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ORIGINAL ARTICLE

Safety and efficacy of bosutinib in fourth-line therapy of chronic myeloid leukemia patients

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Abstract

Bosutinib is a second-generation tyrosine kinase inhibitor (2GTKI) approved at 400 mg once daily (QD) as first-line therapy in patients with chronic myeloid leukemia (CML) patients and at 500 mg QD in patients who are resistant to or intolerant of prior therapy. In clinical practice, bosutinib is often given to patients who have failed imatinib, nilotinib, and dasatinib (i.e., as fourth-line treatment), despite the limited data on its clinical benefit in this setting. We have retrospectively evaluated the results of bosutinib in a series of 62 CML patients who have failed to prior treatment with all three, imatinib, nilotinib, and dasatinib. Median time on TKI treatment before bosutinib start was 105 (9–163) months, and median duration on bosutinib was 9 months (1–30). Overall, probabilities to achieve complete cytogenetic response (CCyR) and major molecular response (MMR) were 25% and 24% respectively. After a median follow-up period of 14 months, the event-free survival and progression-free survival were 68 and 85%, respectively. Sixty-four percent of patients in CCyR at the time of bosutinib start were able to achieve MMR. In contrast, patients without CCyR, probabilities to obtain CCyR and MMR were 25% and 14%. Bosutinib was well tolerated in this heavily pretreated patients' cohort. Pleural effusions and diarrhea were the most frequent grade II–IV side effects, leading to treatment discontinuation in 16% of patients. Bosutinib is an effective treatment option for patients who have failed previous 2GTKIs due to intolerance. However, efficacy seems to be related to the molecular response that the patient achieved prior to bosutinib.

Keywords Chronic myeloid leukemia · Bosutinib · Intolerant · Resistance · Treatment

Introduction

The outstanding results of the current treatment of chronic myeloid leukemia (CML) are on account of the availability of several tyrosine kinase inhibitors (TKIs) [1]. In reality, only 50% of CML patients will continue treatment with first-line imatinib or second-generation TKI (2GTKI) long-term due to either lack of efficacy or intolerance of these agents [2, 3]. Data from different clinical trials showed how around 60% of CML patients treated with 2GTKI in second or even third line discontinued treatment [4–6]. More recently, bosutinib, an alternative 2GTKI [7] has become available for patients not responding to imatinib [8, 9]. Ponatinib, a 3G-TKI [10], has efficacy in patients with the T315I mutation as well as for those not responding to a 2GTKI. These two agents have widened the spectrum of therapy available in later-line

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approaches. Bosutinib is a second-generation TKI with significant activity against the BCR-ABL1 kinase and most imatinib-resistant BCR-ABL1 mutations except T315I and V299L [11, 12]. Bosutinib was approved by the European Medicines Agency (EMA) in 2013, for patients previously treated with one or more TKI, and for whom imatinib, nilotinib, and dasatinib are not appropriate treatment options [13]. However, at present, there is scarce information on the outcome of bosutinib treatment in patients who have failed to three TKIs, mainly imatinib, nilotinib, and dasatinib. Recently, results from BEFORE study showed superiority for bosutinib 400 mg compared to imatinib in terms of major molecular response (MMR) rates (primary endpoint of the study), which led to the approval in CML first line [14].

We have previously published our preliminary experience with 30 CML patients treated with bosutinib in fourth line. We now present a greater series of fourth-line bosutinib-treated patients and a longer follow-up of the original patient cohort. These data provide further evidence to support the safety and efficacy of bosutinib in this clinical setting [15].

Methods

Patients and treatment

Data from 62 CML patients treated with bosutinib in fourth line were retrospectively collected between November 2011 and 20 January 2016. Bosutinib was prescribed according to clinical practice after intolerance or failure to previous TKIs (imatinib, nilotinib, and dasatinib). All 62 patients were classified as resistant or intolerant to previous TKIs according to investigator judgment (supplementary Table 1). Preliminary results of the first 30 patients included in the study have already been published [15]. A summary of the baseline clinical characteristics of the patients from the previous series and the current one is shown in the supplementary Table 2. The study was performed in 36 institutions from the Spanish CML Group (GELMC) and one English center. Chronic, accelerated, or blast disease phase (CP, AP, BP) were evaluated acording to European LeukemiaNet (ELN) 2013 recommendations [1].

