Rare Cancers Ther (2015) 3:35–46
DOI 10.1007/s40487-015-0010-y

REVIEW

Bosutinib for Chronic Myeloid Leukemia

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Received: July 18, 2015 / Published online: August 26, 2015

ABSTRACT

In recent years the availability of several tyrosine kinase inhibitors (TKI) in the therapeutic armamentarium for chronic myeloid leukemia has dramatically changed the objectives and expectations of healthcare providers and patients. For many, but not all, patients the forerunner of TKI, imatinib, is still an excellent treatment option. Unfortunately, nearly 30–40% of imatinib-treated patients discontinue therapy in the long-term, because of failure and/or intolerance. Second-generation tyrosine kinase inhibitors are more potent drugs which are suitable for treatment of approximately 50% of patents for whom imatinib is unsuitable, and with high success and rapid responses. Bosutinib, an orally bioavailable Src/Abl tyrosine kinase inhibitor, has proved to be effective in vitro against resistant chronic myeloid leukemia cells that do not harbor the T315I or V299L ABL kinase domain mutations. During clinical development the manageable safety profile of bosutinib have become evident for both simple and more advanced treatment. In this review we summarize preclinical and clinical data for bosutinib and discuss its ideal field of action in comparison with other TKI.

Keywords: Bosutinib; Chronic myeloid leukemia; Efficacy; Imatinib; Safety

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INTRODUCTION

The Src and Abl families of non-receptor protein tyrosine kinases have been extensively studied as targets for anticancer therapy because of their involvement in signaling pathways promoting tumor growth and progression [1–3]. Moreover, the presence of the constitutively active chimeric protein BCR-ABL, an oncogenic product arising from reciprocal translocation between chromosomes 9 and 22 (Philadelphia chromosome) [4], is regarded the pathogenetic characteristic of chronic myeloid leukemia (CML).

Selective inhibition of BCR-ABL autophosphorylation and phosphorylation of its substrates by tyrosine kinase inhibitors (TKI) resulted in a substantial and dramatic improvement of survival of CML patients, and has become one of the most important examples of target therapy [5].

Nowadays, paradoxically (although luckily) treatment of CML has become more complicated, because of the availability of second and third-generation TKI, which are used as both salvage therapy and alternative simple options [6].

Several studies have confirmed the long-term efficacy and manageable safety profile of imatinib, the first approved TKI. However, approximately 40% of patients have to switch to different treatment because of intolerance or resistance [7, 8]. Second-generation TKI have resulted in a favorable outcome for approximately half of non-responding patients after primary or secondary resistance [9, 10]. In addition, use of new TKI as initial treatment resulted in improved efficacy with evidence of an extremely good molecular response and lower progression, irrespective of features and risk at diagnosis, but with inconsistent long-term overall survival compared with imatinib [11, 12].

Bosutinib, a second-generation dual inhibitor of Src and Abelson (Src/Abl) kinases, is currently approved in Europe and USA for treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome-positive CML previously treated with one or more TKI and for whom imatinib, nilotinib, and dasatinib are not regarded as appropriate treatment options. The purpose of this review is to focus on efficacy and safety data for bosutinib for treatment of resistant and/or intolerant CML or for newly diagnosed CP-CML patients.

This article is based on previously conducted studies and does not include any new studies of human or animal subjects performed by any of the authors.

MECHANISM OF ACTION

Bosutinib is an orally bioavailable 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline-3-carbonitrile originally identified by Boschelli, in 2001, to act as a Src tyrosine kinase inhibitor [13]. Two years later, Golas documented potent antiproliferative and pro-apoptotic activity of bosutinib, at concentrations between 1 and 20 nM, against CML culture (K562, KU812, and Meg-01) [14]. Reduced BCR-ABL, CrkL, STAT5, and Lyn phosphorylation were consistent with both Src and Abl kinase inhibitory activity. Bosutinib was demonstrated to bind the kinase domain of BCR-ABL in an active or inactive conformation. Puttini and colleagues reported the activity of Bosutinib against BaF3 murine myeloid cells expressing resistant forms of BCR-ABL, with mutations Y253F, E255K, and D276G; no inhibition was observed against cells expressing the T315I or V299L mutation [15]. Later studies by Konig et al. focused on bosutinib activity against specific CML progenitors, and reported effective BCR-ABL and Src kinase inhibition in CML progenitor cells and growth suppression of CML primitive and committed progenitor cells. However, bosutinib did not significantly inhibit non-dividing CML primitive progenitors [16]. In 2009, by use of a chemical proteomics approach in combination with in-vitro kinase assays against a large number of recombinant kinases, Remsing Rix provided more insight into bosutinib's kinase target profile. Bosutinib, similar to dasatinib, was shown to target TEC

family kinases, including BTK; however, in contrast with dasatinib, bosutinib did not inhibit KIT or PDGFR, but rather had activity against the STE family of kinases, in particular the STE20 subfamily. CAMK2G, a Ca^{2+}/calmodulin-dependent protein kinase was also identified as a novel kinase target inhibited by the drug [17].

