CASE REPORT | LIVER

A Case of Severe, Nilotinib-Induced Liver Injury

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ABSTRACT

Idiosyncratic hepatotoxicity is a leading reason for the discontinuation or dose modification of Food and Drug Administration (FDA)-approved medications in the United States. We report the case of a 53-year-old woman with chronic myeloid leukemia who developed acute cholestatic hepatitis in response to the tyrosine kinase inhibitor nilotinib. Nilotinib was discontinued, and the patient's liver function tests normalized over the next 3 months. We conclude that nilotinib may cause life-threatening hepatotoxicity and recommend that patients on the medication undergo regular monitoring of their liver tests.

INTRODUCTION

Chronic myeloid leukemia (CML) is a common bone marrow disorder, with approximately 8,500 new cases diagnosed in the United States each year.[1] Tyrosine kinase inhibitors have transformed the treatment of CML and have resulted in markedly decreased morbidity and mortality. Since the first approval of imatinib for the treatment of CML in 2001, a growing list of tyrosine kinase inhibitors have been developed.[2] Nilotinib is a novel BCR-ABL inhibitor that has improved potency and selectivity compared with imatinib, as well as increased activity in patients with acquired BCR-ABL resistance mutations.[3] We report the case of a patient with CML who developed significant, clinically apparent liver toxicity in response to nilotinib.

CASE REPORT

A 53-year-old woman of Peruvian origin without previous history of chronic liver disease initially presented after being struck by a car while walking. While being evaluated in our hospital's emergency department, a complete blood count showed a leukocytosis of $58.6 \times 10^3/\mu L$, with 11 metamyelocytes and 13 myelocytes. This finding prompted a bone marrow biopsy, which revealed CML. Molecular studies revealed the characteristic BCR-ABL t (9;22)(q34;q11.2) translocation.

The patient deferred treatment of her CML until 1 year later. She was started on imatinib at a dose of 400 mg daily. Within a few days, she developed hip and thigh pains and fevers. Imatinib was withheld and restarted 1 week later, with prompt recurrence of her symptoms leading to its discontinuation in 2 weeks. While on imatinib, the patient's transaminase and alkaline phosphatase levels became moderately elevated (Figure 1). She drank no alcohol and denied any illicit drug use or use of over-the-counter remedies with possible liver toxicity. Her family history was unremarkable. She was working in a bakery. She had a history of a previous episode of isoniazid-induced liver injury that required discontinuation of the drug.

The patient was started on nilotinib 2 weeks later at a dose of 150 mg twice daily, following downtrending liver chemistries, representing 50% of the standard dose. The reduced dose was chosen because of the patient's concerns over possible drug toxicity. Two weeks after starting nilotinib, the alkaline phosphatase levels remained slightly elevated, but the transaminase levels had continued to improve compared with the pre-nilotinib testing (Figure 1). Two months after starting nilotinib, the patient developed pruritus, nausea, fatigue, and dark urine. She presented in November of 2017 with laboratory changes of mixed, hepatocellular, and cholestatic liver injury and
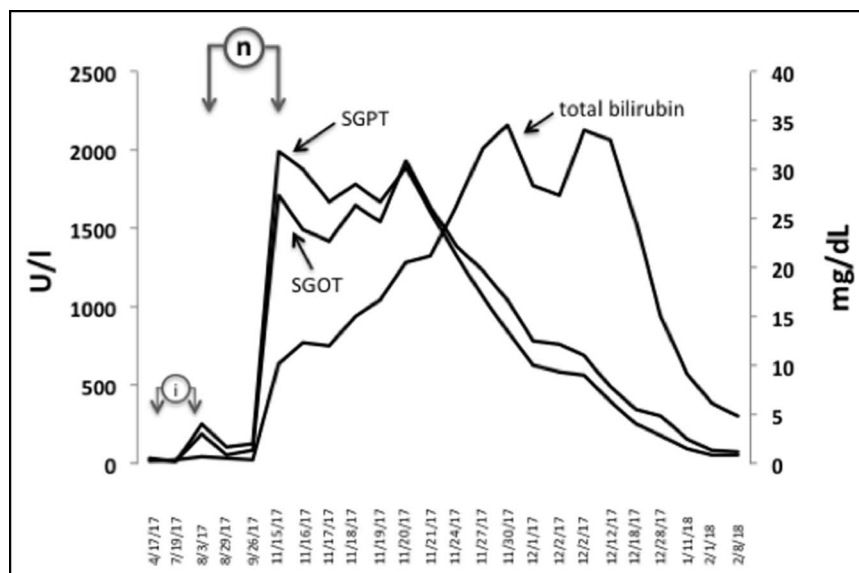
Figure 1. Serum transaminase and total bilirubin levels before and after nilotinib treatment. n, nilotinib; i, imatinib.

