Case study

Myocardial infarction in a young patient with chronic myeloid leukemia after nilotinib use.

Abstract:

Nilotinib is an analog of imatinib increasingly used for the treatment of imatinib-resistant chronic myeloid leukemia. It has been considered a well-tolerated drug with little side effects. The most common adverse effects to nilotinib are skin rash, pruritus, headache, nausea, and fatigue. Nilotinib-induced vascular events are rare, including peripheral artery occlusive disease, Raynaud syndrome, cerebrovascular accidents. Myocardial infarction has rarely been reported. In this paper, we describe the case of a 37-year-old female who developed a severe myocardial infarction after nilotinib use.

There are two different vascular events reported with nilotinib: a progressively worsening of preexistent occluding vascular lesions and vasospastic events. In our patient, myocardial infarction seems to be secondary to severe coronary occlusive event.

Nilotinib might facilitate the development of vascular events in patients with preexisting risk factors. However several patients have been shown to experience such events in the absence of any cardiovascular risk factor.

The mechanism of nilotinib-induced myocardial infarction is still controversial. It is reported to be induced via mitochondrial damage, a negative effect of the substance on pre-existing atherosclerotic changes or ischaemic processes.

Our report emphasizes the importance of early detection and evaluation of cardiotoxicity in order to prevent fatal consequences of such an adverse event even in young patients.

Keywords: Philadelphia chromosome; Chronic myeloid leukemia; Nilotinib; Myocardial infarction.

Introduction:

The second generation BCR/ABL kinase inhibitor nilotinib is increasingly used for the treatment of imatinib-resistant chronic myeloid leukemia (CML). Nilotinib is an analog of imatinib with higher potency for BCR/ABL kinase inhibition and it is usually used in cases of resistance against imatinib [1]. It has been considered a well-tolerated drug with little side effects. The most common non-hematologic adverse effects to nilotinib are skin rash, pruritus, headache, nausea, and fatigue. Other metabolic adverse effects including elevated lipase and/or amylase levels and hyperglycaemia have been reported. Although rare, nilotinib-induced vascular events have also been reported and include peripheral artery occlusive disease, Raynaud syndrome, cerebrovascular accidents [2]. Myocardial infarction has rarely been reported. To our knowledge, this is the first report of a young patient developed a severe myocardial infarction (MI) after nilotinib use.

Case report:

A 37-year-old female patient without any personal or familial history of coronary heart disease or artery disease was diagnosed with CML since 2011. She was initially treated by imatinib but was switched to nilotinib one year later for resistance to imatinib. Three months after nilotinib initiation, the patient presented to the emergency department complaining about retrosternal oppression associated with anxiety lasting for approximately three hours. The patient was afebrile with blood pressure of 140/80 mmHg .The electrocardiogram (ECG) yielded an elevated ST segment across the entire front wall. Troponin level was markedly elevated (188 g/L) [Reference Range: 0.00 - 0.80 g/L]. Liver function test values, electrolytes and creatinine level were in normal ranges. Glycaemia and lipeamia were also within normal ranges. A coronary angiography showed a stenosis of the coronary artery. An angioplasty and stent implantation were performed.

According to the Naranjo probability scale, nilotinib-induced myocardial infarction was probable. The patient did not have any comorbidities or cardiac risk factors (such as diabetes, hypertension, or smoking). No other drugs consumption was found in this patient. No increase in the dosages of nilotinib was found.

The outcome was favorable. The patient was discharged home two weeks later. Nilotinib was withdrawn and the patient was switched on imatinib.

Discussion:

Nilotinib is highly effective for the treatment of patients with CML generally used after imatinib failure. It inhibits the activity of the tyrosine kinase BCR-ABL through competitive

inhibition of the binding site for ATP with a higher binding affinity and selectivity than imatinib and dasatinib [3]. Further receptors targeted by nilotinib include the receptor tyrosine kinase DDR1 (discoidin domain receptor 1), the NQO2 (nonkinase target NAD (P)H:quinone oxidoreductase), ARG, KIT, PDGFR). Although the inhibition of these new targets seems to play a role in the clinical activity and efficiency of nilotinib, it is still unknown their impact in the toxicity of nilotinib in CML [4].

Nilotinib is a generally well tolerated kinase inhibitor [5]. However, severe cases of nilotinib-induced vascular events have recently been reported. The exact incidence of these adverse effects is uncertain [6]. There are two different vascular events reported with nilotinib: a progressively worsening of preexistent occluding vascular lesions and vasospastic events. In our patient, myocardial infarction seems to be secondary to severe coronary occlusive event. Although the incidence of clinically significant vascular events is low, such complications may be fatal and may lead to sudden death. In fact, 5 cases of sudden death were reported in patients receiving nilotinib in a phase I/II study and were considered at least possibly related to nilotinib use (7). Pericardial and pleural effusion, pulmonary oedema, left ventricular dysfunction, atrial fibrillation as well as death due to MI, coronary artery disease, and/or heart failure have rarely been reported in clinical trials with nilotinib [8-9]. In a cohort of 233 patients with CML receiving nilotinib, 5 had severe artery occlusive disease. A 59 year-old patient experienced a recurrent Raynaud syndrome, a 50-year old female had a recurrent cerebrovascular accidents and three aged respectively of 61, 77 and 68-year old had peripheral artery occlusive disease including coronary artery disease and pulmonary emboli[6]. A case of fatal myocardial infarction has been reported in a 60-year old male patient [10].

To the best of our knowledge, we report the first case of myocardial infarction occurring in a young patient aged of 37-years old, without any cardiovascular risk factor. Our patient did not complain previously of chest pain, angina or any artery or coronary disease. Her metabolic and biological tests were within normal range even in the routine tests.

Nilotinib might facilitate the development of vascular events in patients with preexisting risk factors (such as diabetes or coronary or peripheral artery disease). However several patients, like our patient, have been shown to experience such events in the absence of any cardiovascular risk factor.

The mechanism of nilotinib-induced myocardial infarction is still controversial. It is reported to be induced via mitochondrial damage, a negative effect of the substance on pre-existing atherosclerotic changes or ischaemic processes, a key risk factor for vascular disease, and

second, nilotinib has been shown to produce coronary vasoconstriction in rabbit hearts as well as in isolated human coronary arteries [11]. Mitochondrial damage to cardiomyocytes seems to be mediated via the target receptor C-Abl [12]. Nilotinib also targets the receptor for cytokine stem cell factor KIT or CD117 receptor with tyrosine kinase activity located on haemangioblasts, which are precursors for haematopoietic stem cells and endothelial progenitor cells. KIT activation is, amongst others, supposed to be necessary for endothelial progenitor cells to migrate to injured tissue, e.g. after MI [13].

Conclusion:

This report highlights a severe adverse effect to nilotinib occuuring in a young patient. Cardiac monitoring of patients under nilotinib is essential. Investigations and coronary angiography in patients treated with nilotinib and presenting with angina pectoris-like symptoms should be considered. This report emphasizes the importance of early detection and evaluation of cardiotoxicity in order to prevent fatal consequences of such an adverse event.

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