PHARMACOKINETIC DATA

The pharmacokinetic (PK) profile of the drug in the orally bioavailable form was extensively studied in phase I/II trials among either adult healthy volunteers of cancer patients. Population PK analysis of three clinical studies among patients with cancer suggested that baseline characteristics (age, body weight, gender and race) did not affect the PK data. Drug absorption was relatively slow, with a median time to peak concentration of 4–6 h and a half life $t_{1/2}$ ranging from 33 to 39 h, thus supporting a once-daily dosing regimen [18].

The effect of food was studied among 55 healthy subjects randomly assigned to receive bosutinib 200, 400, 600, or 800 mg with food or 200 or 400 mg without food, or placebo [19]. Significant increase in bosutinib exposure was observed for maximum serum concentration (C_{max}), and area under the curve (AUC) increased by 1.6–1.7-fold when taken with food, the effect being more evident at lower doses. The interaction, resulting in increased drug exposure, was explained by an increase in bosutinib solubility when taken with food [19].

After administration of a single dose of 500 mg bosutinib, mean apparent volume of distribution for patients with CML was 6080 ± 1230 L, which correlated with extensive partitioning into tissues. Bosutinib is highly bound to human plasma proteins in vitro (94%) and ex vivo in healthy subjects (96%), and binding was not concentration-dependent. The major circulating metabolites identified in plasma were oxydechlorinated (M2) bosutinib (19% of parent exposure) and *N*-desmethylated (M5) bosutinib (25% of parent exposure), with bosutinib *N*-oxide (M6) a minor circulating metabolite. All the metabolites were inactive [20].

For patients with CML given single oral doses of 500 mg bosutinib with food, the mean terminal phase elimination half-life was 22.5 h; 91.3% of the dose was recovered in the feces and 3% in the urine. Undergoing extensive first-pass-metabolism, bosutinib was deemed to interact with CYP3A inducers and inhibitors. Early studies showed that bosutinib is primarily metabolized by hepatic CYP3A4. In a trial of 24 healthy volunteers, a single dose of 100 mg bosutinib was administered either alone or in combination with 5 daily doses of 400 mg ketoconazole under fasting conditions. Ketoconazole increased bosutinib C_{max} and AUC 5.2-fold and 8.6-fold, respectively. Moreover, co-administration reduced the mean apparent clearance of bosutinib approximately ninefold and increased the mean terminal half-life from 46.2 to 69.0 h. Despite this increase in bosutinib exposure, the incidence of adverse side effects was comparable with that for administration of bosutinib alone [21]. In a cross-over trial of 24 healthy volunteers, a single dose of 500 mg bosutinib was administered alone or in combination with six daily doses of 600 mg of rifampicine, a potent CYP3A4 inducer, under fed conditions. Rifampicine decreased bosutinib C_{max} and AUC by 86% and 94%, respectively [22]. According to these data, concurrent use of bosutinib with strong or moderate CYP3A inhibitors (and inducers) should be avoided whenever possible. Furthermore, P-glycoprotein (P-gp) inhibitors and grapefruit or grapefruit juice

should be avoided because their administration may result in increased drug plasma concentrations. In-vitro data showed no effect of bosutinib as an inducer or inhibitor of the metabolic liver enzymes CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4.

Interaction of bosutinib with gastroprotective drugs was tested in a trial with 24 healthy fasting subjects. A single 400-mg dose of bosutinib was given concurrently with repeated doses of lansoprazole 60 mg. Bosutinib C_{max} and AUC decreased by 46% and 26%, respectively [23]. Therefore, concomitant administration of proton-pump inhibitors with bosutinib should be avoided whenever possible; otherwise, short-acting antiacids or histamine-2 receptor antagonists should be considered if taken 2 h before or after bosutinib.

