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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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 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[36]. 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[37]. 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.

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### Table 1: Development of cardiovascular markers, n = 27 patients

<table>
<thead>
<tr>
<th>Newly diagnosed cardiovascular marker</th>
<th>Number of patients (%)</th>
<th>Median time to occurrence (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAOD</td>
<td>4 (14.8%)</td>
<td>5.5 (range 2-9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3 (11.1%)</td>
<td>1 (range 1-2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1 (3.70%)</td>
<td>16</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1 (3.70%)</td>
<td>9</td>
</tr>
<tr>
<td>Stroke</td>
<td>3 (11.1%)</td>
<td>15 (range 10-23)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1 (3.70%)</td>
<td>4</td>
</tr>
<tr>
<td>Acral amputation</td>
<td>1 (3.70%)</td>
<td>8</td>
</tr>
<tr>
<td>Pathological cardiac ultrasound</td>
<td>1 (3.70%)</td>
<td>3</td>
</tr>
</tbody>
</table>

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### REFERENCES

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