The study was approved by the Spanish Drug Agency and the Ethics Committee of the Hospital Universitario Ramón y Cajal (Madrid).

All patients were Philadelphia chromosome-positive with confirmed *BCR-ABL1* based on qualitative PCR at presentation.

Patients were treated in line with the Summary of Product Characteristics. Bosutinib was started at 500 mg/day and adjusted according to the clinician's judgment during treatment.

Evaluation of responses

Sixty-one patients were evaluated for treatment responses as follows: hematological, cytogenetic, and molecular responses required either maintenance of previous response or achievement of these milestones according to ELN2013 response criteria [1]. Figure 1 shows the patients' disposition and the number of patients who were evaluable for each specific treatment.

Molecular analysis was not centralized. ABL1 kinase domain mutation analysis was performed in all patients prior to bosutinib initiation and in any patients with an unsatisfactory response to bosutinib.

In order to identify a group of patients that could benefit the most from bosutinib, we classified patients and evaluated responses according to cytogenetic status (complete cytogenetic response (CCyR) or no CCyR) at the time of starting bosutinib therapy.

Event-free survival (EFS) is defined as time from first dose of bosutinib to on-treatment death, progression to advanced phase, confirmed loss of CCyR, loss of complete hematologic response (CHR), treatment discontinuation for any reason (intolerance or lack of efficacy), or death for any reason. Progression-free survival (PFS) is defined as time from first dose of bosutinib to on-treatment death, progression to advanced phase, loss of CHR, or death for any reason.

Toxicities were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0.

Statistical analysis

A descriptive analysis of all the variables was carried out. Qualitative variables were analyzed by absolute and relative frequencies, while the quantitative variables have been represented by the mean, standard deviation, and confidence intervals if they have been distributed normally, or through the median, minimum, maximum, and interquartile range if they have not have followed the Gaussian distribution.

In order to describe event-free survival (EFS) and progression-free survival (PFS), the survival function was performed using the Kaplan-Meier method, the median time to the event, and its 95% confidence interval. In order to study the existence of statistically significant differences in survival functions based on variables for analysis, the Log Rank test was used.

In patients in whom an event does not occur, the survival function is determined as the time from the start of bosutinib treatment and the date of the last revision in which the patient continues with bosutinib or date of the last patient follow-up.

The necessary tests have been carried out to determine the fulfillment of the assumptions necessary for the use of

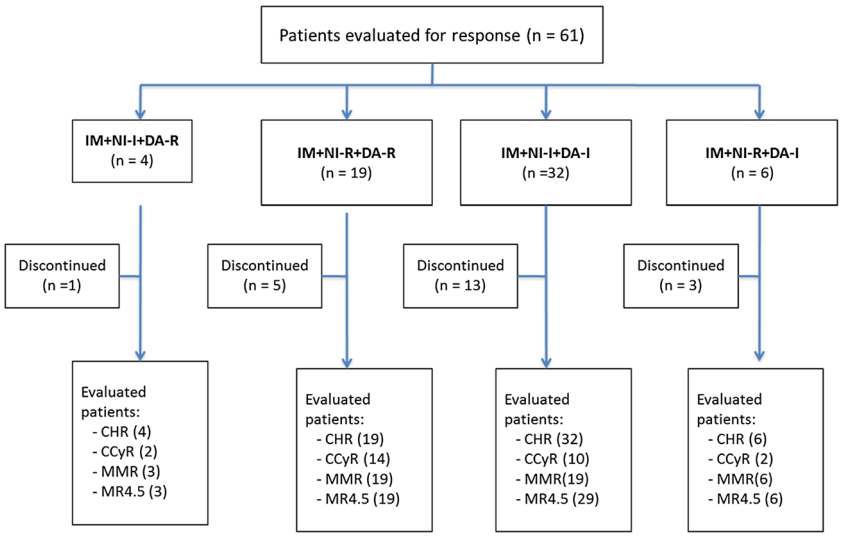

Fig. 1 Patients flow and number of patients evaluated for each specific response

parametric contrasts. Estimates were made with a confidence level of 95%, using the statistical package SPSS V19.0.