The relationship between bosutinib exposure at steady state and most common adverse side effects (i.e., diarrhea, thrombocytopenia, rash, transaminases (ALT/AST) increase, nausea, vomiting, and neutropenia) was recently investigated by Hsyu et al., who combined data from phase III and phase I/II clinical studies on 749 patients with newly diagnosed CP-CML or with CP-CML resistant and/or intolerant to previous imatinib therapy, respectively [24]. Associations between bosutinib exposure at steady state and key efficacy endpoints from each of the two studies were also investigated. An exposure–response relationship was identified for the incidence (but not severity) of diarrhea; a weak relationship was also observed for the incidence of rash. No evidence of an exposure–response relationship was documented for nausea, vomiting, neutropenia, thrombocytopenia, or liver enzymes elevation. For patients with newly diagnosed CP-CML, exposure–response relationships were observed for complete cytogenetic response at 1 year (predicted probability, 0.476–0.650), major molecular response (MMR) at 1 year (0.238–0.497), and cumulative complete hematologic response (CHR) at 1 year (0.605–0.763). For patients with previously treated CP-CML, no exposure–response relationship was observed for major cytogenetic response (MCyR) at 24 weeks (0.320) [24].

Pharmacokinetic of bosutinib in the context of hepatic impairment was investigated in a dedicated trial in which a single dose of 200 mg was administered with food to 18 volunteers with A, B, and C Child-Pugh classes and to 9 matched healthy volunteers. C_{max} of bosutinib was found to be increased 2.4-fold, twofold, and 1.5-fold, respectively, for Child-Pugh classes A, B, and C, and bosutinib AUC increased 2.3-fold, twofold, and 1.9-fold, respectively. On the basis of these data, use of bosutinib is contraindicated in Europe for patients with hepatic impairment [25].

The effect of renal impairment on bosutinib pharmacokinetic profile was evaluated in a phase-1 two-stage trial in which a single dose of 200 mg was administered, with food, to 26 subjects with mild (CLcr 51–80 mL/min), moderate (CLcr 30–50 mL/min), or severe (CLcr <30 mL/min) renal impairment and to 8 subjects with normal renal function. Although bosutinib exposure was unchanged for subjects with mild renal impairment, moderate and severe renal impairment were associated with increases in AUC of 35% and 60%, respectively, compared with subjects with normal renal function. Specific recommendations concerning dose adjustment were made for patients with severe (CLcr <30 mL/min) or moderate (CLcr between 30 and 50 mL/min) renal impairment [26].

PHASE 1/2 STUDY: CLINICAL EFFICACY

In the phase 1 portion of a phase 1/2 study that enrolled imatinib-treated CML patients, the bosutinib dose of 600 mg/d was the maximum tolerated dose. Part 1 was a dose-escalation study with 3 + 3 design with subsequent cohorts of 3–6 imatinib-resistant patients. The dose of 500 mg once-daily was selected for phase 2 of the trial; the trial was later amended to include nilotinib and dasatinib-treated patients when these drugs became commercially available. Escalation to 600 mg daily was allowed after lack of efficacy (failure to achieve CHR by week 8 or complete cytogenetic response (CCyR) by week 12). Imatinib resistance was defined as no hematological improvement within 4 weeks, no CHR by 3 months, no cytogenetic response by 6 months, or no MCyR by 12 months, for at least 600 mg imatinib daily. Imatinib intolerance was defined as grade IV hematologic toxicity lasting for more than 7 days, grade 3–4 non-hematological toxicity, or grade 2 toxicity that did not improve despite adequate management or adjustment of the dose of the drug. The primary endpoint of the study was MCyR at 24 weeks for patients with no previous TKI exposure other than imatinib.

Part 1 included 17 patients with imatinib resistance in the chronic phase and 1 accelerated-phase patient: bosutinib was well tolerated without dose limiting toxicity (DLT) in the 400–500 mg cohorts; indeed, in the 600 mg cohort, one patient developed vomiting, rash, and nausea related to the drug. In the second part of the trial, the median dose intensity reported was 484.9 mg/day for imatinib-resistant and 394.1 mg/day for imatinib-intolerant patients.

