Efficacy and safety of second-line ponatinib after failure of a single previous tyrosine kinase inhibitor for chronic myeloid leukemia patients in chronic phase

Ponatinib (Iclusig, ARIAD Pharmaceuticals) is a 3rd-generation structure-guided, rationally designed tyrosine kinase inhibitor (TKI) aimed at overcoming the resistance of the T315 mutation. Ponatinib is currently indicated for adult Philadelphia positive (Ph+) chronic myeloid leukemia (CML) patients in all phases of disease resistant and/or intolerant to dasatinib or nilotinib, for whom imatinib is not clinically indicated or for patients with identified T315I mutation or adult Ph+ acute lymphoid leukemia resistant or intolerant to dasatinib, for whom imatinib is not appropriate or with identified T315I.[1] The phase II PACE trial showed 50%-60% of heavily pre-treated patients were rescued, allowing a major cytogenetic response (McyR) to be achieved.[2] The majority of patients enrolled in the PACE trial had received at least two prior TKIs and only limited information was available in reports of a failure or severe intolerance to 2nd-generation TKI started as front-line treatment. Overall, in the trial, only 6 patients were reported to have received ponatinib as second-line treatment. We read with great interest the letter by Sanford et al., which described 5 patients who received ponatinib as second-line treatment (3 after imatinib and 2 after dasatinib failure) included in a phase II trial that prematurely closed after FDA recommendations based on safety concerns.[3] We here describe a series of 10 patients who switched to ponatinib as second-line treatment, the majority after failure of front-line 2nd-generation TKI. Median age was 55.7 years (range 35.7-71.8 years) According to the Sokal Risk Score, one patient was classified as low risk, 7 as intermediate risk, and 2 as high risk (Table 1). According to the EUTOS score, only 3 patients were classified as high risk. Only one patient had an additional cytogenetic aberration in the Ph+ clone (ACA) at baseline. Eight patients were treated with front-line 2nd-generation TKI (4 with nilotinib 300 mg BID and 4 with dasatinib 100 mg QD), whereas 2 patients were treated with imatinib 400 mg QD, and both had T315I mutation. Four patients treated with 2nd-generation TKIs switched to ponatinib for primary resistance (3 to dasatinib and 1 to nilotinib), whereas another 4 patients switched for secondary resistance [loss of complete cytogenetic response (CCyR)]. Median time to switch to ponatinib was 16 months. Initial dose was 45 mg/day in 5 patients and 30 mg/day in 5 patients. Two patients did not reach an optimal response after switching; both experienced a severe thrombocytopenia and one patient with primary resistance subsequently progressed to blast phase and died. Four patients (40%) achieved an MR3 as best response, whereas 4 patients (40%) achieved an MR4; 2 patients reduced the dose from 45 mg to 30 mg due to a skin rash. As regards safety, 2 patients experienced hypertension (successfully treated with antihypertensive medication), 4 patients had skin rash, one patient had increased lipase. No arterial or venous thrombotic events were observed in any patients. Only one patient died after progression to blast phase. Two patients who switched from imatinib to ponatinib for T315I mutation achieved an MR4. All patients had long-lasting responses. No other mutations were observed at baseline or during treatment.

Our results confirm the activity of ponatinib after failure with only one TKI, which, in the majority of the cases, was a 2nd-generation drug used as front-line treatment. In the PACE trial, responses were higher in patients treated with only one TKI, with a CCyR rate of 74% and MR3 rate of 47%.[2] Moreover, in the recent study reported by the MDACC, the rate of deep molecular responses was high, but the majority of patients were pre-treated only with imatinib. None of the patients in our series experienced a thrombotic event, probably due to the low rate of predisposing comorbidities at baseline. In fact, only 2 patients had pre-existing risk factors, such as hypercholesterolemia and diabetes, previously described to be associated to arterial thrombotic events during ponatinib.[2] It is also possible that the absence of cardiovascular events was due to dose reduction to 30 mg from baseline in 4 patients and from 45 to 30 mg in another 2 patients due to side effects. In the PACE trial, after October 2013 the dose was reduced, as suggested, in patients who had achieved the primary end point. The rate of newly occurring thrombotic events was 7% in patients without any previous thrombotic event and 10% in patients who maintained the starting dose without previous events.[2] It has been reported that a dose reduction of 15 mg/day was associated to a 40% relative risk

Table 1. Clinical features and outcome of patients treated with second-line ponatinib.

