Bosutinib in the treatment of patients with Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia: an overview

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Abstract: Bosutinib is an orally bioavailable SRC/ABL tyrosine kinase inhibitor with activity against all phases of resistant chronic myeloid leukemia that do not express the *T315I* or *V299L* ABL kinase domain mutations. Bosutinib has a unique toxicity profile that is manageable. This paper provides an overview of bosutinib, covering pharmacodynamics and pharmacokinetic properties, results of treatment in newly diagnosed and previously treated chronic myeloid leukemia patients, as well as common side effects.

Keywords: bosutinib, chronic myeloid leukemia (CML), pharmacodynamic, pharmacokinetic, safety, tolerability, tyrosine kinase inhibitors (TKIs)

Chronic myeloid leukemia: overview

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder of the hematopoietic stem cells characterized by a triphasic clinical presentation, and by the presence of a reciprocal translocation between chromosomes 9 and 22 or the Philadelphia chromosome (Ph+). The juxtaposition of the breakpoint cluster region (BCR) on chromosome 22 with the Abelson gene (ABL) on chromosome 9 leads to a dysregulation of the ABL intrinsic nonreceptor tyrosine kinase activity. By controlling downstream pathways involved in cell proliferation, adhesion, and survival, the hybrid oncogene BCR-ABL is the major driver of leukemogenesis in CML [Konig *et al.* 2008; Sawyers, 1999].

Through the development of tyrosine kinase inhibitors (TKIs), the first successful clinical application of targeted therapy in cancer became a reality. Imatinib (Gleevec®, Novartis Oncology, East Hanover, NJ) was the first approved agent followed by dasatinib (Sprycel®, Bristol-Meyers Squibb Company, Princeton, NJ), nilotinib (Tasigna®, Novartis Oncology, East Hanover, NJ), and in 2012 by bosutinib (Bosulif®, Pfizer, New York, NY) and ponatinib (Iclusig®, Ariad Pharmaceuticals, Cambridge, MA). Bosutinib (BOS) is approved in the United States for the treatment of resistant chronic, accelerated, or blast phase Ph+ CML. This review focuses on BOS, describing pharmacodynamic and pharmacokinetic properties, clinical activity in both previously treated and newly diagnosed CML, as well as a discussion of common side effects and their management.

Bosutinib pharmacokinetics

BOS is an orally bioavailable 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline-3-carbonitrile that acts as a dual inhibitor of BCR-ABL and SRC kinases. In cancer patients, when given as a single dose of 500 mg with food, the median time-to-peak concentration is 4–6 hours. Dose proportional increases in both maximum concentration (C_{max}) and area under the curve (AUC) are observed at doses ranging from 200 to 800 mg. BOS' absorption increases when administered with a high-fat meal, with a 1.8-fold increase in C_{max} and 1.7-fold increase in AUC. BOS is distributed extensively into tissues, as evidenced by a mean apparent volume of distribution of 6080 ± 1230 l. In addition, BOS has been found to be highly protein bound (96%) independently from serum drug concentration. Metabolism of BOS occurs primarily in the liver through CYP3A4. Following the administration of a single 500 mg dose with

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food in patients with CML, the mean (± standard deviation) clearance was 189 (± 48) l/h and the mean terminal phase elimination half-life was 22.5 (± 1.7) hours. Approximately 91% of the BOS dose is eliminated in the feces and 3% in the urine [PfizerLabs, 2013] The solubility of BOS is pH dependent and, therefore, can be affected by the concomitant use of proton-pump inhibitors. When a single 400 mg dose of BOS was given concurrently with repeated doses of lansoprazole 60 mg to 24 healthy fasting subjects, the BOS C_{max} and AUC decreased by 46% and 26%, respectively. Therefore, when possible, the concurrent use of proton-pump inhibitors with BOS should be avoided; otherwise, short-acting antacids or histamine-2 receptor antagonists are good alternatives if taken 2 hours before or after BOS. Since BOS is a major substrate of CYP3A4, the concurrent administration of drugs that are known CYP inhibitors (e.g. ketoconazole, posaconazole, clarithromycin [Lexi-Comp Online, 2013] or inducers (e.g. rifampin, phenytoin, oxcarbazepine [Lexi-Comp Online, 2013] may affect BOS plasma concentrations. Furthermore, P-glycoprotein (P-gp) inhibitors and grapefruit or grapefruit juice should be avoided as their administration may result in increased BOS plasma concentrations [PfizerLabs, 2013].

