Case Report

Acute Ischemic Intestinal Necrosis as a Rare Side Effect of Nilotinib

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Abstract

Tyrosine kinase inhibitors (TKIs) are highly effective therapies for chronic myeloid leukemia (CML). However, continuous administration of TKIs could lead to toxicity that could induce serious vascular disorders. Nilotinib, a second-generation TKI, has been approved for patients with CML in the chronic phase or accelerated phase, after resistance to imatinib has been identified, or as a first-line treatment. In comparison to other TKIs, nilotinib has been associated with a higher incidence of cardiovascular events, such as peripheral artery occlusive disease. We present a CML patient who developed acute ischemic bowel necrosis and perforation during nilotinib therapy.

Keywords: *Acute ischemic bowel necrosis, chronic myeloid leukemia, nilotinib, prothrombotic state*

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Introduction

Nilotinib is a second-generation tyrosine kinase inhibitor (TKI) with enhanced selectivity and potency for BCR-ABL, in comparison to imatinib. *In vitro* studies demonstrate that nilotinib is 20–50-fold more potent than imatinib.[1] In addition, nilotinib exhibits inhibitory activity against the majority of mutant BCR-ABL kinases that may be present after the development of imatinib resistance (with the exception of the T315I mutation).[1] The approval of nilotinib for imatinib-resistant and imatinib-intolerant patients with chronic phase and accelerated phase chronic myeloid leukemia (CML) was based on the results of a pivotal phase II trial.[2,3] Notably, the safety profile of nilotinib is distinct from that of imatinib. Among the patients in the Evaluating Nilotinib Efficacy and Safety in Clinical Trials – Newly Diagnosed trial, low-grade chronic adverse events (AEs) that significantly reduced quality of life after 4 years of follow-up included fatigue, peripheral edema, muscle spasm, arthralgia, and insomnia.[4] Overall, there are fewer AEs associated with nilotinib therapy, compared to imatinib. However, pancreatitis, hyperbilirubinemia, and hepatotoxicity are listed as common AEs associated with nilotinib treatment.[5,6] Although generally uncommon, cardiovascular events, including ischemic heart disease, ischemic cerebrovascular disease, and peripheral arterial occlusive diseases (PAOD), occur more frequently in patients using nilotinib,[6,7] suggesting that nilotinib-associated toxicity occurs mostly in the arteries. Recent reports of cardiovascular AEs associated with nilotinib have raised concerns about long-term sequelae of the administration of certain drugs over a number of decades. However, some short-term and acute AEs can be mild. In this report, we present a CML patient who developed acute ischemic bowel necrosis during nilotinib therapy.

Case Report

A 26-year-old female was diagnosed with chronic phase CML in April 2015. She had no previous history of smoking or cardiovascular disease. Blood analysis showed a white blood cell count (WBC) of 193.6 × 10^9/L, HGB (hemoglobin) of 8.6 g/dL, and a platelet count (PLT) of

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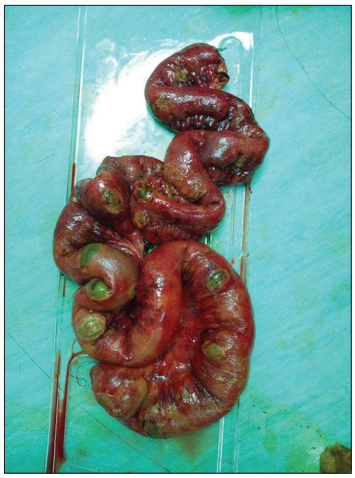

Figure 1: Within 1 m of the ileum, there were approximately 20 sites necrosis of the intestinal wall with the same 2 cm diameter range

462 × 10^9/L. Abdominal ultrasound showed an enlarged spleen. The karyotype was 46, XX, t(9;22) (q34; q11),[10] and BCR-ABL transcript level (international scale [IS]) was 81.128%. Initial treatment with imatinib was administered at 400 mg/day. However, medication was withdrawn because of low blood counts. Three months later, the treatment was considered a failure.