concomitant coagulopathy (international normalized ratio 2.2). The patient tested negative for hepatitis B surface antigen, hepatitis B core IgG and IgM, hepatitis C Ab, and hepatitis E Ab IgM. She was cytomegalovirus Ab IgG positive, cytomegalovirus Ab IgM negative, Epstein-Barr virus Ab IgM negative, Epstein-Barr virus Ab IgG positive, and Epstein-Barr nuclear antigen positive. The serum ferritin level was elevated at 1,684 ng/mL and the creatine kinase level was 77 U/L. The antinuclear antibody screen was positive, antismooth muscle Ab negative, anti-liver-kidney microsomal Ab negative, C-antineutrophil cytoplasmic antibody <1:20, P-antineutrophil cytoplasmic antibody <1:20, and antimitochondrial Ab <0.1. Toxicology testing for alcohol, acetaminophen, and illicit drugs was negative. A liver ultrasound showed normal hepatic parenchyma and spleen, a contracted gallbladder without gallstones, no biliary dilatation, and a common bile duct diameter of 3 mm. Doppler studies demonstrated patent hepatic artery and veins, portal vein, and inferior vena cava. Nilotinib was stopped. The patient was given supplementary vitamin K, without any demonstrable effect on the prothrombin time.

A percutaneous liver biopsy in December of 2017 showed features of a severe acute cholestatic hepatitis (Figure 2). The trichrome and reticulin stain revealed areas of bridging necrosis, comprising 30%–40% of the parenchyma, and no abnormal fibrosis. The portal tracts contained a mixed inflammatory cell infiltrate, including occasional groups of plasma cells and periodic acid-schiff stain-positive, foamy macrophages. Cholestasis, bile ductular proliferation, and injury to native bile ducts were present. Significant injury to periportal hepatocytes was observed, featuring acidophil body formation and ballooning degeneration. Regenerating hepatocytes and other features of resolving injury were also present. The lobular parenchyma revealed similar cholestasis and patchy necroinflammatory activity. Copper and iron stains were

negative. The pathologist's overall impression was that the patient's liver injury was acute and most likely due to nilotinib-induced, acute liver toxicity, with features of regeneration and resolving injury. The possibility of autoimmune hepatitis was considered but thought to be less likely.

A comprehensive pharmacogenomics analysis was performed on genomic DNA obtained from the patient's buccal swab. No definitive high-risk alleles were discovered. Of note, the patient's uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) genotype was *36/*36, which is present in approximately 0.02% in South American natives. This genotype confers increased enzymatic activity to UGT1A1. Because nilotinib inhibits UGT1A1 activity, we hypothesized that the patient's genotype might have resolved in a phenoconversion and a resulting change in the metabolism of concomitant medications.[4] However, a review of the patient's chart revealed lisinopril as the only concomitant medication. Because lisinopril is not metabolized, we conclude that this medication was not involved in the patient's liver injury. Further analysis also demonstrated the presence of a NAT2 slow acetylator allele, which is associated with a higher risk of isoniazid-induced liver injury, as previously observed in our patient.

