Unintentional overdosing of ponatinib in a patient with chronic phase chronic myeloid leukaemia

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Ponatinib is a potent third generation tyrosine kinase inhibitor (TKI) and is the only TKI with activity against the gate keeper T315I mutant*BCR-ABL1* which confers resistance to all other approved BCR-ABL

TKIs [1]. With this efficacy comes an unfavourable toxicity profile, which necessitated the FDA to temporarily suspend its use given the increased incidence of vascular occlusive events[2]. Toxicities secondary to ponatinib were shown to be dose related [3] and hence unintentional overdoses are expected to be complicated by proportionally severe toxicities. Apart from incidences of overdosing highlighted in the summary of product characteristics [4], and to the best of our knowledge, overdosing in the real life practice was not previously reported. Herein, we report an incidence of unintentional ponatinib overdosing in real life and summarize the adverse events the patient encountered.

A 48 years-old black African man with chronic myeloid leukaemia in chronic phase under regular outpatient follow up in our haematology department was prescribed ponatinib 45 mg daily as 4thline for treatment failure. He presented to our day care unit with headache and skin desquamation and was found to have been receiving double the dose (90 mg daily) unintentionally for 26 days. The headache was severe (graded as 10/10 by the patient), was periorbital initially and then became generalised, and the skin desquamation involved the extremities ($< 30\%$ body surface area). Other systems' review was unremarkable. On direct questioning with the help of an interpreter, it transpired that the patient was prescribed a 2-month supply of ponatinib dispensed as thirty 45 mg tablets in 2 packets. As the instructions on each packet stated "one tablet to be taken once daily", the patient took one tablet from each packet not recognizing that both packets had the same medication. Repeat full blood counts during this period showed thrombocytopenia (grade 2 at its nadir) and a decrease in neutrophil, basophil and eosinophil counts with a more or less stable haemoglobin level (figure 1). Kidney and liver function test and amylase level were all normal during the duration of overdose. A computed tomography scan of the brain performed to rule out intracranial haemorrhage in view of the headache and thrombocytopenia was unremarkable as was an electrocardiograph performed to exclude a cardiac event. Ponatinib was withheld with resolution of the headache and skin rash, and count recovery. The incident was reported to the MHRA via the yellow card scheme and locally as per the Trust policy.

Our patient received double the maximum licensed dose of ponatinib for nearly a month. Contrary to what would have been expected, the toxicities he exhibited were not severe. In the phase 2 PACE trial, the larger proportion of encountered skin toxicities (rash and dry skin) and headache were graded as 1-2, whereas for thrombocytopenia more patients experienced grades 3-4 than grades 1-2 [1]. Dorer*et al,* quoted an odds ratio of 2.7, 2.4, and 1.9 for pancreatitis, rash and thrombocytopenia, respectively, for each 15 mg dose increase [3]. Our patient, despite being on a 90 mg daily dose, experienced grade 2 toxicities only, which did not include pancreatitis. Although no other medications that would have affected ponatinib metabolism were co-administered while he was receiving the overdose, being of black African ethnicity might have contributed to a lower serum level of the drug and hence the observed severity of side effects which was less than expected [5,6].

In conclusion, we reported the first real life incidence of ponatinib overdosing at 90 mg daily for nearly a month. The severity of the toxicities our patient experienced were out of proportion to the dose he had. Although no clear explanation was elucidated, his ethnic background might have resulted in a lower serum level through various mechanisms. Whether special dosing is required for patients from different ethnicities is needed requires further exploration.

Key clinical message

We reported the first real life incidence of ponatinib overdosing. The severity of the toxicities our patient experienced were less than expected for the dose level. One possible explanation is a lower serum level due to his ethnicity.

Author contribution statement

GN: wrote the manuscript and collected the data.

GF and SA: reviewed and critically appraised the manuscript.

Conflict-of-interest disclosure

None

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