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Case report

Second generation tyrosine kinase inhibitor therapy associated with significant carotid stenosis onset: A clinical case report and literature review

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Abstract. *Introduction:* Tyrosine kinase inhibitors (TKI) are employed in the treatment of chronic myeloid leukemia (CML). Concerns about cardiovascular side effects have evolved, especially in patients with cardiovascular risk factors. Recommendations published in 2020 stress the need for preventative, biannual peripheral arterial evaluations, but there is no mention of carotid artery surveillance. We describe significant carotid artery stenosis onset in a young patient with CML treated with TKI therapy, without baseline cardiovascular risk factors. *Case:* A 55-year-old man was diagnosed with CML in 2016 and was prescribed Nilotinib 300 mg twice daily. Anamnesis reported identified a positive family history for cardiovascular disease only. Supra-aortic vessels Doppler ultrasound (DUS) in 2021 confirmed insignificant left internal carotid artery (ICA) stenosis, which increased to ICA stenosis with hemodynamic consequences, observed in 2023. A computed tomography angiography (CTA) confirmed stenotic progression, estimated between 80-85% over a 2-year period. A multidisciplinary team suggested revascularization with carotid endarterectomy (CEA) performed under general anesthesia with instrumental cerebral intraoperative monitoring. The patient had an uneventful post-procedural course and was discharged post-operative day 2. Post-operative 30-day DUS confirmed ongoing technical success. *Conclusion:* Our case report emphasizes the need for clinician awareness of a potential risk of carotid artery disease onset in patients undergoing Nilotinib therapy, independently of age and baseline cardiovascular risk factors. (www.actabiomedica.it)

Key words: carotid stenosis, chronic myeloid leukaemia, tyrosine kinase inhibitors

Introduction

Chronic myeloid leukemia (CML) is a clonal disease of pluripotent stem cells and is related to the fusion of the BCR Breakpoint Cluster Region (BCR) and Abelson murine Leukemia virus (ABL) genes, resulting in the BCR-ABL oncoprotein. Deregulated Tyrosine Kinase (TK) activity of the BCR-ABL oncoprotein is implicated in the pathogenesis of CML (1,2).

Highly reliable and effective drugs for the treatment of CML TK include TK inhibitors (TKI), that specifically inhibit BCR-ABL (3). However, some studies have described toxic cardiovascular effects caused by second generation TKI Nilotinib, Dasatinib, and Ponatinib. These off-target side effects are related to the involvement of a specific secondary drug target (4-6). Additionally, the onset of severe peripheral artery disease has also been published in patients who were being treated with Nilotinib therapy or who had switched from another TKI to Nilotinib (1,7).

It is well reported that these serious side effects are commonly expressed in patients with cardiovascular

disease risk factors, such as smoking, hypertension, diabetes, obesity or advanced age (8). It is currently unclear if off-target side effects of Nilotinib therapy should include vascular effects and, which subgroups of patients receiving TKI therapy are at risk.

We report a case of a young adult patient without significant cardiovascular disease risk factors who developed an asymptomatic carotid stenosis whilst receiving TKI therapy and was treated with surgical carotid revascularization. Informed consent was obtained from the patient for publication of this case report and accompanying images.

Case Report

A 55-year-old male was diagnosed in March 2016 with CML (co-expression of p210 and p190 proteins) and was prescribed Nilotinib (300 mg twice a day) as a first-line treatment. Patient anamnesis was negative for smoking history and other cardiovascular risk factors, with the exception of a positive family history for cardiovascular disease.

An asymptomatic patent foramen ovale was diagnosed two years later (2018) and the patient was prescribed an adjunctive, single antiplatelet therapy (Aspirin 100mg daily). Due to documented positive incidence of right-to-left shunt during the Valsalva maneuver by transthoracic echocardiography in 2020, therapy was modified to a Dual Antiplatelet Therapy (DAPT): Aspirin 100mg and Clopidogrel 75mg daily. There was no evidence of any increase in lipid markers, hypertension or weight gain at regular, biannual clinical surveillance. However, with the suspicion of potential cardiovascular side effects from Nilotinib therapy and family history of cardiovascular disease, a Doppler ultrasound (DUS) of the supra-aortic vessels was performed. A bilateral carotid intima-media thickness, 1.3 mm for the left and 1.1 mm for the right one, without atherosclerotic plaque was revealed.

Annual instrumental surveillance with DUS was recommended, and in May 2021 a non-significant left internal carotid artery (ICA) stenosis was observed; DUS revealed a 30-35% stenosis of hypoechoic plaque, defined according to North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria (9), without any hemodynamic effect. Examination was again performed in March 2022 and an increase in the left ICA stenosis to 50% with hemodynamic consequences (270 cm/sec peak systolic velocity) was revealed. Subsequent examination in February 2023 revealed a significant increase in left ICA stenosis to 70-75%, with a peak systolic velocity of 290 cm/sec. To assess and characterize the stenotic grade, the patient underwent a computed tomography angiography (CTA). CTA reported a 80-85% stenosis of the first segment of left ICA (Figure 1) along with a negative computed tomography (CT) scan.

