International Journal of Medical and Pharmaceutical Case Reports
7(5): 1-5, 2016; Article no.IJMPCR.28909
ISSN: 2394-109X, NLM ID: 101648033

SCIENCEDOMAIN *international*
www.sciencedomain.org

Myocardial Infarction in a Young Patient with Chronic Myeloid Leukemia after Nilotinib Use

Neila Fathallah[1], Kmira Zahra[2*], Rania Bouneb[3], Mohamed Mahjoub[4], Wafa Guetari[2], Monia Zaier[2], Chaker Ben Salem[1] and Abderrahim Khelif[2]

[1]Department of Clinical Pharmacology, Faculty of Medicine of Sousse, Sousse University, Tunisia.
[2]Department of Hematology, University Hospital Farhat Hached, Sousse 4000, Tunisia.
[3]Department of Intensive Care, University Hospital Farhat Hached, Sousse 4000, Tunisia.
[4]Department of Hospital Hygiene Unit, University Hospital Farhat Hached, Sousse 4000, Tunisia.

Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/IJMPCR/2016/28909
Editor(s):
(1) Rakesh Kumar Tiwari, Chapman University School of Pharmacy, Chapman University Harry and Diane Rinker Health Sciences Campus, Irvine, CA, USA.
Reviewers:
(1) Burak Uz, Gazi University, Turkey.
(2) Moacir Marocolo Júnior, Federal University of Juiz de Fora, Brazil.
Complete Peer review History: http://www.sciencedomain.org/review-history/16150

Case Study

Received 12th August 2016
Accepted 3rd September 2016
Published 11th September 2016

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

**Corresponding author: E-mail: Kmira_zahra@yahoo.fr;*

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.

1. INTRODUCTION

The second generation BCR/ABL kinase inhibitor nilotinib is increasingly used for the treatment of imatinib-resistant chronic myeloid leukemia (CML) [1]. 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.

2. 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 (at 12 months, the BCR-ABL transcript level was 0.5% (>0.1%)). 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 dasatinib. At 3 months of dasatinib treatment, the BCR-ABL transcript level became 0.1%.

3. 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), the ARG, the KIT, and the 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 [6]. The exact incidence of these adverse effects is uncertain [7]. A recent study points out an occurrence more frequent than expected of vascular adverse events associated with nilotinib (> 30% vs. < 1% in summary of product characteristics), and particularly of vascular events of late onset in patients with no pre-existing risk factors [8].

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 [7-9]. In addition, nilotinib more than imatinib or dasatinib lead to blockade of HERG K+ channels which may explain the prolonged QT interval seen more frequently with nilotinib [9]. QT interval prolongation appears to be an off-target class III electrophysiologic effect, possibly related to the presence of a fluorine-based pharmacophore [10]. It was demonstrated in a recent study that when liposomes were injected prior to nilotinib, the liposomes decreased the effects on the QTc interval and therefore, the use of liposomal encapsulated QT-prolongation agents, or giving liposomes in combination with drugs, may decrease their cardiac liability [11]. Detailed information on nilotinib's cardiac safety profile is lacking. Whereas new electrocardiographic abnormalities were recorded in 20% of all patients and some of them developed severe or even life-threatening coronary artery disease, QT prolongation, changes in left ventricular ejection fraction, and clinical cardiac adverse events were uncommon in patients treated with nilotinib [12]. 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 [13-15]. 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 [7]. Several retrospective studies have described the clinical manifestation of peripheral artery occlusive disease in patients receiving nilotinib [16]. However, the characteristics of this adverse drug reaction are poorly described since its frequency is low [17]. A case of fatal myocardial infarction has been reported in a 60-year old male patient [18].

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 [19]. Mitochondrial damage to cardiomyocytes seems to be mediated via the target receptor C-Abl [20]. 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 [21].

4. CONCLUSION

This report highlights a severe adverse effect to nilotinib occuring in a young patient and emphasizes the importance of early detection and evaluation of cardiotoxicity in order to prevent fatal consequences of such an adverse event. Therefore, the data indicate the need to adhere to current practice guidelines for monitoring patients with CML who are receiving TKI therapy [22].

