

Progressive thrombosis of cervical and intracranial arteries related to Ponatinib treatment for Chronic Myeloid Leukemia

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Ponatinib is a third-generation Tyrosine Kinase Inhibitor (TKI), approved as first-line treatment for Chronic Myeloid Leukaemia (CML) chronic phase.

Here we describe a CML patient with a history of subsequent TIAs and an ischemic stroke during Ponatinib treatment. Patient was admitted for a 3-day history of sudden onset left hemiparesis due to an acute ischemic stroke. MRI showed bilaterally the almost total absence of signal in the intracranial tract of anterior circulation and low signal of cerebral posterior circulation. Digital Subtraction Angiography showed multiple steno-occlusions of both anterior and posterior circulation large vessels.

The association between cerebrovascular events and TKIs of second and third-generation has been widely described. So Ponatinib was stopped. To our knowledge, this is the first case of multiple ischemic strokes and recurrent TIAs during treatment with Ponatinib, pointing out the importance of accurate quantification of cardiovascular risk before starting Ponatinib.

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Chronic Myeloid Leukaemia (CML) accounts for 15–20% of leukaemia in the Western World.¹ In most patients it is associated with the BCR-ABL fusion gene.² CML has been treated for a long time with interferon-alpha and cytarabine, until in 2002 the Tyrosine Kinase Inhibitor (TKI) Imatinib was approved as first-line treatment for CML chronic phase.³ Imatinib dramatically improved the prognosis of CML patients with a 10 years-survival rate of 83%.⁴ The high rate of resistance to first generation TKIs (25–30% of patients) led to second and then third-generations TKIs. Ponatinib, a third generation TKI, can inhibit BCR-ABL with the gatekeeper T315I

kinase domain mutation, known to be the cause for 20% of resistant or relapsed CML cases, overcoming specific resistance to second-generation TKIs.^{5, 6} Despite its great specificity, Ponatinib showed an increased rate of cardiovascular, cerebrovascular and peripheral arteriosus ischemic events, in particular in patients with pre-existent cardiovascular risk factors.^{7–10}

Here we describe a 62 year-old male patient with CML treated with Ponatinib 15 mg. His past medical history was remarkable for hypertension, treated with ramipril 10 mg and furosemide 25 mg daily. Moreover he reported previous subsequent TIAs and an ischemic stroke during Ponatinib treatment in in 2018 (three months after Ponatinib initiation). At that time, stroke work up showed normal glucose, creatinine, lipid profile and coagulation tests. MRI demonstrated an ischemic lesion in deep fronto-basal right area; extra and intracranial CT angiography excluded occlusive or subocclusive stenosis of large vessels [Fig. 1A], so ponatinib treatment was not stopped and aspirin was initiated at the dose of 300 mg and continued at a dose of 100 mg. The patient was admitted to our hospital 7 months later for a 3-day history of sudden onset left hemiparesis (NIHSS 4). Lab tests were within normal

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Received May 4, 2020; revision received June 18, 2020; accepted June 21, 2020.

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1052-3057/\$ - see front matter

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<https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.105085>

