Nilotinib-associated Multiple Silent Arterial Stenosis in a Patient with Chronic Myeloid Leukemia
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To the Editor,

Nilotinib, a second-generation tyrosine kinase inhibitor (TKI), is employed in the treatment of chronic myeloid leukemia (CML) [1]. However, previous studies have indicated an association between nilotinib and vascular adverse events, including peripheral arterial occlusive disease, cerebrovascular disease, and coronary artery disease [2,3]. We report a case of significant bilateral carotid artery stenoses without any neurologic symptom and, at the same time, left subclavian and celiac artery stenoses without any atherosclerotic or cardiovascular risk factors except age in a patient treated with nilotinib.

A 70-year-old non-smoking, non-diabetic Caucasian female with no history of vascular disease was diagnosed with CML in 2004. The patient was initially treated with imatinib 400 mg/day, but due to loss of cytogenetic response, it was switched to dasatinib in the 6th year. Then, the patient was complicated with recurrent pleural effusion despite appropriate management (dose reduction, diuretic along steroid interventions), and therapy was replaced with nilotinib 2x400 mg/day in 2016. The nilotinib dose was reduced to 2x300 mg due to bicytopenia after a few weeks of initiation. Although a major molecular response was not achieved, a cytogenetic remission was obtained with that dose, and the patient well tolerated it. Serum hemoglobin A1c (5.3%) and low-density lipoprotein cholesterol (92 mg/dL) were within the normal range during follow-up. In the 3rd year of nilotinib therapy, an inter-arm blood pressure difference (150/90 mmHg on the right arm and 110/70 mmHg on the left arm) was detected in a routine visit. A computed tomography angiogram (CTA) showed significant stenosis in the left subclavian artery, total occlusion in the celiac artery, and severe stenosis in the right internal carotid artery (ICA) [North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria: more than 50% stenosis] and stenosis in the left vertebral artery orifice (NASCET criteria: more than 50% stenosis) with a fibrofatty plaque in February 2019. Endovascular stent placements were performed into celiac and left subclavian arteries. Dual antiplatelet therapy (aspirin 100 mg/day and clopidogrel 75 mg/day) was initiated. A diffusion magnetic resonance imaging of the brain showed no ischemic pathology. The use of nilotinib was continued to control the CML. One year later, subsequent CTA showed progressive stenosis of the right ICA (NASCET criteria: 70%) and new stenosis of the left proximal ICA (NASCET criteria: less than 50%) within fibrofatty plaque (Figure 1). Although she still had no neurologic symptoms, nilotinib was replaced with bosutinib to reduce the risk of vascular disease progression. Bosutinib was started at a dose of 200 mg and increased to 500 mg/day within weeks for better tolerability. After a few months, the patient left our follow-up and has not been admitted to our center for a long time. Therefore, further information about the course of arterial stenosis after drug change could not be provided.

According to long-term evidence, arterial occlusive diseases are more strongly associated with nilotinib than other TKIs [2]. In most of the reported cases, the patients have baseline vascular risk factors, such as hypertension, coronary artery disease, smoking, diabetes mellitus, or dyslipidemia. They also dramatically presented with stroke, transient ischemic attack, or myocardial infarction [4-6]. In our case, significant bilateral ICA stenoses developed asymptomatically without major vascular risk factors except age. To the best of our knowledge, only one report described bilateral severe ICA stenoses without neurologic complications in a patient...
with ten years of nilotinib usage [7]. Our case also indicates multiple and radiologically severe but asymptomatic arterial stenoses may occur in nilotinib-using CML patients. A study of nilotinib-induced vasculopathy shows that nilotinib has pro-atherogenic and anti-angiogenic effects on endothelial cells by suppressing normal endothelial cell proliferation and migration [8]. Nevertheless, recent reports and our case show that future studies are needed to investigate causality between nilotinib and arterial stenotic disease except for atherogenic pathways. We suggest that patients using nilotinib must be under active clinical surveillance to detect possible arterial stenosis, even if they are asymptomatic. Routine cardiovascular examination and awareness of these complications are of vital importance in detecting nilotinib-associated vascular stenoses.

Ethics
Informed Consent: Written informed consent for publication of their details was obtained from the patient.

Authorship Contributions
Conception and design: M.T, R.I; analysis and interpretation of the data: M.T, R.I, O.E.C; drafting of the article: M.T; critical revision of the article for important intellectual content: O.E.C, I.C.H; final approval of the article: M.T, R.I, O.E.C, I.C.H.

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References
Figure 1. Computed tomography angiography. Arrows show right and left internal carotid artery stenosis (>50%) and endovascular stent in the left subclavian artery.