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Case Report

Severe peripheral arterial occlusive disease in chronic myeloid leukemia patient during nilotinib therapy: report of a case and review of literature

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Abstract: Nilotinib, the second-generation tyrosine kinase inhibitor (TKI), is initially designed and used to overcome resistance or intolerance of the first-generation agent imatinib. Despite improvements in complete cytogenetic response (CCyR) and deep molecular response compared with the first generation TKI, cardiovascular safety is becoming a big problem for patients with chronic myeloid leukemia (CML) receiving nilotinib. Such cardiovascular adverse events (CVE) include peripheral artery occlusive disease (PAOD), myocardial infarction, stroke, unstable angina. Hypertension, dyslipidemia, coronary arterial disease, congestive heart failure and chronic renal failure are associated with a higher risk of CVE. Here we described a patient suffering from unexpected and rapid onset of symptomatic PAOD during nilotinib treatment. Although arterial damage was irreversible, functional outcome was satisfactory upon rapid drug withdrawal and surgery.

Keywords: Nilotinib, peripheral arterial occlusive disease, chronic myeloid leukemia

Introduction

Chronic myeloid leukemia (CML) is a hematopoietic neoplasm characterized by the BCR/ABL oncoprotein which is produced by BCR/ABL fusion gene located in the Philadelphia chromosome. Imatinib, the first generation tyrosine kinase inhibitor (TKI), is used as frontline therapy in chronic phase CML (CML-CP) with good long-term results with respect to efficacy and safety. However, resistance against imatinib has been reported, often related to BCR-ABL mutations [1, 2]. Also some patients cannot tolerate imatinib treatment. Novel TKIs are in need. The second generation TKI, nilotinib, structurally similar to imatinib, is more potent than imatinib and additionally, effectively breaks up imatinib resistance among a majority of patients with CML [3, 4], with moderate and manageable side effects. Common non-hematologic side effects include skin rash, pruritus, headache, nausea, and fatigue [5, 6]. Frequent laboratory abnormalities involve increased pancreatic enzymes, hyperbilirubinemia and elevated fasting glucose level [3, 5-7]. And there are several reports on severe peripheral arterial occlusive disease (PAOD) [7-15]. Risk factors related to CVE were hypertension, dyslipidemia, coronary arterial disease, congestive heart failure and chronic renal failure [16]. We presented here a case of rapid and unexpected onset of symptomatic PAOD in a nilotinib-treated patient in our centre. The possible mechanism underlying PAOD in patients receiving nilotinib and related risk factors were described, as well as managements of PAOD in CML patients.

Case report

A 68-year-old female patient was diagnosed with CP CML, low Sokal risk in 2009 and no other co-morbidities were evident. She initially received a daily regimen of 400 mg imatinib. Three months later, she entered complete cytogenetic response (CCyR) with concentrations of triglyceride (TG) (normal range: <88.9 mg/dl), total cholesterol (TC) (normal range: 96.7-199.9 mg/dl), high-density lipoprotein- cholesterol (HDL-C) (normal range: 34.8-154.7 mg/dl) and

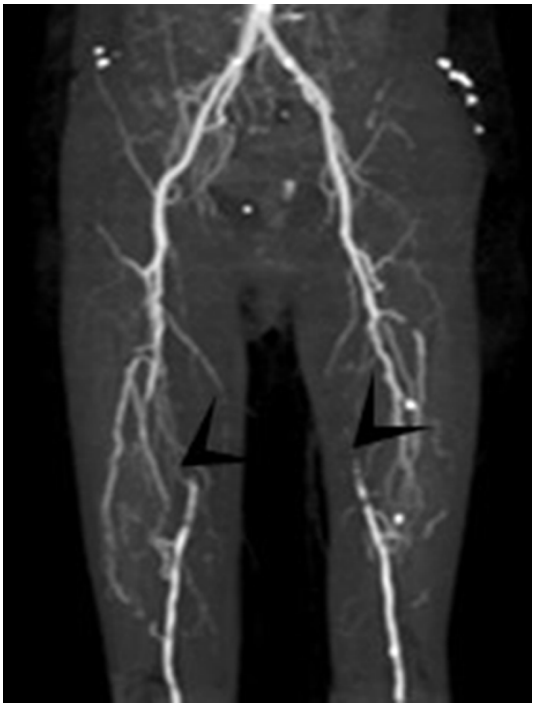

Figure 1. CT angiography of the lower limbs revealed an incomplete occlusion of both femoral arteries.