The patient's clinical status and liver enzymes were closely monitored. She did not develop hepatic encephalopathy, and her coagulopathy resolved within a few weeks after having stopped nilotinib. The transaminases and bilirubin peaked in late November and then gradually normalized. The patient developed transient lower extremity edema and was put on diuretics. Her nausea resolved in February. At the time of her most recent clinic visit in April 2018, the patient's edema had resolved, and her liver tests were near normal (total bilirubin 1.4 mg/dL, aspartate aminotransferase 54 U/L, alanine aminotransferase 47 U/L, albumin 3.5 g/dL, and alkaline phosphatase 175 U/L).
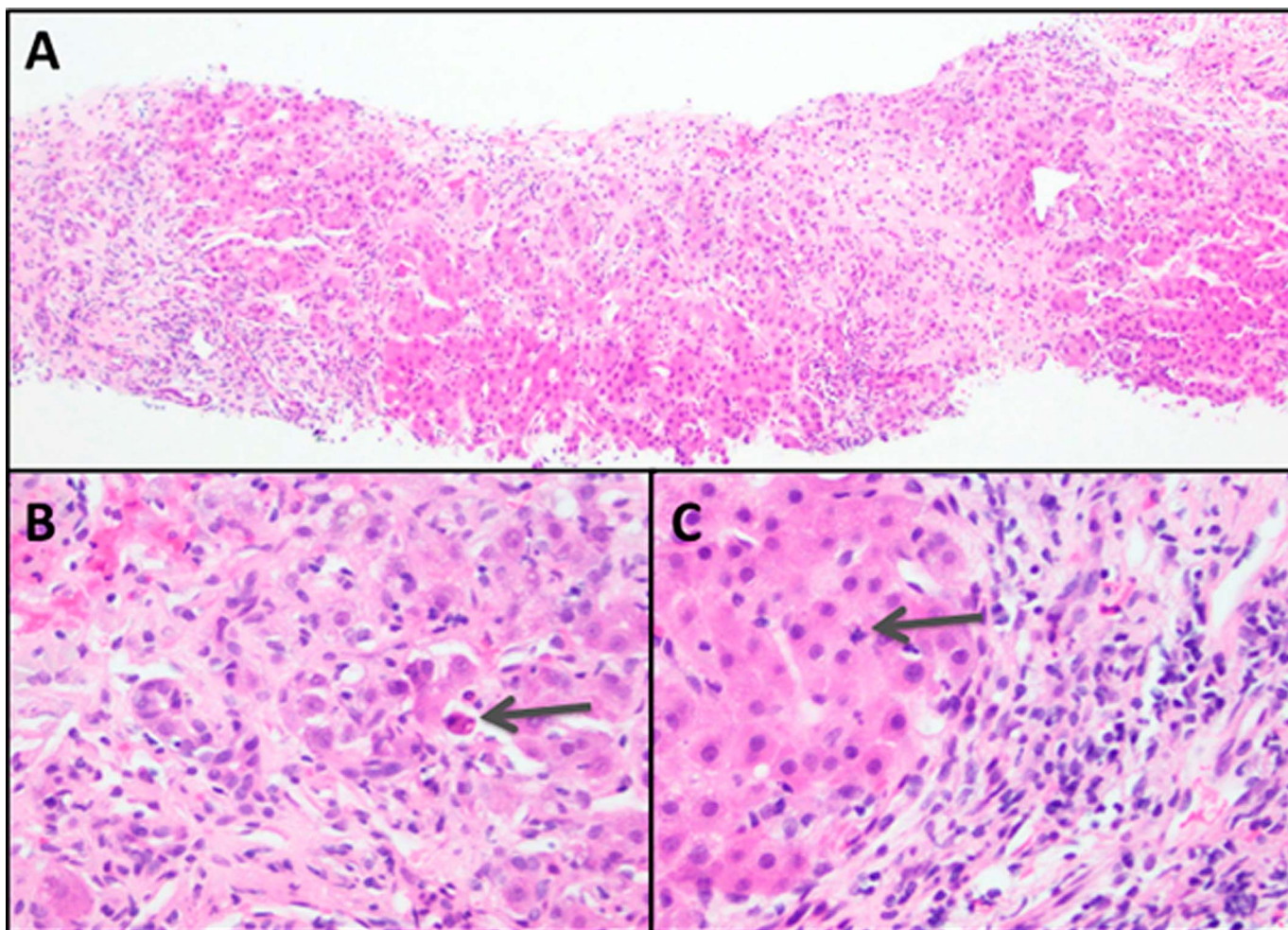
Figure 2. Acute cholestatic hepatitis with exuberant portal and lobular inflammation highlighted by trichrome and reticulin stains. (A) Portal and lobular inflammation with bridging necrosis in 30%–40% of parenchyma (10×). Portal tracts demonstrating a mixed inflammatory cell infiltrate, including occasional groups of plasma cells and periodic acid-schiff stain-positive, foamy macrophages. Cholestasis, bile ductular proliferation, and injury to native bile ducts were present. The lobular parenchyma revealed similar cholestasis and patchy necroinflammatory activity. (B) Active hepatocyte injury: ballooning degeneration and acidophil body formation (arrow). (C) Regenerating hepatic parenchyma: bile ductular proliferation, foamy macrophages, and a mitotic figure (arrow) (40×).

DISCUSSION

Since its approval in 2007, nilotinib has emerged as a remarkably effective and reasonably safe medication for the treatment of CML and other malignancies.[5,6] Its common and typically manageable side effects include fatigue, diarrhea, anorexia, abdominal discomfort, anemia, cough, and pruritus. Rare side effects include QT interval prolongation, congestive heart failure, and pancreatitis.[7]

With regard to liver toxicity, we did not find any reports of clinically apparent liver injury in the literature.[8] Elevations in transaminase levels of more than 5 times the upper limit of normal were reported in 4%–9% of the seminal clinical trials, and minor elevations were reportedly observed in up to 15% of patients.[9] The enzyme level elevations were typically transient, normalizing with continuation of treatment or after temporary treatment interruption and resumption of the drug. Hyperbilirubinemia and jaundice have been described in a small percentage of patients. The hyperbilirubinemia is typically unconjugated and has been linked to the $(TA)_7/(TA)_7$ promoter polymorphism of the UGT1A1 enzyme.[10] No grade 4 events (total bilirubin >10 times the upper limit of normal) were observed, and the effect was reversible despite continuation of therapy. Interestingly, the mechanism of this effect is unclear because nilotinib is not metabolized via UGT1A1.

