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Nilotinib

Updated: May 10, 2020.

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 has been only a single published case report 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 latency to onset was 2 months and the pattern of injury was hepatocellular initially, but evolved into a severe and prolonged cholestatic hepatitis. 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.

Likelihood score: D (possible rare cause of clinically apparent liver injury).

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®

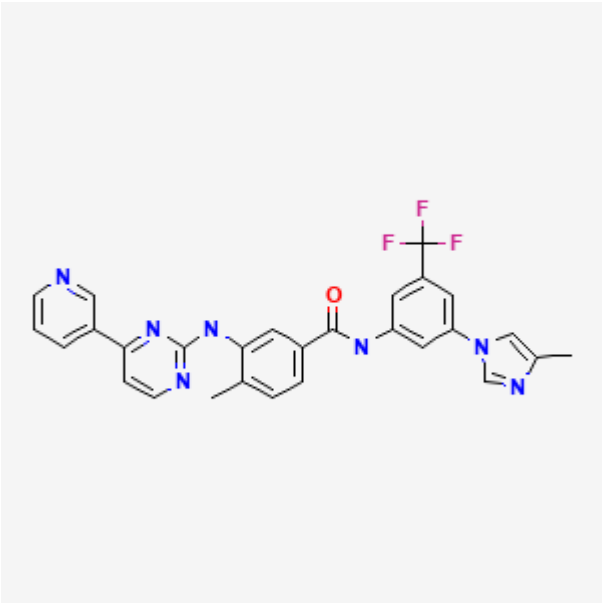
DRUG CLASS

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: 10 April 2020

Abbreviations: CML, chronic 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 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).

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).

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. Med Clin (Barc). 2011;137:329–30. [Fulminating hepatitis for imatinib in a patient with chronic myeloid leukaemia]. 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).

Hughes TP, Hochhaus A, Kantarjian HM, Cervantes F, Guilhot F, Niederwieser D, le Coutre PD, et al. Safety and efficacy of switching to nilotinib 400 mg twice daily for patients with chronic myeloid leukemia in chronic

phase with suboptimal response or failure on front-line imatinib or nilotinib 300 mg twice daily. Haematologica. 2014;99:1204–11. PubMed PMID: 24532039.

(Among 283 patients with CML who were treated with imatinib [400 mg once daily] in a controlled trial [Kantarjian 2011], 57 discontinued therapy because of a suboptimal response, 35 of whom were switched to nilotinib [400 mg twice daily] in whom adverse events included rash [29%], headache [23%] and ALT elevations [74%], all of which except one were less than 5 times ULN, and no patient stopped therapy because of liver test abnormalities).

Hochhaus A, Saglio G, Hughes TP, Larson RA, Kim DW, Issaragrisil S, le Coutre PD, et al. Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. Leukemia. 2016;30:1044–54. PubMed PMID: 26837842.

(Among 846 adults with CML in chronic phase treated with imatinib or nilotinib in a controlled trial, 5 year follow up was available on 50-60% of patients in whom the rate of ALT elevations above 5 times ULN on nilotinib was 4.3% [300 mg twice daily] and 9.4% [400 mg twice daily], and none of the 50 deaths were attributed to liver failure, only half being due to progression of disease).

Hiwase D, Tan P, D'Rozario J, Taper J, Powell A, Irving I, Wright M, et al. Efficacy and safety of nilotinib 300 mg twice daily in patients with chronic myeloid leukemia in chronic phase who are intolerant to prior tyrosine kinase inhibitors: Results from the Phase IIIb ENESTswift study. Leuk Res. 2018;67:109–15. PubMed PMID: 29494928.

(Among 20 patients with CML intolerant to first and second generation BCR-ABL1 inhibitors who were switched to nilotinib [300 mg twice daily], 10 achieved a deep molecular response by month 12 and there were no withdrawals because of adverse events; 2 patients [10%] had transient ALT elevations, all were less than 5 times ULN, asymptomatic and without jaundice).

Kuo CY, Wang PN, Hwang WL, Tzeng CH, Bai LY, Tang JL, Chang MC, et al. Safety and efficacy of nilotinib in routine clinical practice in patients with chronic myeloid leukemia in chronic or accelerated phase with resistance or intolerance to imatinib: results from the NOVEL study. Ther Adv Hematol. 2018;9:65–78. PubMed PMID: 29531660.

(Among 85 patients with CML treated with nilotinib over a two year period in 12 Taiwanese centers, common drug related adverse events were thrombocytopenia [21%] and ALT elevations [21%], only 1 of which was greater than 5 times ULN).

Iurlo A, Bucelli C, Cattaneo D, Levati GV, Viani B, Tavazzi D, Consonni D, et al. UGT1A1 genotype does not affect tyrosine kinase inhibitors efficacy and safety in chronic myeloid leukemia. Am J Hematol. 2019;94:E283–E285. PubMed PMID: 31364196.

(Genotypes of the uridine-50-diphosphate glucuronosyltransferase [UGT]-1A1 gene in 105 patients with CML treated with various tyrosine kinase inhibitors found no correlation of homozygosity of 7/7* [TA7TAA] and either efficacy [progression-free survival] or hematologic or extra-hematologic adverse event rates except for hyperbilirubinemia which occurred in 15 of 17 patients with Gilbert syndrome).*

García-Gutiérrez V, Hernández-Boluda JC. Tyrosine kinase inhibitors available for chronic myeloid leukemia: efficacy and safety. Front Oncol. 2019;9:603. PubMed PMID: 31334123.

(Review of current therapy of CML using first [imatinib], second [nilotinib, dasatinib, bosutinib], and third generation [ponatinib] tyrosine kinase inhibitors, posatinib being used only after failure of 1 or 2 other agents, its major shortcoming being high rate of adverse effects including major cardiovascular complications particularly with high doses of ponatinib; no discussion of hepatotoxicity).

Belopolsky Y, Grinblatt DL, Dunnenberger HM, Sabatini LM, Joseph NE, Fimmel CJ. A case of severe, nilotinib-induced liver injury. ACG Case Rep J. 2019;6:e00003. PubMed PMID: 31616712.

(53 year old woman with CML developed fever and leg pains soon after starting imatinib with mild increases in ALT and Alk P, improving on stopping but then developing jaundice 2 months after initiating nilotinib therapy [bilirubin ~ 10 rising to 35 mg/dL, ALT 2000 U/L, Alk P not given, biopsy showing severe cholestatic hepatitis], with prolonged jaundice and incomplete resolution when seen 6 months later [bilirubin 1.5 mg/dL, ALT 47 U/L, Alk P 175 U/L]).

Lopina N, Dmytrenko I, Hamov D, Lopin D, Dyagil I. Novel score-based decision approach in chronic myeloid leukemia patients after acute toxic imatinib-induced liver injury. Cureus. 2019;11:e4411. PubMed PMID: 31245199.

(Discussion of factors in deciding whether to restart tyrosine kinase inhibitors in patients with CML who develop liver test abnormalities during therapy, five major factors being [1] the severity of the liver injury, [2] the presence of cirrhosis or a liver transplant, [3] the degree of response to the kinase inhibitor, [4] whether other drugs may have contributed, and [5] the presence of hepatitis virus infection and risk of reactivation).