Overall, for the 200 imatinib-resistant and 88 imatinib-intolerant CP-CML patients enrolled in this trial, after 1 year, CHR was achieved for 86% of imatinib-resistant and 85% of imatinib-intolerant patients; this was sustained for 72% and 87%, respectively and was obtained in a median time of 2 weeks. Fifty-four percent of imatinib-resistant and 49% of imatinib-intolerant patients had a decrease in Ph+ metaphases to <35% (MCyR); this was maintained for 72% of imatinib-resistant and 92% of imatinib-intolerant patients. Median time of MCyR was 12.3 weeks. CCyR was detected in 41%; among those patients who achieved CCyR and were evaluable for molecular response, 64% of imatinib-resistant and 65% of imatinib-intolerant patients achieved a MMR. Complete molecular response (CMR) was achieved by 49% and 61% of patients, respectively [27]. Mutational analysis was assessed for 115 patients at baseline (most frequently observed M351T, F359V, F317L, L248V, G250E, M244V, T315I) and responses were observed for all mutants except T315I [27]. At 1 year, progression-free survival (PFS) was 91% and overall survival (OS) was 97% [27]. After 2 year, CCyR was 48% and MMR was 35%, not expressed on international scale (IS), with 28% of patients achieving CMR. Median time reported to achieve MMR was 35.9 weeks for imatinib-resistant and 12.2 weeks for imatinib-intolerant patients. At 2 years, PFS was 81%; progression to blast phase occurred for 11 patients and 2-year OS was 91% [28] (Table 1).

Long-term outcome for patients treated in the advanced phase of disease has recently been reported for 79 patients in the accelerated phase (AP), 64 in the blast phase (BP), and 24 with acute lymphoblastic leukemia (Ph+ ALL). After 4 years, 14 AP, 2 BP, and 1 ALL patients remained in the study, with a median duration of treatment of 10.2 months. Among AP patients, 57% achieved an overall

Table 1 Best overall response observed for bosutinib-treated patients, for both first and subsequent treatment

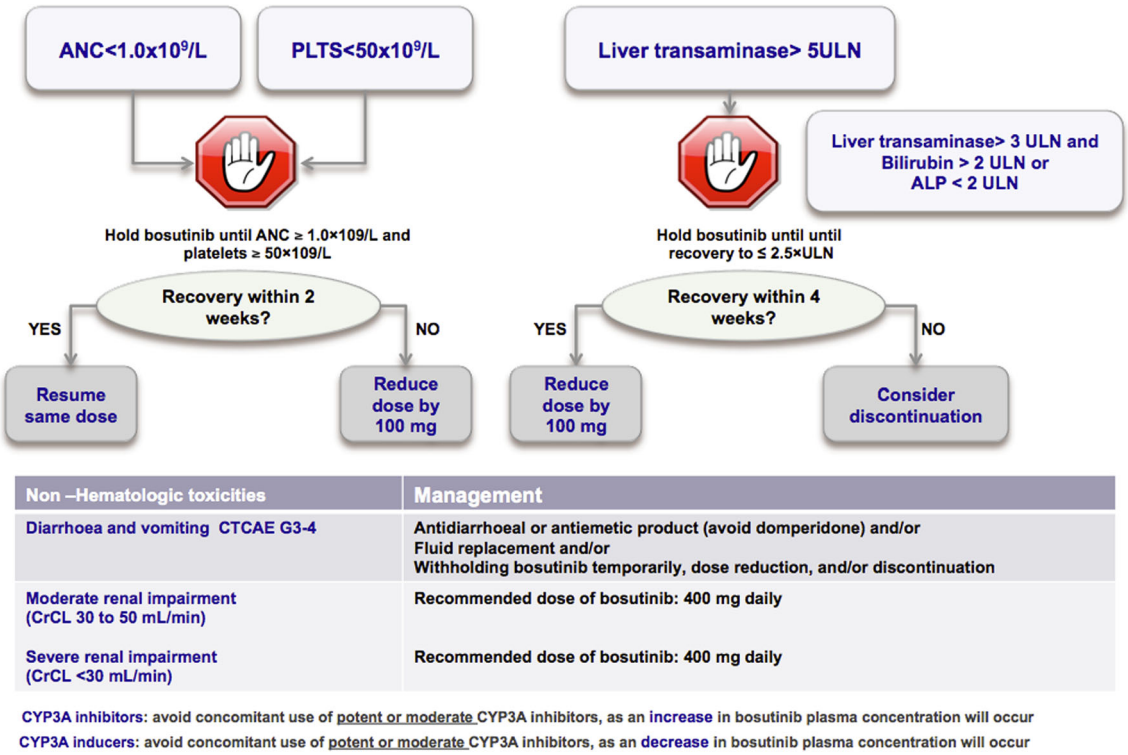
Response (% of evaluable patients)	Phase I/II trial [26, 27]		BELA trial [29, 30]	
	IMA-R ($n = 200$)	IMA-I ($n = 88$)	Bosutinib ($n = 248$)	Imatinib ($n = 251$)
CHR 24 months	85	82	NR	NR
CCyR 12 months	36	50	70	68
24 months	46	54	87	81
MMR 12 months	22	31	41	27
24 months	29	31	59	49
CMR 12 months	16	13.5	12	3
24 months	25	32	NR	NR
PFS	95	91	NR	NR
Progression to AP/BP	5	1.1	2	5
OS (24 months)	98	89	97	95