CONSENT

All authors declare that ‘written informed consent was obtained from the patient for publication of this paper and accompanying images.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Sattler M, Griffin JD. Molecular mechanisms of transformation by the BCRABL oncogene. Semin Hematol. 2003; 40:4–10.
2. Gambacorti-Passerini C, Antolini L, Mahon FX, et al. Multicenter independent assessment of outcomes in chronic myeloid leukemia patients treated with imatinib. J Natl Cancer Inst. 2011;103: 553-61.
3. Kantarjian H, Giles F, Wunderle L, et al. Nilotinib in imatinib-resistant CML and Philadelphia chromosome-positive all. N Engl J Med. 2006;354:2542–51.
4. Hantschel O, Rix U, Furga GS. Target spectrum of the BCR-ABL inhibitors imatinib, nilotinib and dasatinib. Leukemia & Lymphoma. 2008;49:615–619.
5. Kantarjian HM, Giles FJ, Bhalla KN, et al. Nilotinib is effective in patients with chronic myeloid leukemia in chronic phase after imatinib resistance or intolerance: 24-month follow-up results. Blood. 2011; 117:1141-5.
6. Dahlén T, Edgren G, Lambe M, et al. Cardiovascular events associated with use of tyrosine kinase inhibitors in chronic myeloid leukemia: A population-based cohort study. Ann Intern Med. 2016; 165(3):161-6.
7. Alfonso Quintás-Cardama, Hagop Kantarjian, Jorge Cortes. Nilotinib-associated vascular events. Clinical Lymphoma, Myeloma & Leukemia. 2012; 12:337-40.
8. Stève-Dumont M, Baldin B, Legros L, Thyss A, Re D, Rocher F, Ajmia F, Spreux A, Drici MD. Are nilotinib-associated vascular adverse events an under-estimated problem? Fundam Clin Pharmacol. 2015;29(2):204-8.
9. Atallah E. Nilotinib cardiac toxicity: Should we still be concerned? Leuk Res. 2011;35 (5):577-8.
10. Shah RR, Morganroth J, Shah DR. Cardiovascular safety of tyrosine kinase inhibitors: with a special focus on cardiac repolarisation (QT interval). Drug Saf. 2013;36(5):295-316.
11. Shopp GM, Helson L, Bouchard A, Salvail D, Majeed M. Liposomes ameliorate crizotinib- and nilotinib-induced inhibition of the cardiac IKr channel and QTc prolongation. Anticancer Res. 2014; 34(9):4733-40.
12. Kim TD, le Coutre P, Schwarz M, et al. Clinical cardiac safety profile of nilotinib. Haematologica. 2012;97(6):883-9.
13. Kantarjian H, Giles F, Wunderle L, et al. Nilotinib in imatinib-resistant CML and Philadelphia chromosome-positive ALL. N Engl J Med. 2006;354:2542–51.
14. Kantarjian HM, Giles F, Gattermann N, et al. Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is effective in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase following imatinib resistance and intolerance. Blood. 2007;110:3540–6.
15. Moslehi JJ, Deininger M. Tyrosine kinase inhibitor associated cardiovascular toxicity in chronic myeloid leukemia. J Clin Oncol. 2015;33(35):4210-8.
16. Kim TD, Rea D, Schwarz M, et al. Peripheral artery occlusive disease in chronic phase chronic myeloid leukemia patients treated with nilotinib or imatinib. Leukemia. 2013;27(6):1316-21.
17. Bondon-Guitton E, Combret S, Pérault-Pochat MC, et al. Cardiovascular risk profile of patients with peripheral arterial occlusive disease during nilotinib therapy. Target Oncol. 2016;11(4):549-52.
18. Le Coutre P, Ottmann OG, Giles F, et al. Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is active in patients with imatinib-resistant or -intolerant accelerated-phase chronic myelogenous leukemia. Blood. 2008;111:1834 –9.
19. Yolanda B, Wais T, Gratwohl A, et al. Fatal myocardial infarction during nilotinib treatment in a 60-year-old male patient. Acta Oncologica. 2010;49:523–525.
20. Hazarika M, Jiang X, Liu Q, et al. Tasigna for chronic and accelerated phase Philadelphia chromosome–positive chronic myelogenous leukemia resistant to or intolerant of imatinib. Clin Cancer Res. 2008;14:5325-31.

21. Ferri N, Carragher NO, Raines EW. Role of discoidin domain receptors 1 and 2 in human smooth muscle cell-mediated collagen remodeling: Potential implications in atherosclerosis and lymphangioleiomyomatosis. Am J Pathol 2004;164:1575-85.

22. García-Gutiérrez V, Jiménez-Velasco A, Gómez-Casares MT, et al. Cardiovascular management of patients with chronic myeloid leukemia from a multidisciplinary perspective and proposing action protocol by consensus meeting. Med Clin (Barc). 2016;146(12):561.e1-8.

Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/16150