BOS inhibits proliferation of human and murine BCR-ABL1 expressing leukemia cell lines at concentrations ranging between 1 and 20 nM. Imatinib-resistant human cell lines, such as Lama84R, KCL22R and K562R or murine pro-B Ba/F3 cells transfected with imatinib-resistant mutated forms of BCR-ABL1 are sensitive to BOS, with the exception of the cells expressing the *V299L* and *T315I* mutations. BOS inhibits tyrosine phosphorylation of BCR-ABL, the Lyn SRC family kinases and the transcription factor Stat5, albeit at much lower concentrations for the latter. Indeed, contrary to imatinib, dasatinib and nilotinib, CrkL phosphorylation is generally less sensitive to the inhibitory effect of BOS as compared to Stat5 or AblY245.

In a nude mouse xenograft transplant model, BOS given by gavage at 75 mg/kg twice daily or 150 mg/kg once daily for up to 40 days results in complete regression of K562 or KU812 tumors [Golas *et al.* 2003; Puttini *et al.* 2006]. As expected, BOS does not affect proliferation of highly imatinib-resistant *T315I* expressing BCR-ABL1 BaF3 cells [Puttini *et al.* 2006].

Clinical activity of Bosutinib

The safety and efficacy of BOS was assessed in a phase I/II study that enrolled 288 CML patients, initially with imatinib resistance or intolerance [Cortes *et al.* 2011], and later with resistance or intolerance to nilotinib (NIL) or dasatinib (DAS) when these agents were approved commercially (an additional 119 CML patients in chronic phase) [Khoury *et al.* 2012]. The dose escalation phase of this trial determined that BOS 500 mg once daily was the recommended phase II dose. In the phase II portion of this trial, and with a median follow-up of 24 months, 86% of the patient in chronic phase (CP) achieved a complete hematological remission (CHR) and 53% achieved a major cytogenetic remission (MCyR). Cytogenetic response was complete in 41% (Table 1). Progression-free survival was 79% and overall survival was 92%. Among the 134 patients enrolled beyond the CP [Gambacorti-Passerini *et al.* 2010], 63 had accelerated phase (AP), 48 blast phase (BP), and 23 had Philadelphia chromosome positive acute lymphoid leukemia (Ph+ ALL). With a median follow up of 8.3 months, CHR or hematological response were achieved in 47% (61% AP, 32% BP, and 25% Ph+ ALL), and complete cytogenetic remission (CCyR) in 34% (33% AP, 29% BP, 100% Ph+ ALL). Overall, progression free survival was 11.6 months for AP, 7.8 months for BP, and 2.7 months of Ph+ ALL. In the subgroup of 119 CP patients who received BOS beyond the second-line treatment [Khoury *et al.* 2012], responses were also very encouraging with CHR achieved in 73% and MCyR in 41% of patients. With a median follow-up of 24 months, progression-free survival was 75% and overall survival was 84%.

The efficacy of BOS in newly diagnosed CP-CML was assessed in a phase III randomized trial where 502 patients were randomized 1:1 to BOS 500 mg/day or imatinib (IM) 400 mg/day [Cortes *et al.* 2012]. At 12 months, the rates of CCyR were comparable in both arms (70% with BOS *versus* 68% with IM; see Table 2). However, BOS did demonstrate a significantly higher rate of major molecular response (MMR) at 12 months as compared with IM (41% *versus* 27%) as well as a faster time to both CCyR (12.9 *versus* 24.6 weeks) and MMR (37.1 *versus* 72.3 weeks). Fewer patients treated with BOS experienced on-treatment transformation to the advanced AP/BP (2 *versus* 4%), and fewer on-study disease-related deaths occurred in the BOS arm (2% *versus* 6%). In the intent-to-treat analysis, with the failure to

Table 1. Response to treatment with bosutinib given as second or third line in patients with chronic myeloid leukemia and Philadelphia chromosome positive acute lymphoblastic leukemia.