AP/BP accelerated/blastic phase, *BELA* bosutinib efficacy and safety in newly diagnosed CML, *CCyR* complete cytogenetic response, *CHR* complete hematological response, *CMR* complete molecular response, *IMA-I* imatinib-intolerant, *IMA-R* imatinib-resistant, *MMR* major molecular response, *PFS* progression-free survival, *NR* not reported, *OS* overall survival

hematologic response and 40% a MCyR with a 4-year probability of maintaining this response of 65%; among BP patients, 28% achieved an hematologic response and 37% a MCyR with a 21% probability of 4-year duration. Responses were durable, suggesting possible use of this drug while awaiting transplant [29].

SAFETY OF PHASE 1/2 STUDY

The most common adverse side effects observed were gastrointestinal, for example diarrhea, nausea, vomiting, abdominal pain, rash, fever, fatigue and increased alanine aminotransferase. Most frequent grade 3/4 side effects were low incidence of diarrhea, increased ALT, and rash. Only 3% of patients experienced a pleural effusion related to the drug. Gastrointestinal side effects occurred early, and usually of low severity; transient diarrhea was managed with loperamide in 69% of cases, with temporarily interruptions in 15% of cases, or reduction of dose for 6% of patients. Forty-five percent of patients used antiemetic for nausea and 33% for vomiting. Cardiac side effects were reported for 14% of patients, the most frequent being atrial fibrillation and palpitations; two patients discontinued as a result of cardiac side effects and one died of unrelated cardiac failure. With regard to hematologic toxicity, 24% of patients experienced grade 3/4 thrombocytopenia in a median time of 21 days, whereas 17% experienced grade 3/4 neutropenia and 8% anemia (Fig. 1). The most frequent laboratory abnormalities were elevated ALT (58% overall and 10% as grade 3/4), hypophosphatemia (43% overall and 9% as grade 3/4), and elevated lipase (28% overall and 8% as grade 3/4). Also in the advanced phase of the disease, the most common side effects were gastrointestinal with diarrhea among 85% of AP patients and among 64% of BP patients, mostly of grade 1/2. The most common serious adverse side effects reported were pneumonia



Non –Hematologic toxicities	Management
Diarrhoea and vomiting CTCAE G3-4	Antidiarrhoeal or antiemetic product (avoid domperidone) and/or Fluid replacement and/or Withholding bosutinib temporarily, dose reduction, and/or discontinuation
Moderate renal impairment (CrCL 30 to 50 mL/min)	Recommended dose of bosutinib: 400 mg daily
Severe renal impairment (CrCL <30 mL/min)	Recommended dose of bosutinib: 400 mg daily

CYP3A inhibitors: avoid concomitant use of potent or moderate CYP3A inhibitors, as an increase in bosutinib plasma concentration will occur
CYP3A inducers: avoid concomitant use of potent or moderate CYP3A inhibitors, as an decrease in bosutinib plasma concentration will occur

Fig. 1 Suggested management of the most frequent adverse side effects for patients treated with bosutinib

among AP patients (9 patients) and pyrexia for 6 BP patients [27] (Table 2).

BOSUTINIB FOR NEWLY DIAGNOSED CML PATIENTS

The BELA study was a phase 3 randomized trial that compared bosutinib with imatinib for newly diagnosed CP-CML patients [30]. Five hundred and two patients were randomly assigned 1:1 to bosutinib at a dose of 500 mg per day or imatinib at 400 mg per day. Follow-up at 1 year reported CCyR, the primary endpoint of the study, of 70% for bosutinib and 68% for imatinib, without significant difference. Median time to achieve CCyR was faster with bosutinib. MMR was higher for bosutinib (41% compared with 27% for imatinib) and CMR was also higher for bosutinib (12% versus 3%). The median time to reach MMR was faster with bosutinib, 37 weeks compared with 72.3 weeks with imatinib. No differences were observed for different Sokal risk groups. Eleven side effects were recorded for bosutinib and 18 for imatinib, with estimated side-effect-free survival of 94% and 93%, respectively. Two percent of patients with bosutinib experienced progression, compared with 10.4% in the imatinib group [30].