A multidisciplinary committee (including vascular surgeons and hematologists) decided upon elective surgical carotid revascularization treatment with carotid endarterectomy (CEA). The patient was advised to change TKI therapy to Bosutinib (300 mg once a day) one month before surgery. CEA was performed in April 2023. General anesthesia with instrumental cerebral intraoperative monitoring using carotid artery stump pressure and near infrared spectroscopy was performed. Intra-procedural administration of unfractionated heparin (UFH) 5000 IU/mL was administered at the time of cross-clamping. CEA was performed using eversion surgical technique with reconnection of ICA to the carotid bulb with continuous polypropylene sutures. During CEA, plaque biopsy specimens were collected for histological examination (Figure 2). A histological referral was not made available due to processing, technical problems. No Protamine was administered for heparin reversal. Technical success was confirmed by intra-operative DUS.

The patient had an uneventful post-procedural course and was discharged two days post-operative, with indications to continue pre-operative DAPT.

A 2-month post-operative DUS confirmed technical success (ICA patency) without any evidence of restenosis.

Discussion

Compared to other chemotherapeutics, TKI therapy for CML reports fewer side effects, making TKI the standard of care for CML. However, second generation TKI have been associated with cardiovascular

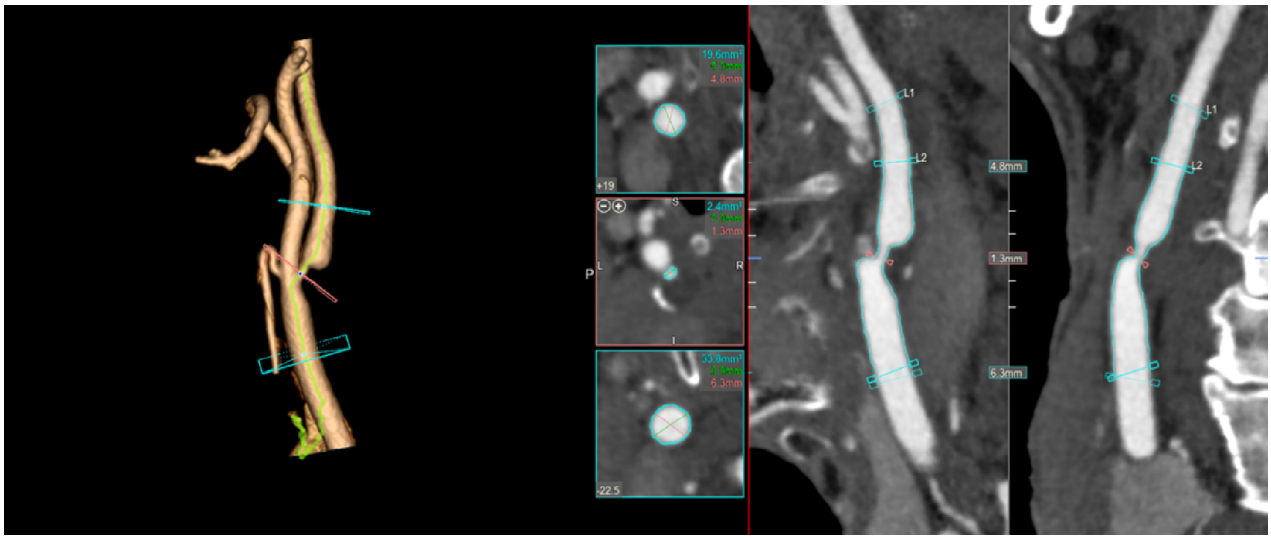

Figure 1. Pre-operative cerebrovascular assessment. A computed tomography angiography of carotid arteries and vertebrobasilar system was performed demonstrating the presence of an 80-85% carotid stenosis of the first segment of left internal carotid artery.