Imatinib-induced acute liver injury and liver failure resulting in death or necessitating liver transplantation are well known but rare complications. In a recent case report, Nacif referenced 11 published cases of fulminant liver failure in the literature.[11] In most cases, the onset of detectable liver injury occurred after more than 20 weeks of uninterrupted imatinib treatment, although there was 1 case with an exposure of 2 weeks' duration. We consider it unlikely that a brief exposure to imatinib would have resulted in clinically apparent liver injury several months later. In addition, imatinib results in a predominantly hepatocellular injury pattern, whereas a mixed hepatocellular and

cholestatic picture—which was observed in our patient of peak bilirubin 34 mg/dL, alkaline phosphatase 271 U/L, aspartate aminotransferase 1,640 U/L, and alanine aminotransferase 1,613 U/L—is rare.

Despite their similar mechanism of action and chemical structures, there seems to be minimal cross-intolerance between imatinib and nilotinib.[12] In fact, we are aware of at least 1 case report in which nilotinib was successfully used to treat CML in a patient who had imatinib-induced liver failure.[13]

A detailed pharmacogenomic analysis did not reveal a likely causative allele in the patent's drug-metabolizing enzymes. We did perform therapeutic drug monitoring and can therefore not rule out increased nilotinib plasma concentrations. However, we consider this possibility unlikely, given low nilotinib dose in our patient.

To our knowledge, our patient represents the first reported case of grade 4 nilotinib-induced liver injury, as defined by the Drug-Induced Liver Injury Network.[14] Our patient met the criteria of increased transaminase and alkaline phosphatase levels, a serum bilirubin increase of >2.5 mg/dL, prolonged jaundice and symptoms beyond three months, and coagulopathy with an international normalized ratio of greater than 1.5. In addition to her liver test abnormalities, the patients also developed significant anemia and thrombocytopenia (data not shown), consistent with the known hematologic toxicity of nilotinib. Fortunately, the patient did not develop ascites, encephalopathy, or renal failure, or any other features of liver failure. On withdrawal of the medication, her liver injury slowly resolved over a period of several months. We conclude that nilotinib-induced liver injury should be considered in patients who develop significant liver enzyme level elevations on the drug.

DISCLOSURES

REFERENCES

1. Bhatia R. Novel approaches to therapy in CML. *Hematol Am Soc Hematol Educ Program*. 2017;2017(1):115–20.
2. Pophali PA, Patnaik MM. The role of new tyrosine kinase inhibitors in chronic myeloid leukemia. *Cancer J*. 2016;22(1):40–50.
3. Larson RA, Hochhaus A, Hughes TP, 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(10):2197–203.
4. Miura M. Therapeutic drug monitoring of imatinib, nilotinib, and dasatinib for patients with chronic myeloid leukemia. *Biol Pharm Bull*. 2015; 38(5):645–54.
5. Emole J, Talabi T, Pinilla-Ibarz J. Update on the management of Philadelphia chromosome positive chronic myelogenous leukemia: Role of nilotinib. *Biologics*. 2016;10:23–31.
6. Saglio G, Kim DW, Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N Engl J Med*. 2010;362(24):2251–9.
7. Medeiros BC, Possick J, Fradley M. Cardiovascular, pulmonary, and metabolic toxicities complicating tyrosine kinase inhibitor therapy in chronic myeloid leukemia: Strategies for monitoring, detecting, and managing. *Blood Rev*. 2018;32:289–99.
8. Health NIo. Nilotinib 2018. https://livertox.nlm.nih.gov//Nilotinib.htm. Accessed on August 8, 2018.
9. Kantarjian HM, Giles F, Gattermann N, et al. Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is effective in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase following imatinib resistance and intolerance. *Blood*. 2007;110(10):3540–6.
10. Singer JB, Shou Y, Giles F, et al. UGT1A1 promoter polymorphism increases risk of nilotinib-induced hyperbilirubinemia. *Leukemia*. 2007; 21(11):2311–5.
11. Nacif LS, Waisberg DR, Pinheiro RS, et al. Imatinib-induced fulminant liver failure in chronic myeloid leukemia: Role of liver transplant and second-generation tyrosine kinase inhibitors: A case report. *J Med Case Rep*. 2018;12(1):63.
12. Cortes JE, Hochhaus A, le Coutre PD, et al. Minimal cross-intolerance with nilotinib in patients with chronic myeloid leukemia in chronic or accelerated phase who are intolerant to imatinib. *Blood*. 2011;117(21): 5600–6.
13. 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(12):e234–5.
14. Health NIo. Severity Grading 2018. https://livertox.nlm.nih.gov/Severity. html. Accessed on August 8, 2018.