low-density lipoprotein- cholesterol (LDL-C) (normal range: <120.7 mg/dl) within normal limits. Furthermore, BCR-ABL transcripts were undetectable (deep molecular response) after six months' imatinib therapy. However, the patient complained about poor appetite and recurrent diarrhea in November 2013. Nilotinib was initiated at a dose of 300 mg twice daily from January 2014. At that time, no abnormalities of laboratory examination were revealed. One month later, plasma TC concentration increased from 126.1 mg/dl to 267.2 mg/dl, LDL-C from 76.2 mg/dl to 197.6 mg/dl. In September 2014 (8 months on nilotinib treatment), she presented with pain in lower limbs for one month. Duplex ultrasonography showed plaques of both anterior tibial arteries. She chose rehabilitation and Chinese traditional treatment, and the pain decreased. In January 2015, the patient received nilotinib at the dose of 200 mg twice daily. Five months later, it was reported that the patient suffered repeated pain in both lower limbs. Duplex ultrasonography and CT angiography (CTA) of the lower extremities revealed an incomplete occlusion of both femoral arteries (**Figure 1**). Nilotinib was discontinued. The patient underwent a percutaneous transluminal angioplasty (PTA) of the right superficial femoral artery (SFA) as well as stent implantation into it. However, PAOD further developed and required additional PTA of the right superficial femoral artery and popliteal artery. To date, the patient is still in deep molecular response.

Discussion

PAOD is an increasingly emerging issue in patients with CML receiving nilotinib therapy. In recent years, several studies have been reported (**Table 1**) [7, 10, 12-15]. Eleven of 179 CML patients who received nilotinib developed severe peripheral arterial disease (PAD) [8]. Kim et al. [9] prospectively screened for PAOD in 159 CML-CP patients treated with TKIs. Five patients developed clinically manifest PAOD, all with nilotinib exposure. Levato et al. [11] described 4 (14.8%) patients experienced severe PAOD or other vascular disease during nilotinib treatment in their single-institution study. However, no PAOD was reported in a phase 3 study of nilotinib vs imatinib in Chinese patients with newly diagnosed CML in chronic phase (ENESTchina) [17]. In this study, 134 of 265 patients received nilotinib treatment. Taken together, the prevalence of PAOD varied considerably. And more studies are needed to reveal the exact incidence of PAOD.

PAOD is a systemic disease which is due to atherosclerosis leading to arterial stenosis or occlusion, usually in the lower limbs. Common risk factors for PAOD include age, male gender, diabetes mellitus, hypercholesterolemia, hypertension, nicotine consumption, family history and pre-existing vascular disease. As is shown in **Table 1**, most of the patients diagnosed with PAOD have risk factors, for example, over 60 years old. Similarly, age is the only risk factor in our patient. The exact relationship between nilotinib treatment and PAOD is still not clear. One potential mechanism may be binding to the discoidin domain receptor 1 (DDR1) [18, 19] which contributes to plaque formation in arteriosclerosis [20-22], though imatinib also interacts with DDR1. Nilotinib may take part in vascular events through other targets, for example, KIT and PDGFR, two receptor kinases regulating various vascular and perivascular cells [18, 23]. However, both DDR1 and KIT are targets of nilotinib, as well as imatinib. Additional targets may be recognized by nilotinib. Another potential mechanism may be