Results

Patients

Median time on previous TKIs until bosutinib started was 105.4 months (9.2–163.2). Baseline characteristics for the entire population and according to prior therapy are shown in supplementary Table 1. Adverse events suffered with previous TKIs were in line with published data. Of interest, the most common grade II–IV side effects on other TKIs were prior to bosutinib were pleural effusion in 25 patients (40%), diarrhea in 17 (27%), rash in 13 patients (20%), and hepatotoxicity in 10 patients (16%). Similarly, cardiovascular events were observed in 19 patients (30%): peripheral arterial occlusive disease in 8 patients (12%), 7(11%) ischemic heart disease, and 4 patients suffered cerebral vascular event (6%). Other side effects suffered with previous TKIs are shown in supplementary Table 3.

Median duration on bosutinib treatment was 9.12 months (P25: 6.5-P75:18.37) and varied between 7.8 months for patients resistant to both dasatinib and nilotinib and 17.9 months from patients resistant to nilotinib and intolerant to dasatinib. Median follow-up for the entire population was 14.3 months (0.5–36.1). Median intensity dose was 450 mg/day (range, 150–550 mg/day).

Efficacy

Sixty-one patients were evaluated for efficacy. Probabilities to achieve CCyR, MMR, and molecular response 4.5 (MR4.5%)

Table 1 Bosutinib treatment responses according to prior TKIs therapies

			IM + NI-I + DA-R (4)	IM + NI-R + DA-R (19)	IM + NI-I + DA-I (32)	IM + NI-R + DA-I (7)	Total (61)
Best response to bosutinib	All patients	CHR[a]	4/4 (100)	19/19 (100)	32/32 (100)	6/6 (100)	61/61 (100)
		CCyR[a]	2/4 (50)	6/19 (31)	25/32 (78)	5/6 (83)	40/61 (65)
		MMR[a]	1/4 (25)	2/19 (10)	19/32 (59)	3/6 (50)	25/61 (41)
		MR4.5[a]	1/4 (25)	0/19 (0)	8/32 /25)	1/6 (16)	10/61 (16)
	Patients without response at baseline	CCyR[b]	1/2 (50)	1/14 (7)	4/10 (40)	1/2(50)	7/28 (25)
		MMR[b]	0/3 (0)	2/19 (10)	7/19 (38)	3/6 (50)	12/47 (24)
		MR4.5[b]	0/3 (0)	0/19 (0)	6/29 (20)	1/6 (16)	7/57 (12)

IM, imatinib; *D*, dasatinib; *N*, nilotinib; *CHR*, complete hematological response; *CCyR*, complete cytogenetic response; *MMR*, major molecular response; *MR4.5*, detectable disease with BCR-ABL1IS < 0.0032%

[a] Patients with CHR, CCyR, MMR, or MR4.5 at baseline were evaluable for hematologic, cytogenetic, or molecular response and were considered responders if they maintained their response. [b] Evaluable patients without a CCyR, MMR, or MR4.5 at baseline

were 25%, 24%, and 12%, respectively. When patients with a baseline response who maintained their response were evaluated as responders, probabilities of CHR, CCyR, MMR, and MR4.5 were 100%, 65%, 41% and 16%, respectively (Table 1). We found no differences when comparing new patients and patients from previous publication (supplementary Table 4). EFS and PFS with a maximum follow-up of 36 months was 68.3% and 85.2% respectively (Fig. 2). Median EFS was 27.14 months (CI 95% = [11.95_42.32]), while median PFS has not been reached.

We found no differences in probabilities to obtain CCyR, MMR, MR4.5, EFS, or PFS when analyzing by subgroups showed in supplementary Table 1.

In order to identify the group of patients who benefited the most from the use of bosutinib in this setting, we classified patients according to cytogenetic response at the time of starting bosutinib: CCyR at baseline (group 1) and patients without CCyR at baseline (group 2). No significant predictive baseline characteristics were found in patients with CCyR at baseline (group 1) compared to patients without CCyR at baseline (group 2) when comparing age, previous time on TKIs, or prognostic index factors (supplementary Table 5). Of note, significant differences in terms of efficacy were found. In group one, the probability to either maintain or improve CCyR was 94% (31/33) and probability to achieve MMR and MR4.5 in patients without response at baseline was 42% (8/19) and 21% (6/29). In contrast, in group 2, the probability to achieve CCyR and MMR was 25% (7/28) and 14%/4/28) (Table 2). No differences were found between the two groups in EFS; however, a significance difference was shown in PFS with an improved outcome for those patients with CCyR at baseline ($p = 0.041$) (Fig. 3).

