Nilotinib-induced thromboembolic Events: report of a case and focus on the main mechanisms involved

**ABSTRACT:**

Nilotinib has significantly improved the treatment of chronic myeloid leukemia (CML) by offering enhanced efficacy and tolerability. However, studies have revealed a concerning link between nilotinib and an increased risk of thromboembolic events. This case report presents a forty-four-year-old male with CML treated with nilotinib, who developed dyslipidemia and multiple arterial occlusive events, including renal thrombosis and carotid artery atheroma. The potential mechanisms underlying nilotinib-induced thromboembolic events, such as endothelial cell dysfunction, altered lipid metabolism, and pro-inflammatory and prothrombotic effects. Various studies have demonstrated that nilotinib is associated with a higher incidence of vascular events compared to other tyrosine kinase inhibitors (TKIs). Identifying preexisting cardiovascular risks and implementing proactive measures, such as cardiovascular risk stratification and prophylactic anticoagulation, may aid in reducing the occurrence of thromboembolic events in high-risk patients treated with nilotinib. Understanding and addressing this associated risk are vital to improving patient safety and optimizing treatment outcomes in CML patients treated with nilotinib.

**KEYWORDS:** Nilotinib; thromboembolic Events; Outcome.

**INTRODUCTION:**

Nilotinib, a second-generation tyrosine kinase inhibitor (TKI), has revolutionized the treatment of chronic myeloid leukemia (CML). It offers improved efficacy and tolerability compared to its predecessor, imatinib. However, as with any treatment the use of nilotinib is not without potential risks. Recent studies and clinical reports have highlighted a concerning association between nilotinib therapy and an increased risk of thromboembolic events. This case presentation sheds light on the link between nilotinib and thromboembolic events by underlying the potential mechanisms and available evidence and it serves as a valuable resource for the care of CML patients treated with nilotinib. Understanding this associated risk can implement clinicians to take proactive measures to improve patient safety and provide optimal treatment outcomes.

**CASE REPORT:**

A forty-four-year-old male was diagnosed with chronic myeloid leukemia (CML) in May 2015. He had a medical history of a gastric ulcer in 2005 that was attributed to the intake of non-steroidal anti-inflammatory pills. The diagnosis of CML was made after observing gum bleeding and the presence of an eight-centimeter splenomegaly during the physical examination. The complete blood count revealed leukocytosis with a white blood cell count of 172,000 × 10^3/L. The blood smear showed an increased myeloid precursor cell count of 25%, along with 26% neutrophils, 9% lymphocytes, 8% eosinophils, 13% basophils, and 7% erythrocytes. In addition, normocytic anemia was present with a hemoglobin level of 10.2 g/dL (mean corpuscular volume [MCV] of 89 fL) and a platelet count of 714,000. The bone marrow showed hypercellularity with a predominance of granulopoietic cells. The diagnosis of CML was confirmed by the detection of Bcr-Abl rearrangement type b3a2 and the presence of the translocation t (9;22). The patient's prognostic Sokal score was 1.44, putting him at a high-risk category. Treatment with the tyrosine kinase inhibitor (TKI) imatinib 400 mg per day was initiated in July 2015. However, after nine months of treatment, the patient did not achieve a major molecular response (BCR-ABL at 1.5%). Consequently, a switch to a new generation TKI, nilotinib, was warranted, and it was started in July 2016. The patient attained a major molecular response after six months (February 2017), which has been maintained since then. In February 2018, the patient was diagnosed with hyperlipidemia, evidenced by an increase in triglyceride levels to 4.7 mmol/L and elevated cholesterol levels to 4.9 mmol/L (LDL=2.2 mmol/L, HDL=1 mmol/L). Treatment with fenofibrate 145 mg per day was initiated.

In March 2022, the patient developed high blood pressure, and a renal ultrasound revealed a significant stenosis (approximately 50%) in the right renal artery. As a result, the patient was prescribed bisoprolol, a beta-blocker. Subsequently, a Doppler ultrasound of the supra-aortic trunks performed in August 2022 showed the presence of a 3 mm atheroma in the right carotid bulb and increased systolic velocity in the right internal carotid artery. Furthermore, a computed tomography angiography of the supra-aortic trunks demonstrated an atheroma plaque measuring 3 mm in thickness and 11 mm in length in the right internal carotid artery, leading to a 50% endoluminal stenosis. In September 2022, the patient developed right renal thrombosis, and a renal scan revealed asymmetrical renal function, with 23% function in the right kidney and 75% function in the left kidney. Nilotinib treatment was discontinued in October 2022 when a pharmacovigilance survey implicated the new generation TKI in the development of multiple arterial occlusive events in the patient.

As of now, the patient has been off treatment for eight months while still maintaining a major molecular response.

**DISCUSSION:**

The instauration of targeted therapies with TKIs in CML improved survival outcomes and the prognosis in these patients, however these drugs are not completely safe and here we present the link between vascular events (VE) ~~with~~ and TKIs, mainly nilotinib, as the prevalence of VE was proved to be higher in patients treated with this treatment (1) and we summarize the potential mechanisms for developing these adverse events. Numerous studies reported VE occurrence for patients treated with TKI, the risk of developing these events depends on the type of drugs, treatment duration and of the cardiovascular risks and patient’s predisposition. A variety of mechanisms are described in literature. In 2016, a meta-analysis of clinical trials showed that CVE occurred in 5% of patients treated with second generation TKI compared with only 1% of patients treated with Imatinib (2).

