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LETTER TO THE EDITOR

Cerebrovascular events during nilotinib treatment

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To the Editor,

The *BCR/ABL* tyrosine kinase inhibitor nilotinib is used for the treatment of chronic myelogenous leukaemia (CML). Nilotinib is considered well tolerated with few side effects including elevated levels of pancreatic enzymes (lipase and amylase), hyperbilirubinaemia and hyperglycaemia.[1,2] However, several reports on the occurrence of accelerated atherosclerosis and peripheral arterial occlusive disease (PAOD) in patients treated with nilotinib were published recently.[3-7]

We report a patient who subsequently developed angina pectoris, caused by a left anterior descending (LAD) stenosis, intermittent claudication and three ischaemic cerebrovascular events in a relatively short timeframe after starting nilotinib.

CASE

The 69-year-old patient was diagnosed with breast cancer 20 years ago, for which she was curatively treated with surgery and radiotherapy. Fifteen years before presentation, she was diagnosed with CML, which was initially treated with hydroxycarbamide and interferon-alpha until the cytogenetic response decreased and imatinib (400 mg once daily) was started. Three years ago, a second primary breast tumour was diagnosed, with metastases in the pleura and lymph nodes, for which letrozole (2.5 mg once daily) was started. Last year, after 14 years of imatinib treatment, *BCR/ABL* positive cells were detected by PCR (>10% of all cells), after which imatinib was discontinued and nilotinib (400 mg twice daily) was started. Shortly hereafter, our patient developed hyperglycaemia, for which metformin was started. A few months after the initiation of nilotinib, the plasma concentration was determined to be 2061 mg/l, far above the minimum threshold set at our clinic (500 mg/l). Because of the very high plasma concentration, the dosage was reduced to 400 mg once daily. Seven months after commencing nilotinib treatment the patient suffered from angina pectoris due to a stenosis in the LAD. A drug-eluting coronary stent was inserted and acetylsalicylic acid, clopidogrel, amlodipine and bisoprolol were started. Despite antiplatelet therapy, the patient started to suffer from intermittent claudication. This year, 12 months after the start of nilotinib, the patient presented with partial aphasia due to an ischaemic cerebrovascular accident (CVA), for which simvastatin was added. Unfortunately, the patient had a second ischaemic CVA three months later, resulting in severe aphasia and wheelchair dependency. Acetylsalicylic acid was discontinued and acenocoumarol was started. Another three months later, despite adequate anticoagulation, the patient developed a third ischaemic CVA, resulting in epilepsy.

DISCUSSION

Our patient, without cardiovascular risk factors, developed angina pectoris, intermittent claudication and three ischaemic CVAs during her short course of treatment with nilotinib. Vascular events started soon after initiation of nilotinib, suggesting a causal relationship. We found several recent case reports in which PAOD[3-7] and an ischaemic CVA,[8] respectively, were diagnosed during nilotinib therapy. Also, the clinical development program of another TKI, ponatinib, was very recently halted due to a very high incidence of arterial thrombotic events (11.8%) leading to cerebrovascular events in 4.0% of the patients.[9] This might suggest a potential group effect for newer tyrosine kinase inhibitors. In light of these recently reported findings and because of the rapid aggravation of vascular events in our patient just after the start of nilotinib treatment, a role for nilotinib in the development of the ischaemic CVAs is possible.

Additionally, in our patient a high plasma concentration of nilotinib was measured. Efficacy of nilotinib is considered

to be related to the plasma concentration,[1] therefore a minimum threshold of 500 mg/l was set at our clinic. Two reports describe a positive correlation between plasma levels and side effects (pancreatic enzymes and hyperbilirubinaemia), suggesting there is an upper safety limit for the plasma concentration of nilotinib.[1,2] The association between high plasma concentrations of nilotinib and severe adverse events, such as a CVA, has not yet been investigated.

Our patient also used letrozole for breast cancer; a potential contribution of this drug to the vascular events cannot be excluded. Cardiovascular complications including CVAs can occur as a side effect of letrozole in 2-6% of the patients.[10] However, ischaemic events never occurred during our patient's prior treatment and started just after nilotinib was initiated.

The mechanisms by which nilotinib could cause these serious side effects are poorly understood. Potential roles of discoidin domain receptor 1 (DDR1), KIT and the platelet-derived growth factor receptor (PDGFR) are suggested;[6] however, evidence for the contribution of these kinase targets is lacking. We postulate the need for studies to elucidate the mechanism of action of nilotinib and possible other TKIs in the development of serious vascular events, to be able to understand and hopefully prevent future events.

Clinicians should be aware of the potential role of nilotinib in the development of vascular events and take this knowledge into account during clinical decision-making, for example in patients with pre-existing cardiovascular risk factors.

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