Among all 62 patients, 24 (38%) patients had at least one BCR-ABL1 kinase domain mutation (7 patients had two or more mutations). Most common mutations were E255K/V, G250E, and Y253H (supplementary Table 6). Responses were observed across a spectrum of BCR-ABL1 mutations and the probability to obtain CCyR and MMR did not differ for patients with mutations compared to patients without mutations

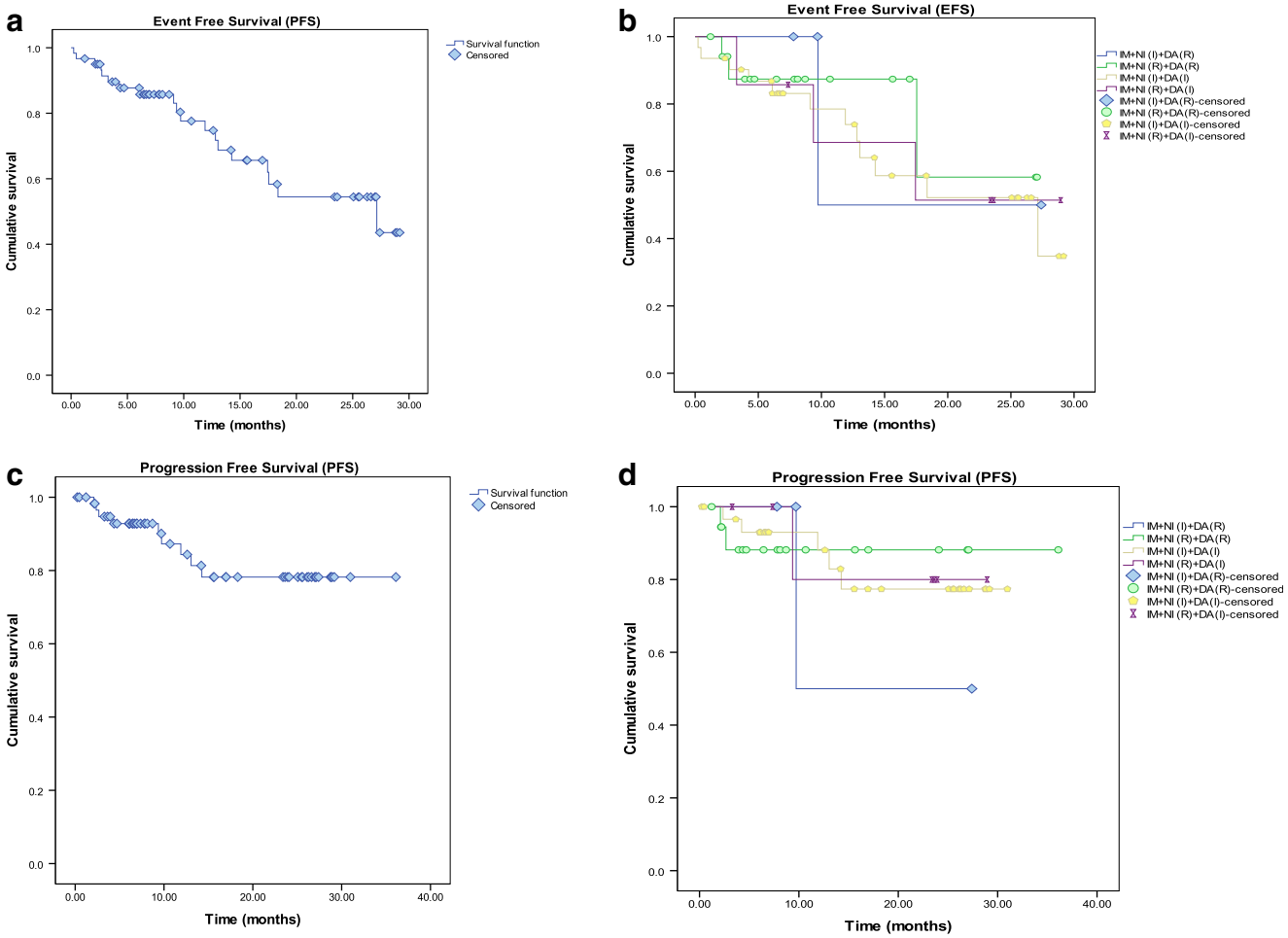

Fig. 2 Event-free survival and progression-free survival for the entire population and by treatment received. Event-free survival for the entire population (**a**). Event-free survival by previous treatments received (**b**). Progression-free survival for the entire population (**c**). Progression-free survival by previous treatment received (**d**)

