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LETTER TO THE EDITOR

Efficacy and safety of bosutinib in chronic phase CML patients developing pleural effusion under dasatinib therapy

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Dear Editor,

Dasatinib is a second-generation (2G) tyrosine-kinase inhibitor (TKI) approved for the first- and second-line treatment of chronic myeloid leukemia (CML) patients. Though highly effective, dasatinib displays a distinct safety profile, with pleural effusion (PE) occurring in a significant proportion of patients [1, 2]. Among factors associated with dasatinib-related PE, concomitant pulmonary and cardiovascular diseases have emerged as the most common [3]. Bosutinib is another 2G-TKI that has proved to be effective in CML patients failing previous TKIs, with relatively limited toxicity, represented mainly by gastrointestinal and cutaneous side effects [4]. Generally considered safe from the cardiovascular point of view, bosutinib has been seldom associated with PE [5]. To date, little is known about cross-intolerance between dasatinib and bosutinib, and scarce data have been reported on the incidence of PE with bosutinib in patients with pleuropulmonary toxicity under dasatinib.

To analyze safety and efficacy of bosutinib therapy in chronic phase CML patients developing PE with dasatinib, we retrospectively collected patients referring to several Italian hematology centers who have been receiving bosutinib in second line or subsequent line, after the development of one or more PE episodes under dasatinib treatment. Cytogenetic and molecular responses were evaluated according to the ELN recommendations, with major molecular response (MMR) defined as BCR-ABL^{IS} ratio < 0.1% and deep molecular response (DMR) as BCR-ABL^{IS} ratio ≤ 0.01% or undetectable disease with ≥ 10,000 ABL copies [6]. Toxicities under TKIs treatment were graded according to the Common Terminology Criteria for Adverse Events (CTC-AE) v4.03.

Twenty patients (12 males and 8 females) with a median age at CML diagnosis of 60 years (range 44–78) were included in the present study. Four patients received dasatinib as first TKI, while 16 started imatinib and then switched to dasatinib, three of them after second-line nilotinib, for resistance ($n = 9$) or intolerance ($n = 7$). Dasatinib starting daily dose was 100 mg in 15 patients, 80 mg in two, and 50 mg in three. Median time from dasatinib start and first PE was 20 months (range 1–58); first PE grade was 1 in three, 2 in fifteen, and 3 in two patients, respectively. Eleven patients (55%) developed at least a second PE, with a median number of PE episodes of

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2 (range 1–6). The median duration of dasatinib therapy was 32 months (range 6–75).

Median age at bosutinib start was 68 years (range 49–82), and 17/20 patients (85%) had at least one comorbidity requiring therapy, the most common being cardiovascular diseases (n = 9), hypertension (n = 8), diabetes (n = 6), pulmonary diseases (n = 4), secondary neoplasms (n = 3), and thyroid diseases (n = 3). The median numbers of comorbidities and concomitant medications were 4 (range 0–7) and 7 (range 0–11), respectively. At bosutinib start, 9 patients (45%) were at least in MMR (2 in DMR), 6 (30%) were in CCyR without MMR, and 5 (25%) had less than a CCyR; two cases displayed ABL mutations (F317V in one, compound mutations with concomitant Y264H, H295R, F311S, and F486L in one). Only a minority of patients (n = 4) started bosutinib at the standard dose of 500 mg/day, while 10 and 6 cases started with 200 and 300 mg, respectively.

After a median time from bosutinib start of 18 months (range 3–39), 15 patients are still on treatment (median duration of bosutinib therapy 13 months, range 3–38), while 5 patients discontinued bosutinib for resistance (n = 2) or toxicity (n = 3; pleural effusion, in one case with concomitant recurrent skin toxicity); median actual bosutinib daily dose is 300 mg (range 200–500). No patient progressed to accelerated/blast phase; one patient died of cerebral hemorrhage 6 months after stopping bosutinib. Among the 15 patients still on bosutinib therapy, 7 improved their response and 8 maintained response level: at last follow-up, 9/15 (60%) were in DMR, 3/15 (20%) in MMR, and 3/15 (20%) in CCyR.

Among the entire cohort of patients, 6/20 (30%) developed PE during bosutinib treatment: the event was grade 1 in two cases and grades 2–3 in four, and three of these latter patients permanently stopped bosutinib for this reason. Median time from bosutinib to first PE was 3 months (range 1–28) and bosutinib dose at PE was 200 mg in 2 patients, 300 mg in 1, 400 mg in 2, and 500 mg in 1. None of the 6 patients with PE developed either concomitant cardiac effusion or pulmonary arterial hypertension (PAH). One patient who had developed PAH while on dasatinib normalized pulmonary arterial pressure while on bosutinib, despite experiencing a grade 1 episode of PE 3 months after the start of bosutinib.

No patient experienced hematologic toxicities, while non-PE extra-hematologic side effects were recorded in 8 cases (diarrhea = 2, skin rash = 2, nausea = 1, increased creatinine = 1, increased lipase = 1, headache = 1); all these were grades 1–2 and none led to bosutinib discontinuation.

With the limits of the retrospective nature and the small number of patients, we have recorded an acceptable incidence of PE recurrence and lack of other serious toxicities in a population relatively old and with comorbidities. Our incidence of PE under bosutinib (30%) is in line with that reported by a Spanish group in 62 CP-CML patients receiving bosutinib as forth-line treatment; among 25 patients experiencing PE while on dasatinib, 7 (28%) suffered the same toxicity with bosutinib, but only in 2 cases treatment had to be discontinued due to recurrent PE [7]. In the last update of a 2-part, phase 1/2 study of bosutinib in CP-CML patients failing imatinib plus dasatinib and/or nilotinib, 20/119 (17%) developed a PE; while most of them had a history of similar event (14, 70%) and had received prior dasatinib (19, 95%), the rate of recurrence of PE during bosutinib among all cases with dasatinib-related PE is not reported [8]. A French report described four CML patients experiencing under bosutinib therapy a worsening of dasatinib-induced pleural effusion (n = 2) or pulmonary arterial hypertension (n = 2) [9].

Our data suggest that bosutinib is a suitable therapeutic option in CML patients developing PE during dasatinib treatment. Management of this type of patients often represents a clinical challenge, as dasatinib-related PE develops mainly in elderly and in subjects with cardiovascular or pneumo-pulmonary disease [3], that are therefore hardly a candidate to nilotinib or ponatinib, considering the cardiovascular toxicity associated with both these TKIs [10].

Author contribution M. Tiribelli designed the study, analyzed the data, and wrote the draft of the manuscript. All authors provided clinical data, helped in the analysis and interpretation of the results, critically revised the manuscript, and approved the final draft for submission.

Compliance with ethical standards

Conflict of interest M. Tiribelli and G. Binotto received honoraria from Novartis, BMS, Pfizer, and Incyte. A. Iurlo received honoraria from Novartis, Pfizer, and Incyte. M. Bonifacio received honoraria from Amgen, Incyte, Pfizer, and Novartis. M. Crugnola received honoraria from Novartis, Incyte, and Jassen.

All other authors have no conflict of interest to report.

Ethical approval This was a non-interventional retrospective evaluation of patient's chart data, so no ethical approval for its conduct was necessary; for the same reason, no informed consent had to be obtained from the included patients.

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