

LETTER TO THE EDITOR

Frequency of Cardiovascular Events During Ponatinib Therapy: A Single Centre Experience

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ABSTRACT

Over the past 15 years tyrosine kinase inhibitors (TKIs) have become the standard in treating chronic myeloid leukemia (CML), leading to high rates of remission. Nonetheless a small group of patients shows primary or acquired resistance to established TKIs. The third generation TKI ponatinib was found to be effective in patients with resistance to earlier generation drugs but also to promote cardiovascular events, i.e. arterial thrombosis. Here we present data from a relatively large cohort of patients treated with ponatinib at our centre. We observed cardiovascular abnormalities in 14 of 27 patients during treatment including at least five acute events, supporting previously reported findings.

Key words: CML; Chronic phase; TKI; Ponatinib

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The current treatment of BCR-ABL positive chronic myeloid leukemia (CML) in chronic phase is primarily based on targeted therapies involving tyrosine kinase inhibitors (TKIs). Tyrosine kinase inhibitors, such as the first generation drug imatinib, directly affect the oncogenic origin of the disease by inhibiting the BCR-ABL kinase activity^[1]. The second generation drugs nilotinib and dasatinib were found to have even higher rates of efficacy with deeper molecular remissions in the majority of patients^[2,3]. Nevertheless, there still is a group of patients that eventually develops resistance to approved first line TKIs, a main reason being additional mutations of the kinase domain, such as T315I^[4]. As a pan-BCR-ABL inhibitor the third generation drug ponatinib was found to overcome most of these mutations at a starting dose of 45 mg per day showing complete cytogenetic response rates between 39% and 46% in heavily pre-treated chronic phase patients^[5]. Interestingly, in a significant group of patients different types of arterial thrombosis including fatal outcome were observed with this drug^[6,7]. In this regard we examined 27 consecutive patients receiving ponatinib at our centre between March 2011 and December 2013. We retrospectively analysed clinical and paraclinical data of these patients using the CML database at our centre.

Of these 27 patients 21 (78%) were enrolled in ongoing clinical trials and six patients (22%) received the drug as compassionate use due to resistance or minor response to previous generation TKIs. Median age at the start of ponatinib was 57.5 (range 26-82) years while the median time from CML diagnosis to the initiation of the drug was 80 (range 0-249) months. All patients were in chronic phase of CML. Regarding cardiovascular risk factors, 15 patients (55.6%) showed pre-existing arterial hypertension, two (7.4%) had peripheral arterial occlusive disease (PAOD), four (14.8%) had diabetes, two (7.4%) suffered from coronary heart disease and seven patients (25.9%) had a history of nicotine abuse while 13 (48.1%) were male. In seven cases (25.9%) neither cardiovascular risk factors nor comorbidities were present. In total 21 (77.8%) patients were exposed to nilotinib prior to ponatinib, that already has been shown to contribute to cardiovascular diseases such as PAOD^[8]. In the majority of cases (25 of 27 patients, 92.6%) the initial dose of ponatinib was

45mg per day while two patients (7.4%) received 30mg. The median observation time was 20.5 (range 1-32) months. Most common side effects were exanthema (16 patients, 59.3%) and hematotoxicity (12 patients, 44.4%).

While on therapy with ponatinib six patients out of 27 (22.2%) showed a cardiovascular event and eight patients (29.6%) developed a newly diagnosed cardiovascular disease. Regarding acute events, stroke occurred in three cases (11.1%) whereas acute myocardial infarction (AMI), pulmonary embolism and acral amputation were observed in one case (3.7%) each. The patient with pulmonary embolism transformed to blast crisis later and died. In all other cases the patients survived and ponatinib was not stopped but changed in dosage in four of five remaining cases, once from 45 mg to 30 mg and three times from 45 mg to 15 mg per day. In five of these six patients (83.3%) cardiovascular risk factors were found, four (66.7%) had previously been treated with nilotinib. Regarding newly diagnosed cardiovascular diseases, four patients (14.8%) presented with formerly unknown low-grade PAOD revealed by ankle-brachial-index (ABI), three (11.1%) were diagnosed with arterial hypertension and in one case (3.7%) diabetes was newly diagnosed while on ponatinib. In seven of these eight cases (87.5%) both cardiovascular risk factors and a history of nilotinib exposure were found prior to ponatinib.

In total we found cardiovascular abnormalities in 14 of 27 patients (51.8%) including at least five acute events (AMI, stroke, pulmonary embolism) that are directly based on arterial thrombosis, which confirms the previously reported increase in cardiovascular disease and supports the need for management concepts in case of TKI driven atherosclerotic events.

Though most of our patients had cardiovascular risk factors before the introduction of ponatinib, the extend of these factors matches the characteristics of a standard Western society of the same median age, which however shows lower rates of cardiovascular events^[9]. Given its unique profile, especially its activity against many BCR-ABL mutations including T315I, ponatinib should definitely not be suspended completely, being the only therapeutic option for patients resistant or intolerant to first and second generation TKIs. Nevertheless, it should only be administered to patients resistant to earlier generation TKIs using the smallest dose possible. The current product information already advise profound examination of the cardiovascular status both before administration of ponatinib and during treatment as well as active management of possible comorbidities^[10]. Additionally, exposed patients should be informed about the side effects of the drug and asked to minimise other cardiovascular risk factors as well as encouraged to report any subjective change to their health status. Furthermore, prospective data must be collected in order to be able to evaluate the real impact of ponatinib on cardiovascular events and diseases especially considering the currently used lower doses. The future aim should be to identify a drug as potent as ponatinib with a better cardiovascular risk profile.

CONFLICT OF INTEREST

There are no conflicts of interest.

Table 1 Development of cardiovascular markers, *n* = 27 patients.

Newly diagnosed cardiovascular marker	Number of patients (%)	Median time to occurrence (months)
PAOD	4 (14.81%)	5,5 (range 2-9)
Hypertension	3 (11.11%)	1 (range 1-2)
Diabetes	1 (3.70%)	16
Myocardial infarction	1 (3.70%)	9
Stroke	3 (11.11%)	15 (range 10-23)
Pulmonary embolism	1 (3.70%)	4
Acral amputation	1 (3.70%)	8
Pathological cardiac ultrasound	1 (3.70%)	3

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