Table 2 Treatment responses to bosutinib

			CCyR		No CCyR	
			N	%	*N*	%
Best response to bosutinib	All patients	CCyR[a]	31/33	94	7/28	25
		MMR[a]	21/33	64	4/28	14
		MR4.5[a]	9/33	27	1/28	4
	Patients without response at baseline	CCyR[b]	NA	NA	7/28	25
		MMR[b]	8/19	42	4/28	14
		MR4.5[b]	6/29	21	0/28	0

CCyR, complete cytogenetic response; *MMR*, major molecular response; *MR4.5*, detectable disease with BCR-ABL1IS < 0.0032%

[a] Patients with CHR, CCyR, MMR, or MR4.5 at baseline were evaluable for hematologic, cytogenetic, or molecular response and were considered responders if they maintained their response. [b] Evaluable patients without a CCyR, MMR, or MR4.5 at baseline

before bosutinib was started. Four patients developed new mutations while receiving bosutinib (Y253H, E255V, F359V, F317L, V299L) and none of these patients achieved CCyR with Bosutinib.

Safety and treatment disposition

Bosutinib was generally well tolerated, and most common toxicities did not differ to toxicities reported in previous studies. Hematological toxicities were observed in 25% (16/62) of patients: anemia 21% (13/62), thrombocytopenia 21% (13/62), and neutropenia 10% (6/62). Most common grades II–IV non-hematological toxicities were diarrhea, nausea, pyrexia, fatigue, rash, pleural effusions, and liver enzymes alterations (Table 3). Of note, only 3 patients (4%) suffered a vascular event, and all of them had a history of vascular events with the preceding TKIs. No patients suffered significant renal function impairment based on serum creatinine levels during follow-up.

Cross intolerance for most common side effects suffered with previous TKIs were anemia 39%, thrombocytopenia 37%, neutropenia 33%, pleural effusions 28%, liver toxicity 33%, and vascular events 16% (Table 4). Regarding to pleural effusion, 25/62 patients (40%) of the entire cohort previously suffered recurrent pleural effusion (all patients while on dasatinib and 1 patient suffered it with dasatinib and nilotinib). In all patients, pleural effusion was the main reason for treatment change. Twenty-eight percent (7/25) of the patients who experienced pleural effusion while on dasatinib suffered the same side effect with bosutinib. Recurrent pleural effusion led to treatment discontinuation in 2 patients. Two