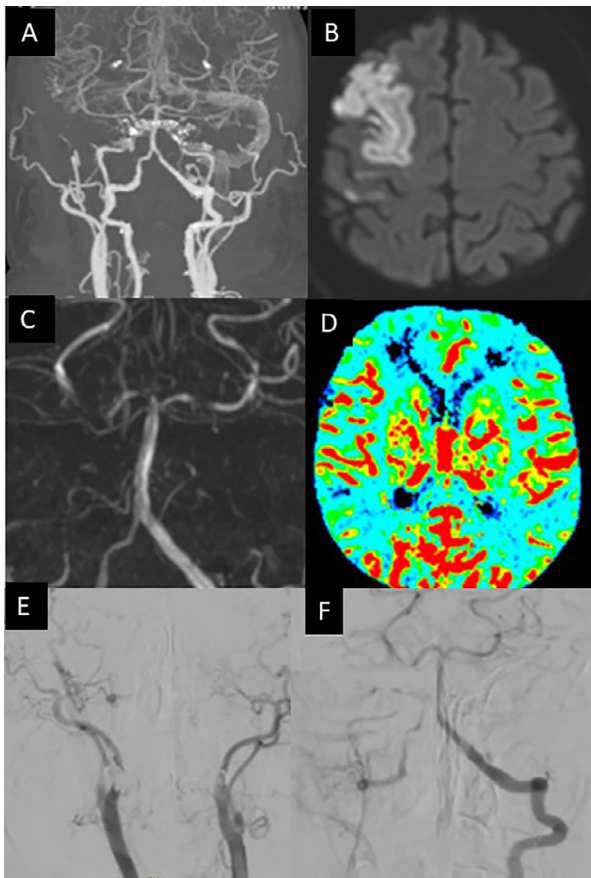


Fig. 1. (A) CT angiography performed in 2018 showing no occlusive or subocclusive stenosis of large vessels. (B) Brain MRI at the time of presentation, Diffusion weighted image (DWI) showing an acute ischemic lesion in right fronto-basal area. (C) MRI Angiography showing bilaterally the almost total absence of signal in the intracranial vessels of anterior circulation and low signal of basilar artery, superior cerebellar arteries and cerebral posterior arteries. (D) Perfusion CT scan showing normal cerebral blood flow values. (E-F) Digital Subtraction Angiography (DSA) at the time of presentation showing a critical stenosis of the cavernous tract of right internal carotid artery (ICA) with partial contribution to middle cerebral artery vascularization from ipsilateral ophthalmic artery (OA); on the left side, occlusion of ICA with partial compensation from contralateral OA; preocclusive stenosis of the right vertebral artery with multiple subsequent stenosis.

range, including coagulation tests. Brain MRI showed a new acute ischemic lesion in right fronto-basal area [Fig. 1B]. Angio-MRI showed bilaterally the almost total absence of signal in the intracranial tract of anterior circulation and low signal of cerebral posterior circulation [Fig. 1C]. The patient was investigated for possible extra-intracranial bypass with a dynamic CT Perfusion Imaging with Acetazolamide Challenge¹¹ that showed a normal cerebral blood flow (CBF) [Fig. 1C] and a 20% CBF increase after Acetazolamide challenge, suggesting that autoregulation was still not exhausted, probably due to slow progression of thrombosis. The progressive course of cervical and intracranial arteries thrombosis is well documented by Digital Subtraction Angiography (DSA) showing multiple steno-occlusions of large vessels of both anterior and posterior circulation [Fig. E and F].

Due to two ischemic strokes and multiple TIAs, Ponatinib was stopped. In consideration of medical priority represented by CML, surgical treatment was postponed and double antiplatelet therapy was started, with no other major cerebrovascular events or TIAs in the following year.

The association between cerebrovascular events and TKIs of second and third-generation has been widely described. Regarding Ponatinib the proposed mechanism is the antagonist activity on VEGF-R, thus determining endothelial dysfunction and predisposing to thromboembolic events.⁹

For these reasons, it was removed from the market in October 2013 because of its increase in cardiovascular risk¹² and was put back on the market for a narrowed patient population, including adults with T315I-positive CML¹³ with a big warning box for vascular events and liver toxicity, particularly in patients with pre-existent cardiovascular risk factors. To our knowledge, this is the first case described of multiple ischemic strokes and recurrent TIAs during treatment with Ponatinib. The increased awareness of dose-dependent cardiovascular side effects of Ponatinib is attested by declining of incidence of adverse events as described in recent case series.¹⁰ This points out the importance of an accurate quantification of cardiovascular risk before starting the treatment and the eventual strategy of reducing the starting dose after achieving clinical or molecular response.⁶

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