Many retrospective studies demonstrated that nilotinib was associated with a higher incidence of VE than imatinib, this incidence varies across studies from 1% to 35% (2–11). In fact, nilotinib was associated with a statistically significant higher risk of peripheral artery occlusive diseases (PAOD) reaching 50 % of TKI induced arterial occlusive disease in some studies (5,12–14). Plus, nilotinib was associated with a higher risk of coronary arterial diseases (1,15).

The ENESTnd trial revealed a higher incidence of ischemic heart diseases, PAOD, and ischemic cerebral vascular events with nilotinib-patients than imatinib (6), this risk was related to longer exposure to nilotinib (16,17). Plus, these adverse events were dose related however lowering the nilotinib dose will surely impacts its efficacy (2,18).

While the exact mechanisms underlying the association between nilotinib and thromboembolic events are not fully understood, several hypotheses have been proposed. Nilotinib is anti-angiogenic that alters endothelial cell, suppresses their development and increases vascular stiffness (19–21) this dysfunction causes the loss of endothelial cells viability (22–24).

A study evaluated kidney and liver biopsies and found ~~a~~ vascular endothelial cell~~s~~ damage in nilotinib-treated patients that was similar to the damage to those who had a poor glycemic control (21). In the same study, an increase in thrombomodulin and coagulation factor VII staining was identified, explaining the occurrence of thromboembolic events with nilotinib (21).

The KIARO prospective study was developed to specify the pathogenesis of arterial occlusive events with TKI treated patients, this study showed that, when compared with imatinib and desatinib, nilotinib lowered IL-10 levels overtime and therefore creating a pro inflammatory environment. Plus, a significant increase of oxidized LDL levels was found with nilotinib, creating a dysfunction in lipids metabolism (1,14,25,26), this same mechanism was also proved in the ENESTnt trial (16). Nilotinib increases the expression of IL-1 inflammatory cytokine as well which leads to hypertension and in atherosclerosis development (27).

With nilotinib, the development of atherosclerosis and atherothrombotic complications involves a close interaction between inflammatory and oxidative mechanisms which induces endothelial activation. This activation leads to the expression of adhesion molecules that promote a pro-atherogenic environment and activates macrophages hence increasing the expression of LOX-1. LOX-1, in turn, contributes to the accumulation of oxidized LDL (oxLDL) within the intima, which fuels the growth of atherosclerotic plaques. Furthermore, LOX-1 enhances the transcription and activity of proteases, thereby increasing the probability of plaque instability and rupture. (19,28–30)

In fact, nilotinib induces a quick rise in LDL and HDL cholesterol levels within three-months of treatment instauration and management of this type of dyslipidemia is well responsive to statins (31).

This mechanism gains further importance when considering recent intervention trials. These studies have shown that combining specific anti-inflammatory therapy with statin treatment leads to a reduction in clinical events.

Blood samples obtained from CML patients treated with nilotinib showed notable changes in several aspects. In laboratory conditions, there was an observed increase in platelet adhesion. In addition, patients exhibited elevated levels of plasma soluble P- and E-selectin, sICAM-1, sVCAM-1, TNF-alpha, and IL-6, which are markers associated with platelet and endothelial activation. Furthermore, in vivo experiments revealed increased levels of endogenous thrombin potential (ETP), indicating enhanced clotting potential. These findings collectively indicate that nilotinib has the ability to augment platelet and endothelial activation, as well as contribute to the formation of platelet thrombus both in laboratory conditions and within the patients (32–34).

Moreover, second generation TKI alters endothelial barrier integrity, leading to increased permeability and, consequently, a higher possibility for atherosclerosis development (35).

In more recent studies demonstrated that nilotinib creates a prothrombotic state by increasing the protease activated receptor PAR1 altering platelet’s activation secretion and adhesion (36). And when compared to other TKIs, high-concentration nilotinib showed a distinct enhancement in adenosine diphosphate, collagen, and collagen-related peptide (CRP)-induced platelet aggregation, explaining the increase of thrombotic events with nilotinib (19,27,36).

Recognizing risk factors associated with increased thromboembolic risk can aid to identify patients who may require closer monitoring or preventive measures.

Several studies focused on the link between preexisting CV risks and thromboembolic events which indeed emphasized the higher incidence of these events for patients with preexisting cardiovascular risks (1,2,12,15).

The European society of cardiology set up a Cardiovascular risk stratification SCORE (Systematic Coronary Risk Evaluation) to distinguish patients with higher risks of developing CVE specially for patients treated with nilotinib and ponatinib (7,37,38). Besides, a consideration for preexisting cardiovascular risks is necessary for the choice of TKI according to the latest recommendations of the ELN (39).

Some studies discussed the introduction of prophylactic anticoagulation treatment considering the strong association of new generation TKI and vascular events, specially for patients with higher cardiovascular risk (30,40). Further prospective studies should be led to identify guidelines for managing these high-risk patients and prevent thromboembolic events (2,41).

This closer speculation on the side effects of new generation TKI is not by far diminishing their value but is guiding practicians to be mindful when these treatments are introduced, not to mention their important role of improving overall survival and maintaining a faster and deeper molecular response for treating CML.

In summary, the association between nilotinib and thromboembolic events in patients with CML necessitates ongoing research and vigilant clinical consideration. Adverse clinical events should be taken in consideration with diligent close monitoring.

**Ethical Approval**

Informed consent has been obtained from the patient.

**Data availability statement**

The data set of the current study is available from the corresponding author upon motivated request.

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