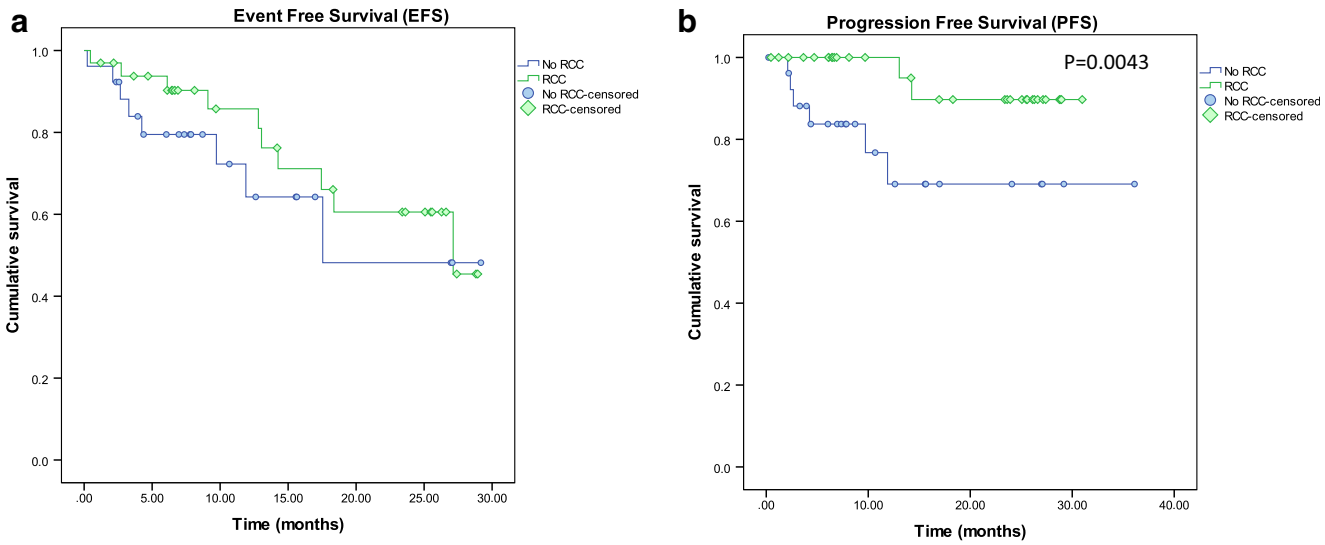

Fig. 3 Event-free survival and progression-free survival by cytogenetic status. Event-free survival for the entire population by cytogenetic status (**a**). Progression-free survival by cytogenetic status (**b**)

Table 3 Grades II–IV side effects on bosutinib therapy

	CCyR		No CCyR		Total	
	N	%	*N*	%	*N*	%
Hematological toxicities						
Anemia	1/34	3	1/28	3	2/62	3
Neutropenia	1/34	3	3/28	10	4/62	6
Thrombocytopenia	1/34	3	3/28	10	4/62	6
Extrahematological toxicities						
Pleural/pericardial effusions	4/34	11	13/28	10	7/62	11
Diarrhea	14/34	41	9/28	33	24/62	39
Abdominal pain	3/34	9	3/28	11	6/62	10
Fatigue	2/34	6	3/28	11	5/62	8
Liver enzymes elevation	6/34	17	2/28	7	8/62	13
Hypertension	1/34	3	1/28	3	2/62	3
Acute pancreatitis	1/34	2	1/28	3	2/62	3
Cerebrovascular disease	1/34	3	1/28	3	2/62	3
Occlusive peripheral arterial disease	0/34	0	1/28	3	1/62	1
Rash	1/34	3	4/28	14	5/62	8

CCyR, complete cytogenetic response

additional patients experienced recurrent but well-tolerated pleural effusion that could be managed with bosutinib dose reductions.

Twenty-two patients (36%) discontinued treatment. Most common causes were intolerance (16%) and lack of efficacy (10%). Treatment discontinuations reasons for both groups are shown in Table 5.

Median dose was lower in group 1 (400 mg) compared to group 2 (500 mg) and no significance differences were found in treatment interruption (46% vs 45% for group 1 and 2 respectively) or dose reduction (64% vs 66% for group 1 and 2 respectively). Dose modifications during follow-up are shown in Fig. 4.

Discussion

We herein report, to our knowledge, the largest cohort of patients treated with bosutinib after resistant or intolerance to imatinib, nilotinib, and dasatinib. As a significant proportion of patients discontinue third-line TKI therapy, it remains important to determine the impact of bosutinib therapy in this setting. At present, there is a lack of information on the use of bosutinib in fourth line and the phase 1/2 study with which bosutinib obtained its indication evaluated only 3 patients in fourth line. The EMA granted a conditional approval requesting a prospective phase 4 clinical trial where half of the patients would be treated in fourth line. As data from this study (NCT02228382) is not available yet, we believe the information presented herein is relevant.

In the current study, bosutinib was shown to be a safe and effective treatment option when used as a fourth-line therapy.

With regard to toxicity, the frequencies are rather similar when comparing with other clinical trials [16]. Seven patients (11%) suffered pleural effusions and all of them previously suffered such side effect while on dasatinib. In the phase I/II, clinical trial which bosutinib obtained its indication with, 72 patients were previously treated with dasatinib. When cross

Table 4 Cross intolerance toxicities

	Previous TKI ($n = 62$)				Bosutinib ($n = 62$)	Cross intolerance
	Imatinib	Nilotinib	Dasatinib	Total		
Anemia	14 (22%)	12/62	18	31 (50%)	13 (21%)	12/31 (39%)
Thrombocytopenia	9 (14%)	16 (35%)	21 (33%)	27 (43%)	13 (21%)	10/27 (37%)
Neutropenia	3 (5%)	9 (14%)	12 (19%)	15 (24%)	6 (10%)	5/15 (33%)
Pleural/pericardial effusions	0	1 (1%)	25 (33%)	25 (40%)	7 (11%)	7/21 (28%)
Diarrhea	12 (19)	8 (13%)	13 (21%)	17 (31%)	24 (39%)	11/17 (64%)
Cardiovascular events[a]	2 (3%)	17 (25%)	3 (5%)	19 (33%)	3 (5%)	3/19 (16%)
Liver enzymes elevation	2 (3%)	5 (8%)	2 (3%)	6 (10%)	8 (13%)	2/6 (33%)
Acute pancreatitis	0	2 (3%)	1 (1%)	2 (3%)	2 (3%)	0/2 (0%)
Pulmonary hypertension	0	0	2 (3%)	2 (3%)	0 (0%)	0/2 (0%)
Rash	7 (11%)	12 (19%)	3 (5%)	13 (21%)	5 (8%)	2/13 (15%)

