who were intolerant or resistant to imatinib were treated with nilotinib for up to 3 years; 14% developed ALT or Alk P elevations, but none had clinically apparent liver injury, and 5 patients who stopped imatinib because of hepatotoxicity tolerated nilotinib without recurrence).

Saglio G, Kim DW, Issaragrisil S, le Coutre P, Etienne G, Lobo C, Pasquini R, et al.; ENESTnd Investigators. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med 2010; 362: 2251-9. PubMed PMID: 20525993.

(Controlled trial of 2 doses of nilotinib vs imatinib in 846 patients with CML found ALT elevations were more frequent with nilotinib than imatinib [66% and 73% vs 20% for any elevation, 4% and 9% vs 2% for elevations >5 times ULN]; hepatobiliary adverse events occurred in 4 nilotinib [0.7%] and in 1 imatinib [0.4%] recipient; details not given).

Martínez Pascual C, Valdés Mas M, de la Peña Moral JM, Miras López M. [Fulminating hepatitis for imatinib in a patient with chronic myeloid leukaemia]. Med Clin (Barc) 2011; 137: 329-30. Spanish. PubMed PMID: 21074222.

(34 year old woman with CML developed jaundice 8 months after starting imatinib [bilirubin 14.5 mg/dL, ALT 1856 U/L, Alk P 254 U/L], progressing to liver failure and liver transplantation).

Spataro V. Nilotinib in a patient with postnecrotic liver cirrhosis related to imatinib. J Clin Oncol 2011; 29: e50-2. PubMed PMID: 20956624.

(41 year old woman with CML developed jaundice 6 months after starting imatinib [bilirubin 9.6 mg/dL, ALT 1374 U/L, Alk P 163 U/L, prothrombin index 27%, biopsy showing massive necrosis], recovering slowly with residual evidence of portal hypertension and subsequent biopsy showing cirrhosis; started on nilotinib for relapse in CML without worsening of liver tests).

Kantarjian HM, Hochhaus A, Saglio G, De Souza C, Flinn IW, Stenke L, Goh YT, et al. Nilotinib versus imatinib for the treatment of patients with newly diagnosed chronic phase, Philadelphia chromosome-positive, chronic myeloid leukaemia: 24-month minimum follow-up of the phase 3 randomised ENESTnd trial. Lancet Oncol 2011; 12: 841-51. PubMed PMID: 21856226.

(Controlled trial of 2 doses of nilotinib vs imatinib for at least 24 months in 846 patients with CML found ALT elevations above 5 times ULN in 4% and 9% of patients on nilotinib vs 3% on imatinib; one patient on nilotinib had a "liver disorder", but no details given).

Usuki K, Tojo A, Maeda Y, Kobayashi Y, Matsuda A, Ohyashiki K, Nakaseko C, et al. Efficacy and safety of nilotinib in Japanese patients with imatinib-resistant or -intolerant Ph+ CML or relapsed/refractory Ph+ ALL: a 36-month analysis of a phase I and II study. Int J Hematol 2012; 95: 409-19. PubMed PMID: 22359103.

(Among 34 Japanese patients with CML treated with nilotinib for 36 months, bilirubin elevations occurred in 29% and ALT elevations in 24%, but ALT above 5 times ULN in only 3% [1 patient]).

Nicolini FE, Masszi T, Shen Z, Gallagher NJ, Jootar S, Powell BL, Dorlhiac-Llacer PE, et al. Expanding Nilotinib Access in Clinical Trials (ENACT), an open-label multicenter study of oral nilotinib in adult patients with imatinib-resistant or -intolerant chronic myeloid leukemia in accelerated phase or blast crisis. Leuk Lymphoma 2012; 53: 907-14. PubMed PMID: 22023530.

(Among 371 patients with CML in accelerated phase or blast crisis treated with nilotinib for up to 2 years found ALT elevations in 8% of patients, but levels above 5 times ULN in only 0.5% [2 patients]; serum bilirubin levels were elevated in 23%).

Larson RA, Hochhaus A, Hughes TP, Clark RE, Etienne G, Kim DW, Flinn IW, et al. Nilotinib vs imatinib in patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase: ENESTnd 3-year follow-up. Leukemia 2012; 26: 2197-203. PubMed PMID: 22699418.

(Further follow up to 3 years of the patients with CML described by Kantarjian [2011] reported ALT elevations above 5 times ULN in 4.3% and 9.4% of nilotinib- vs 2.5% of imatinib-treated subjects).

Hua J, Iwaki Y, Inoue M, Hagihara M. Tumor lysis syndrome soon after treatment with hydroxyurea followed by nilotinib in two patients with chronic-phase chronic myelogenous leukemia. Int J Hematol 2013; 98: 243-6. PubMed PMID: 23649869.

(44 year old man with CML in chronic phase developed metabolic acidosis within 10 hours of starting nilotinib [pH 6.9, creatinine 1.4 mg/dL, ALT 26 U/L] and rapidly decreasing white blood cell count [162,000 to 61,000/uL], followed by multiorgan and hepatic failure [bilirubin 4.4 mg/dL, ALT 1031 U/L], autopsy showing massive necrosis).

Engel T, Justo D, Amitai M, Volchek Y, Mayan H. Nilotinib-associated acute pancreatitis. Ann Pharmacother 2013; 47: e3. PubMed PMID: 23300151.

(69 year old woman with CML developed abdominal pain within a day of starting nilotinib and was admitted with pancreatitis 6 days later [bilirubin 1.7 mg/dL, ALT normal, lipase 308 U/L], resolving on stopping and not recurring when switched to imatinib).

Lai GM, Yan SL, Chang CS, Tsai CY. Hepatitis B reactivation in chronic myeloid leukemia patients receiving tyrosine kinase inhibitor. World J Gastroenterol 2013; 19: 1318-21. PubMed PMID: 23483799.

(3 patients with CML and HBsAg carrier state were treated with imatinib [one had been switched to nilotinib] and developed reactivation of hepatitis B 6, 53 and 15 months later [bilirubin normal, 2.7 and 2.5 mg/dL, ALT 1086, 374 and 592 U/L, HBV DNA 229, 13 and 27 million IU/mL]; all three responded to entecavir therapy and were continued on the tyrosine kinase inhibitor).