In October 2015, the patient complained of arthralgia and fever. Blood analysis showed WBC of 2.26 × 10^9/L, HGB of 8.6 g/dL, and PLT of 51 × 10^9/L, with a differential of 60% neutrophils, 23% lymphocytes, 14% monocytes, and 3% promyelocytes. Bone marrow analysis showed myeloid and erythroid hyperplasia, 9.5% blasts, and a BCR-ABL (IS) level of 63.394%. The karyotype was then 46, XX, t(9;22)[3]/52, idem,+X,+8,+14,+19,+21,+ph[7] indicating progression of the disease. The patient and her family refused chemotherapy and bone marrow transplantation. Subsequently, nilotinib was administered at 400 mg twice daily from October 21, 2015. Three months later, the patient complained of constipation and nausea. Abdominal X-ray revealed an intestinal obstruction, and abdominal computed tomography showed chest, abdominal, and pelvic fluid. A blood coagulation test showed elevated d-dimer (0.678 mg/dL, reference range: 0.001–0.055 mg/dL), plasma fibrinogen (444 mg/dL, reference range: 200–400 mg/dL), and activated partial thromboplastin time (36.7 s, reference range: 20–36 s). Moreover, the high-density lipoprotein level was low (0.04 mmol/dL, reference range: 0.09–0.25 mmol/dL).

Fasting was implemented and an enema, antispasmodic, and analgesic treatment were administered. Exploratory laparotomy was performed under general anesthesia. Along 1 m of the ileum, approximately 20 sites of necrosis were identified in the intestinal wall with a similar range in diameter of 2 cm [Figure 1]. Partial necrosis and perforation were also observed. Thus, partial resection and anastomosis of the intestine were performed. The histological report of the resected bowel showed areas of full thickness perforation and a fibrinopurulent serosal exudate. The bowel wall was thin, with multiple areas of infarction [Figure 2a and b]. Considering that the intestinal necrosis might have been an associated side effect, the physician recommended withdrawal of nilotinib. The patient died on March 24, 2017 because of nonavailability of alternative therapy at our center, even though intestinal necrosis and perforation showed no recurrence after withdrawal of nilotinib.

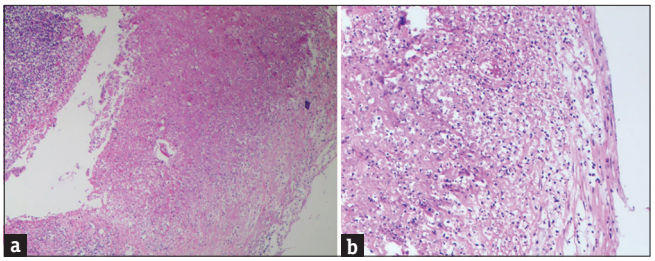

Figure 2: (a) There were full thickness infarction of the muscle layer and infiltration of lymphocytes of the small intestinal submucosa (H and E; ×40). (b) Massively infarcted bowel wall, except for a narrow peripheral rim of fibers. Almost entire thickness is necrotic, strongly eosinophilic, with ghosts of lymphocytes. Infiltration of neutrophils and polymorphonuclear leukocytes identified near margin of necrotic tissue (H and E; ×100)

Discussion

In comparison to imatinib, the second-generation TKI, nilotinib, induces a more rapid, sustained molecular response.[1] However, it also elicits long-term toxicities, such as PAOD.[6,7]

Other causes of intestinal necrosis, such as trauma and intestinal torsion, were ruled out. We hypothesize that the intestinal necrosis observed was caused by intestinal ischemia. Acute bowel ischemic necrosis is divided into two categories, acute obstructive intestinal ischemia and acute nonocclusive intestinal ischemia.[8] The patient showed no evidence of low flow states or shock, particularly cardiogenic shock, and was not on vasoconstrictor or other medications. In addition, the patient showed high levels of prothrombotic factors, like D-dimer and fibrinogen. Therefore, intestinal ischemia might have been caused by mesenteric arterial obstruction. Furthermore, no arterial interventions were made before the patient developed acute abdominal pain. Similarly, she had no arrhythmias (such as atrial fibrillation) or myocardial infarction. Thus, mesenteric thrombosis could have been one cause of mesenteric arterial obstructed necrosis. Nilotinib is known to elicit vascular toxicities such as PAOD.[6,7] Thus, the mesenteric thrombosis observed was likely related to nilotinib therapy.

The time to onset of PAOD in this case seemed to have been shorter than that reported previously. The average time from initiation of nilotinib to PAOD development was 24 months, and particularly longer in patients younger than 60 years, compared to those older than 60 years.[9] The patient in our case developed PAOD within 3 months. This could be attributed to the administration of imatinib that interacts with several ''nilotinib targets''[10] and predisposes the patient to a prothrombotic state. Thus, once the patient was switched to nilotinib, the AEs became evident. In addition, most patients with PAOD are older than 60 years, or affected by other cardiovascular risk factors, such as hypercholesterolemia, arterial hypertension, overweight/obesity, smoking, or diabetes mellitus.[9] The patient in our case was a young female (26 years old) without any of the aforementioned risk factors.

Thus, extensive baseline assessment of cardiovascular risk factors and comprehensive monitoring are recommended for effective management of nilotinib therapy in patients with CML.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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