[a] Ischemic heart disease, cerebrovascular disease, and occlusive peripheral arterial disease

Table 5 Treatment discontinuations

	CCyR (34)		No CCyR (28)		Total (62)	
	N	%	*N*	%	*N*	%
Treatment discontinuation	10	33	12/28	43	22/62	35
Lack of efficacy	2	6	4	14	6	9
Progression to advanced phase	0	0	1	3	1	1
Death	1	3	0	0	1	1
Intolerance	6/34	17	4/28	14	10/62	16
Others	1	3	3/28	11	4/62	6

CHR, complete hematological response; *CCyR*, complete cytogenetic response; *MMR*, major molecular response

intolerance for pleural effusion was studied, 12 patients out of the 23 (52%) who previously suffered pleural effusion with dasatinib suffered same side effect, however, only 2 patients discontinued treatment [17]. In our series, 7 patients out of the 25 (28%) patients who previously suffered pleural effusion with dasatinib experienced cross intolerance for such side effect. It seems clear that pleural effusion in patients previously treated with dasatinib is much higher compare to dasatinib naïve patients. Whether this increase in the incidence is due to a selection of patients who potentially could experience pleural effusions or both, TKIs could share same mechanisms behind treatment-related pleural effusion remain to be elucidated.

Of note, only 3 patients suffered a vascular event on bosutinib. Since an important proportion of patients discontinue treatment due to vascular events suffered with previous TKIs (most cases on nilotinib), the information provided supports the use of bosutinib in this group of patients. However, this information should be taken with caution since median time on bosutinib was only 9 months and first cardiovascular events in previous studies appeared after longer drug exposures.

Renal function declined has been associated with long-term exposure to bosutinib. Renal AEs were reported in 73/570 patients (13%) receiving second line or later bosutinib, and in 22/248 (9%) receiving first-line bosutinib [18]. The reason why renal failure is not so frequent in our series is elusive. However, it is worth to point out that the follow-up of our series is short, comparing with median time for first renal adverse events in clinical trials in second or later lines, which was 497 days.

Long-term patient-reported outcomes from the NCT00261846 trial has been recently published showing how bosutinib CML patients resistance or intolerance to prior therapy largely maintained healthy-related quality of life (HRQOL) after 264 weeks or more of treatment with bosutinib [19]. HRQOL has not been addressed in this manuscript due to the retrospective nature of the study. In fact, an