Table 1. Reported cases about PAOD

No	Reference	Sex	Age diagnosed with PAOD	Previous treatment	Dosage of nilotinib	Risk factors at baseline	Diagnosis	Time to onset (months)	Adverse events	Managementto PAOD	Treatment for CML
1	Aichberger et al. [7]	F	70	Imatinib	400 mg bid	Arterial hypertension	Doppler ultrasound	10	Muscle cramping, intermittent claudication	PTA, Stent implantation, bypass surgery	Dasatinib 100 mg qd
2	Aichberger et al. [7]	M	64	Interferon-alpha, imatinib	400 mg bid	Arterial hypertension, nicotine consumption	MRI scan	11	Intermittent claudication severe pain	Bypass surgery, thrombectomy, PTA, amputation	Nilotinib
3	Aichberger et al. [7]	F	68	Interferon-alpha, hydroxyurea, imatinib	400 mg bid	Arterial hypertension, asymptomatic coronary heart disease	MRI scan	39	Intermittent claudication	PTA, vascular surgery	Nilotinib
4	Giles et al. [10]	M	68	/	400 mg bid	Hypercholesterolemia, nicotine abuse, carotid artery stenosis, carotid endarterectomy	/	42	Intermittent claudication	None	
5	Giles et al. [10]	M	54	/	300 mg bid	Hyperlipidemia, nicotine abuse	/	22	Intermittent claudication, femoral arterial stenosis	Concomitant medication, hospitalization	/
6	Giles et al. [10]	M	51	/	300 mg bid	Diabetes mellitus, hyperlipidemia, smoking	/	26	Arteriosclerosis obliterans	Not reported	/
7	Giles et al. [10]	F	74	/	400 mg bid	Hypercholesterolemia	/	26	Recurrent femoral Arterial stenosis	Concomitant medication, hospitalization	/
8	Giles et al. [10]	M	41	/	400 mg bid	Hypertension, hypertriglyceridemia	/	23	Intermittent claudication	Not reported	/
9	Giles et al. [10]	F	61	/	300 mg bid	Hypertension, type2 diabetes mellitus, hyperlipidemia, angina pectoris, aortic aneurysm	/	21	Bilateral intermittent claudication	Hospitalization	/
10	Giles et al. [10]	M	65	/	300 mg bid	Not reported	/	14	Intermittent claudication	None	/
11	Mirault et al. [12]	M	56	Imatinib	400 mg bid	Overweight, smoking	ABI, Doppler ultrasound, CTA	12	Muscular pain, intermittent claudication	Drug, exercise training	Bosutinib
12	Tefferi et al. [13]	F	66	Interferon-alpha, hydroxyurea, imatinib	400 mg qd (400 mg bid, two months later)	None	Angiogram	49	Claudication	PTA, stent implantation, atherectomy, bypass surgery	Nilotinib 400 mg bid
13	Quintas-Cardama et al. [14]	F	>60	Interferon-alpha, ara-C, imatinib	400 mg qd (400 mg bid, 8 weeks' later)	None	CTA	50	Intermittent claudication	Atherectomy, angioplasties	Nilotinib 400 mg bid
14	Quintas-Cardama et al. [14]	F	>60	Interferon-alpha, hydroxyurea, imatinib, bortezomib, tipifarnib	400 mg qd	Diabetes mellitus	Angiogram	4	Pain	Bypass surgery, amputation	Not reported
15	Quintas-Cardama et al. [14]	F	>60	Imatinib	400 mg bid	None	Angiogram	36	Claudication	Not reported	Dasatinib
16	Maurizot et al. [15]	M	79	Interferon-alpha, imatinib, dasatinib	800 mg qd, 600 mg qd	Smoking	ABI, Doppler ultrasound, CTA	36	Intermittent Calf claudication	Stent implantation	Not reported

No., Number; F, Female; M, Male.

metabolic effect of nilotinib, such as elevation of glucose level, cholesterol and LDL-C. New studies in this area bringing valuable mechanistic information are needed.

Managements to such cases include lipid-lowering treatment, switch in favor of an alternative TKI, surgery and lifestyle modifications. Clinical improvements after discontinuation of nilotinib have already been reported [12, 15]. However, some patients needed repeated PTA and stent implantation, some even amputation. The patient with no hypertension and diabetes mellitus history received early onset hypercholesterolemia and was diagnosed with PAOD after sixteen months of nilotinib therapy. For such a patient without other pre-existing risk factors except age, this unexpected onset of PAOD implied an adverse reaction to nilotinib. Thus, nilotinib was discontinued. And stent implantation was performed. After drug withdrawal, TC fell to 155.61 mg/dl and LDL-C 83.5 mg/dl. At present, the patient continues to be in deep molecular response of her CML, but her life quality has been influenced significantly.

To prevent PAOD from developing, the first step is to select the TKIs individually. Both disease-related parameters, for example, BCR-ABL mutations and patient-related variables, such as comorbidities and over risk factors for adverse event development should be taken into account. Systematic coronary risk evaluation (SCORE) chart evaluation at disease baseline may be an effective tool which identifies patients exposed to high risk of atherosclerotic events during nilotinib therapy. Patients with multiple risk factors should avoid nilotinib if other TKIs are alternative [24]. Thirdly, a close cooperation between the patient, radiologists, hematologists and specialists in vascular medicine is of importance, especially for patients with pre-existing risk factors.

In conclusion, with the treatment of TKIs, patients in CML-CP can expect a nearly normal life expectancy [25]. We strongly recommend physicians pay close attention to TKIs selection and monitor PAOD in patients receiving nilotinib.

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Disclosure of conflict of interest

None.

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