Recently, the trial was updated at 24 months: CCyR was 79% with bosutinib and 80% with imatinib, whereas MMR was 59% and 49%, respectively. Responses were durable and since the previous report at 1 year no new cases of progression were detected with bosutinib whereas another four cases were observed with imatinib [31] (Table 1).

Table 2 Adverse side effects associated with bosutinib treatment among imatinib-resistant, imatinib-intolerant, or previously untreated patients with chronic myeloid leukemia

Adverse side effects % All (% G3–4)	Phase I/II trial [27]		BELA trial [30]	
	IMA-I ($n = 88$)	IMA-R ($n = 200$)	Bosutinib ($n = 248$)	Imatinib ($n = 251$)
Thrombocytopenia	66 (21)	70 (32)	28 (13)	28 (14)
Anemia	91 (12)	86 (18)	25 (8)	22 (6)
Neutropenia	49 (14)	51 (24)	13 (8)	29 (16)
Diarrhea	84 (9)	85 (13)	70 (12)	25 (1)
Nausea	42 (0)	51 (5)	32 (1)	36 (0)
Vomiting	35 (2)	41 (9)	32 (3)	16 (0)
Rash	32 (9)	41 (11)	24 (2)	19 (1)
Pyrexia	27 (1)	16 (0)	18 (1)	12 (1)
Abdominal pain	23 (1)	25 (2)	13 (1)	7 (<1)
Fatigue	23 (1)	25 (2)	13 (1)	14 (1)
Elevated AST	49 (4)	55 (7)	27 (8)	9 (3)
Elevated ALT	55 (10)	66 (11)	32 (18)	8 (3)
Elevated creatinine	37 (1)	41 (0)	NR	NR OK

AST aspartate aminotransferase, *ALT* alanine aminotransferase, *BELA* bosutinib efficacy and safety in newly diagnosed CML, *IMA-I* imatinib-intolerant, *IMA-R* imatinib-resistant, *NR* not reported

SAFETY OF BOSUTINIB AMONG NEWLY DIAGNOSED CP PATIENTS

A recently published update of the BELA trial reported safety analysis after more than 30 months of follow-up. In the bosutinib group gastrointestinal side effects were more frequent, for example diarrhea 70% compared with 26% in the imatinib arm and vomiting in 33% versus 16%, respectively. As in the phase 1/2 trial, elevation of alanine aminotransferase and aspartate aminotransferase was observed in the bosutinib group (33% and 28% versus 9% and 10%, respectively). Less common with bosutinib were recorded edema (7% versus 26%), musculoskeletal pain (cramp 5% versus 22%, bone pain 4% versus 11%), and neutropenia (13% v3ersus 30%). No significant difference was noted between the two groups. Gastrointestinal events were usually transient, manageable with concomitant medications, and usually occurred during the first months of treatment. In particular, diarrhea was managed by dose modification and/or concomitant medication [33] (Table 2).

CARDIOVASCULAR SAFETY ANALYSIS

Retrospective analysis evaluating cardiac toxicity data from the 2 studies (BELA and study 200) has been reported. Patients were excluded at study entry if they required medications that prolong the QT interval, had a history of significant/uncontrolled cardiac disease (congestive heart failure, uncontrolled angina, or hypertension within 3 months, myocardial infarction within 12 months,

clinically significant ventricular arrhythmia, diagnosis or suspected congenital or acquired prolonged QT syndrome, history of prolonged QTc, or unexplained syncope), or had average QTc >0.45 s at screening or uncorrected hypomagnesemia or hypokalemia. Treatment-emergent adverse side effects were monitored throughout the studies and coded according to NCI CTCAE version 3.0.