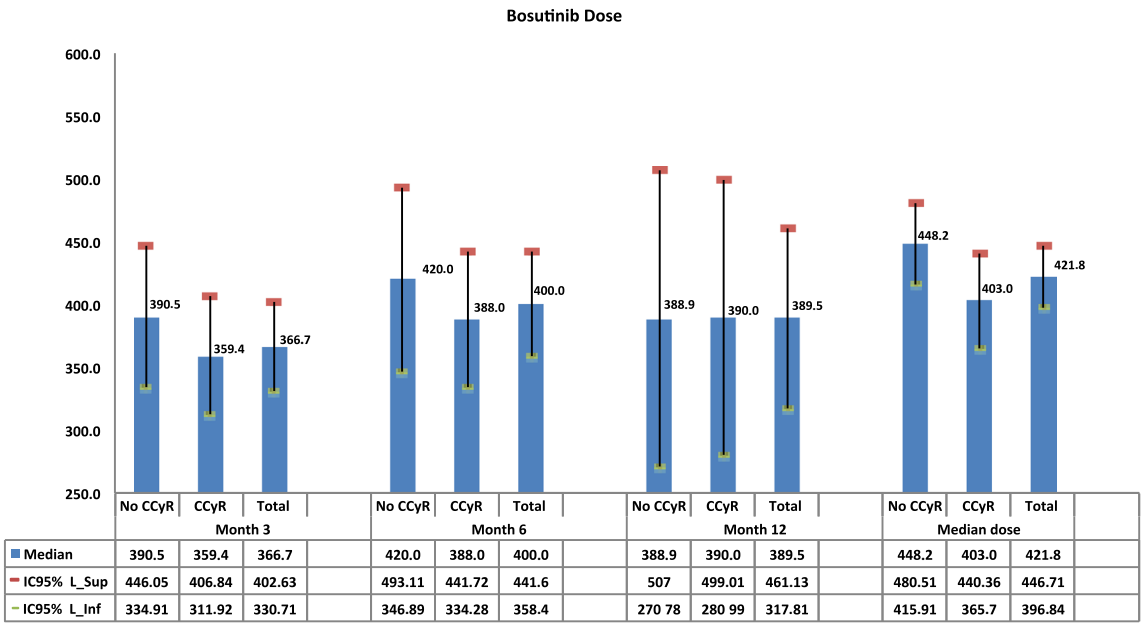

Fig. 4 Bosutinib dose modification during follow-up

important proportion of patients were treated under the Spanish compassionate program for bosutinib.

In terms of efficacy, we are aware of the limitations from retrospective studies such as ours. In this sense, an important challenge was to classify baseline patients according to intolerance or resistance to previous TKIs. For clarity, patients were therefore classified in two different groups, patient with and without CCyR at the time of starting bosutinib.

Outcome was found to be determined according to the patient's response status prior to bosutinib therapy. Thus, patients who received bosutinib maintained or even improved previous responses showing a good safety profile with low cross intolerance to previous TKIs. On the other hand, those patients who had not attained CCyR prior to bosutinib, the subsequent achievement of CCyR occurred only in 25% of patients, with a PFS significant lower to patients in CCyR. Putting all this information together, we believe that bosutinib is an adequate treatment options for CML patients suffering side effects with previous TKIs, especially in those patients suffering serious treatment-related toxicities as vascular events or pancreatic alterations which are quite frequent with ponatinib. Nevertheless, in case of resistant to 2GTKI, the use of ponatinib involves patients in clinical trials or perform stem cell transplantation seems to be better treatment options. In this context, a recent study, comparing data from clinical trials, has shown how responses were more frequent and durable with ponatinib than with bosutinib in terms of CCyR [20].

As has already happened with other 2GTKIs, nilotinib and dasatinib [21, 22], and also with ponatinib [23], the most appropriated dosage of bosutinib is being questioned. Thus, the dose of 400 mg instead of 500 mg has been shown to be more appropriate for CML patients treated with bosutinib first line [14]. Similarly, we have observed that a significant proportion of patients treated initially with 500 mg decreased dose during treatment, and a median dose of 400 mg for patients with CCyR was enough to maintain previous responses and probably necessary to avoid toxicities in the majority of patients. Of note, the median bosutinib dose in those patients without previous CCyR was 500 mg, suggesting the need for a higher dose intensity in resistant patients. At this current moment, several clinical trials are evaluating safety and efficacy of lower bosutinib doses with different regimens [16].

In conclusion, we have shown that the 2GTKI bosutinib is an effective treatment option for heavily treated CML patients who are intolerant to previous TKIs. As expected, for patients who are sequentially treated and have resistance to previous second-generation TKIs, other treatment strategies such as ponatinib, new TKIs, and stem cell transplantation, should be considered in order to provide the best outcome in this challenging situation in light of the limited clinical response.

Authorship contributions VGG and JLS designed the study, coordinated the group, and wrote the manuscript. DM and JHB contributed to clinical data collection and wrote the manuscript. The other authors contributed to clinical data collection and reviewed the manuscript.

Compliance with ethical standards

Conflict of interest VGG: Novartis: Speaker Honoraria, advisory committees; BMS: Speaker Honoraria, advisory committees; Pfizer: Speaker Honoraria, advisory committees. Incyte: Advisory committees; JLS: Novartis: Consultancy, Speaker Honoraria, advisory committees; research grants; BMS: Consultancy, Speaker Honoraria, advisory committees; research grants; Pfizer: Consultancy, Speaker Honoraria, advisory committees; research grants: Incyte: Advisory committees. FC: Novartis: Consultancy, Speaker Honoraria, advisory committees; research grants; BMS: Consultancy, Speaker Honoraria, advisory committees; research grants; Pfizer: Consultancy, Speaker Honoraria, advisory committees; research grants: Incyte: Advisory committees. The rest of authors declare no conflict of interest.

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