Pts	Age	Sokal	Previous TKI	Cause of discontinuation	Dose of ponatinib (mg)	Best response	Outcome
1	65	Int	Nilotinib	Primary resistance	30	None	Progression to BP
2	72	Int	Dasatinib	Secondary resistance	30	None	Discontinued
3	36	Low	Nilotinib	Secondary resistance	30	MR3	Alive
4	63	Int	Dasatinib	Primary resistance	30	MR3	Alive
5	54	Int	Dasatinib	Primary resistance	45	MR3	Alive
6	55	Int	Dasatinib	Secondary resistance	45	MR4	Alive
7	69	High	Nilotinib	Secondary resistance	30	MR3	Alive
8	46	High	Nilotinib	Secondary resistance	45	MR4	Alive
9	41	Int	Imatinib	T315I	45	MR4	Alive
10	56	Int	Imatinib	T315I	45	MR4	Alive

TKI: tyrosine kinase inhibitor; BP: blast phase; MR3: ratio BCR-ABL/ABL < 0.1%; MR4: ratio BCR-ABL/ABL < 0.01%.

reduction of thrombotic events.[4] Our results, in spite of the limitations of the small number of patients, show that ponatinib could be of benefit for patients who fail a 2nd-generation TKI started as front-line treatment without an evident reason for resistance, such as development of mutations or T315I. Further analyses in larger cohorts of patients are needed to confirm the efficacy and safety of second-line ponatinib after failure of 2nd-generation TKI started as front-line treatment.

Massimo Breccia,[1] Elisabetta Abruzzese,[2] Alessandra Iurlo,[3] Antonella Gozzini,[4] Alessandro Isidori,[5] Domenica Gangemi,[6] Patrizia Pregno,[7] and Giuliana Alimena[1]

[1]Department of Hematology, Department of Cellular Biotechnologies and Hematology, La Sapienza University, Rome; [2]Hematology, S.Eugenio Hospital, Rome; [3]IRCCS Cà Granda Policlinico, Milan; [4]Careggi Hospital, Florence; [5]Department of Hematology, Pesaro; [6]Department of Hematology, Frosinone; and [7]S.Giovanni Battista Hospital, Turin, Italy

Correspondence: breccia@bce.uniroma1.it

doi:10.3324/haematol.2016.145623

Key words: chronic myeloid leukemia, ponatinib, prognosis.

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

References

1. Cortes JE, Kim DW, Pinilla-Ibarz J, et al. PACE Investigators. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. New Engl J Med. 2013;369(19):1783-1796.
2. Cortes JE, Kim DW, Pinilla-Ibarz J, et al. Long-term follow-up of ponatinib efficacy and safety in the phase 2 PACE trial. Blood. 2014; 124(21)(Abstract 3135).
3. Sanford D, Kantarjian H, Skinner J, Jabbour E, Cortes J. Phase II trial of ponatinib in patients with chronic myeloid leukemia resistant to one previous tyrosine kinase inhibitor. Haematologica. 2015;100(Suppl 1):e495.
4. Hochhaus A, Pinilla-Ibarz J, Kim DW, et al. Clinical impact of dose modification and dose intensity on response to ponatinib (PON) in patients (pts) with Philadelphia chromosome-positive (Ph+) leukemias. J Clin Oncol. 2014;32(15 suppl):(Abstract 7084).