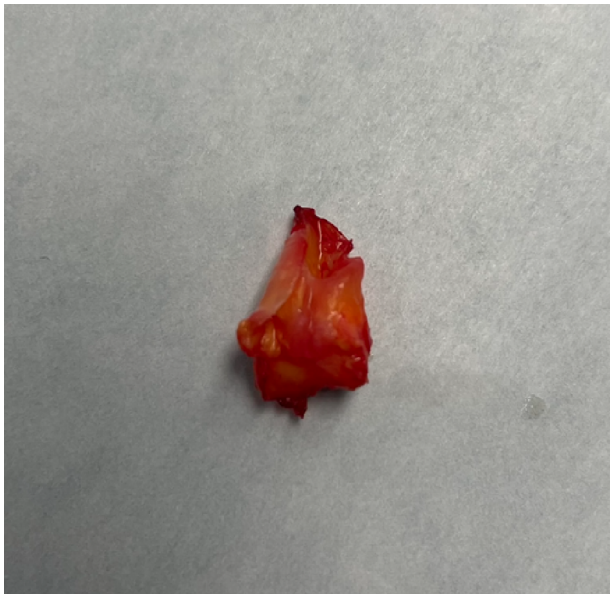

Figure 2. Intra-operative picture. Carotid plaque biopsy specimens were collected during CEA and a thicker layer of fibrous tissue was observed.

toxic effects, observed in elderly patients with cardiovascular risk factors (4-6). Little is known regarding early onset of cardiovascular side effects from TKI in young patients without significant cardiovascular risk factors. Specifically, their association with the development of carotid artery disease (CAD) is unknown.

TK belong to a distinct group of enzymes that are involved in both cellular signal transduction and regulating activities, such as cell division. TK are often expressed in different tissues and therefore represent the target of TKI. This pharmacological class specifically inhibits oncoprotein BCR-ABL, which represents the main target. Some reports have described an association between second generation TKI (Nilotinib, Dasatinib, and Ponatinib) with cardiovascular adverse effects, due to secondary target TK inhibition. This secondary target is represented by Discoidin Domain Receptor 1 (DDR1), responsible for the activation of cellular processes such as adhesion, migration, differentiation or cytokine production in response to extracellular collagen binding. DDR1 seems specifically inhibited by Nilotinib, Ponatinib, and to a lesser extent Dasatinib, but not by other TKIs (6,10,11). In a prospective study by Katgi et al. carotid artery endothelial cell viability was reported to decrease with increasing doses of Nilotinib. The authors suggested that "endothelial regeneration" may be impaired and more prone to thrombosis (12). This unique prothrombotic effect of Nilotinib has been confirmed. Alhawiti et al (13), described the exclusive responsibility of Nilotinib in enhancing thrombus growth.

Current evidence regarding CAD association in CML patients treated with Nilotinib is insufficient for

hypothesis-generation. There are few reports of possible early onset of TKI cardiovascular side effects in young patients without significant cardiovascular risk factors, and among those published, clarification is often lacking (4,5,14). Gugliotta et al. performed a long-term phase 2 trial, including 73 patients receiving Nilotinib. The authors documented an overall incidence of cardiovascular events of 15%, most frequently observed in elderly patients with baseline cardiac risk factors at a time range of between 24–76 months of therapy. In only two cases, carotid arteries were involved (5). Hersant et al. described a single case of a 61-year-old male with CML who developed carotid stenosis after 44 months of TKI Nilotinib therapy, treated with CEA (14). During the pre-surgical surveillance period, the patient developed hypertension, gain weight and developed dyslipidemia. In this case the authors could not exclude that these cardiovascular risk factors contributed to the development of carotid artery disease.

In our case report, the patient was relatively young without any cardiovascular risk factors, except for a positive family history for cardiovascular disease. The patient was treated with Nilotinib for almost seven years, with carotid disease onset following 62 months of therapy. The carotid disease onset presented by our case report is in line with previous experiences in literature (5,14). By contrast, in our experience only two years have passed between carotid stenosis detection in 2021 and CEA in 2023, almost half of the time reported by Hersant et al., suggesting a more aggressive carotid artery involvement (14).

Our case report is intended to increase awareness regarding the possible pathogenetic role of Nilotinib in the rapid development of CAD in young patients without significant cardiovascular risk factors.

The recommendations for treating CML published in 2020 by the European LeukemiaNet network outlined that history of either coronary heart disease, cerebrovascular accidents, or peripheral arterio-occlusive disease are strong contraindications to Nilotinib as a first-line therapy (15). Recommended preventive evaluation includes the assessment of asymptomatic peripheral arterial involvement in elderly patients or patients with cardiovascular risk factors: ankle-brachial index measurements or duplex ultrasonography before initiating therapy and every 6–12 months (15,16).

However, the current recommendations do not mention potential carotid disease involvement (11,15,16). To better characterize the potential evolution of CAD in patients with CML treated with TKIs, long-term, prospective studies of cardiovascular adverse effects, including carotid artery surveillance, are required.

Conclusions

Currently, there is no consensus regarding optimal carotid disease management in patients with CML treated with Nilotinib. Our report emphasizes the importance of clinician awareness of a potential correlation between Nilotinib and CAD onset, even in relatively young patients without significant cardiovascular risk factors.

Ethic Committee: Informed consent was obtained from the patient for publication of this case report and accompanying images.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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