Incidence of exposure-adjusted cardiac adverse side effects was 0.059 for bosutinib and 0.042 for imatinib in the phase 3 BELA study and 0.096 for bosutinib in the phase 1/2 study. The most common cardiac side effect experienced by bosutinib-treated patients in both studies was cardiac arrhythmias (5.7% overall; grade 3/4, 1.5%). Cardiac arrhythmias occurred for 4.0% and 2.0% (grade 3/4, 0.4% and 0%) of bosutinib-treated and imatinib-treated patients, respectively, in the phase 3 BELA study, and in 6.5% (grade 3/4, 1.9%) of bosutinib-treated patients in the phase 1/2 study.

Incidence of heart failures was uncommon overall (2.9% of all bosutinib-treated patients; grade 3/4, 1.7%); it was similar for bosutinib (0.8%; grade 3/4, 0.8%) and imatinib (0.8%; grade 3/4, 0%) in the phase 3 BELA study. The incidence of newly emergent side effects decreased with longer duration of treatment.

In the phase 3 BELA study, discontinuations because of cardiac side effects were numerically higher for bosutinib-treated than for imatinib-treated patients (1.6% versus 0%, respectively). Reasons for discontinuation for the 4 bosutinib-treated BELA patients were pericardial effusion, right bundle branch block, congestive cardiac failure, and ECG QT prolonged.

In both bosutinib studies, few patients (2.0%; grade 3/4, 0.9%) discontinued bosutinib because of cardiac side effects.

In the phase 3 BELA study cardiac side effects leading to dose delays were not significantly more frequent among bosutinib-treated patients than among imatinib-treated patients (3.6% versus 1.6%, respectively; grade 3/4, 0.8% versus 0%). Of 32 patients from both studies whose bosutinib dose was delayed because of adverse side effects, 26 were re-challenged and 6 discontinued bosutinib permanently because of a cardiac side effect.

Analysis of predisposing factors to cardiac events showed that age >65 years, previous history of cardiac disorders, ECOG >0 in the phase 1/2 study and history of hypertension in phase 3 trial, or hypercholesterolemia (in both studies) were significantly associated. Indeed, the incidence of vascular emergent side effects with bosutinib was comparable with that with imatinib in the BELA study [33]. With the exception of hypertension, which was common with bosutinib (in a combined analysis any grade <7%; grade 3/4 <2%), the incidence of vascular side effects was particularly low [34].

CROSS-INTOLERANCE BETWEEN BOSUTINIB AND PREVIOUS TKI

Analysis was conducted to investigate the potential cross-intolerance of bosutinib with previous TKI when used as second or third line treatment. Of 143 patients previously treated with imatinib, 22 (20 in CP and 2 in advanced phase) discontinued the drug for the same effect (prevalently cytopenias). Seventy-one patients previously treated with dasatinib received bosutinib for intolerance: 7 patients in CP and 1 in AP experienced the same side effect (thrombocytopenia and pleural effusions).

Of 7 patients intolerant of nilotinib, 3 patients then discontinued bosutinib for thrombocytopenia also experienced as a result of the previous treatment. This data showed the absence of cross-intolerance between bosutinib and the other drugs [35].

WHICH IS THE IDEAL PLACE FOR BOSUTINIB IN THE CONTEST OF SEVERAL CHOICES?

Considering that agreement on the application of each TKI for management of CML is far from being established, personal perspectives rather specific recommendations for bosutinib use can be drawn.

Undoubtedly, one advantage of this drug is its favorable safety profile. A low incidence of some adverse side effects common with other TKI makes bosutinib a good choice for patients intolerant to other TKI with comorbidities or cardiovascular risk factors. Moreover, bosutinib is active against many BCR-ABL kinase domain mutations resistant to imatinib, dasatinib, and nilotinib, with the exception of T315I and V299L.

Patients who experience treatment failure with a second-generation TKI (2G-TKI) as first or second-line treatment seem to gain limited benefit from sequential use of 2G-TKI; Lipton and colleagues recently reviewed published data and concluded that the probability of complete cytogenetic response ranged from 22% to 26% for the 2G-TKI examined [36].

In conclusion, with the increasing therapeutic options available for CML and continually increasing treatment objectives, healthcare providers have the opportunity to design patient-tailored strategies in accordance with individual characteristics such as age, comorbidities, life-style, treatment history, disease stage, and TKI toxicity profile.

ACKNOWLEDGMENTS

No funding or sponsorship was received for this study or publication of this article. Both authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and the accuracy of the data analysis. Both named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

Conflict of interest. Massimo Breccia and Gianni Binotto declare no conflict of interest.

Compliance with ethics guidelines. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by either of the authors.

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