Response	Second-line CP-CML treatment		Third-line CP-CML treatment			Advanced phases		
	IM resistant (n = 200)	IM intolerant (n = 88)	IM+DAS resistant (n = 37)	IM+DAS intolerant (n = 50)	IM+NIL resistant (n = 27)	AP CML (n = 63)	BP CML (n = 48)	Ph+ ALL (n = 23)
CHR	86%	85%	62%	80%	76%	61%	32%	25%
CCyR	41%	41%	19%	43%	27%	33%	29%	100%
CMR	49%	61%	0%	19%	11%	4%	12%	23%

CP-CML, chronic phase chronic myeloid leukemia; IM, imatinib; DAS, dasatinib; NIL, nilotinib; AP, advanced phase; BP, blast phase; Ph+ ALL, Philadelphia chromosome positive acute lymphoblastic leukemia; CHR, complete hematological remission; CCyR, complete cytogenetic remission; CMR, complete molecular remission.

Table 2. Response to treatment with bosutinib and imatinib in the randomized trial for first-line treatment of chronic phase chronic myeloid leukemia.

Response	Bosutinib		Imatinib	
	%	*Time to response*	%	*Time to response*
CCyR	70%	12.9 weeks	68%	24.6 weeks
MMR	41%	37.1 weeks	27%	72.3 weeks

CCyR, complete cytogenetic remission; MMR, major molecular remission.

reach the primary endpoint of the study, i.e. CCyR, BOS was not considered for an upfront treatment indication. Of interest, a high number of patients discontinued BOS (19% *versus* 6%), due to early adverse side effects, and 31% of these discontinuations occurred before the first post-baseline response assessment at 3 months. Adverse events that led to early discontinuations included elevated aminotransferase (33%), vomiting (20%), anaphylactic shock (13%), and to a lesser extent, dissociative disorder, dyspepsia, elevated lipase, thrombocytopenia, and rash, at 7% each.

With the exception of *V299L* and *T315I*, BOS demonstrated efficacy in IM-resistant CML patients across all phases and regardless of the presence or not of a detectable ABL domain mutation [Cortes *et al.* 2011], including those conferring resistance to DAS and NIL [Khoury *et al.* 2012]. Therefore, and as recommended by the ELN and NCCN, mutation analysis in cases of suboptimal responses at 3, 12, and 18 months, at the time of loss of response or disease progression, provide very useful information to guide change in therapy. Comparable CHR and MCyR rates were observed across all 115 patients with detectable mutations at baseline.

Safety and tolerability of bosutinib

BOS demonstrates a distinct safety profile. Diarrhea is the most common adverse event occurring in 84% of patients [Cortes *et al.* 2011]. Diarrhea usually starts soon after initiation of BOS (median 2 days), and is short-lived (median duration 2 days). Diarrhea is most often (75%) of low severity (grades 1 and 2), self-limited and easily managed with anti-diarrheal medications, such as diphenoxylate atropine or loperamide, which are more effective when administered early at the first sign of diarrhea. Concomitant antidiarrheal medications were effective in controlling and managing this adverse side effect in most cases. In clinical trials, diarrhea led to drug interruption in 14%, and 95% of those did not have diarrhea reoccurrence when rechallenged with BOS.

In addition to diarrhea, nonhematological adverse events that occur in greater than 20% of patients include nausea, vomiting, abdominal pain, rash, fatigue, and headaches [Khoury *et al.* 2012] (Table 3). Nausea and vomiting can be managed with antiemetics such as ondansetron, prochlorperazine, and promethazine. Proton-pump inhibitors, H2 blockers, and antacids should be avoided if possible due to risks of decreasing bosutinib absorption. Skin rashes presenting as macular,

Table 3. Adverse events associated with treatment with bosutinib in imatinib-resistant or imatinib-intolerant patients with chronic myeloid leukemia and Philadelphia chromosome positive acute lymphoblastic leukemia.

Adverse events	Grade 3/4 (%)	All grades (%)
Nonhematological		
Diarrhea	8	81
Nausea	1	46
Vomiting	3	39
Fatigue	2	23
Rash	7	33
Increased ALT	7	17
Increased AST	4	14
Hematological		
Anemia	12	24
Thrombocytopenia	24	33
Leukopenia	11	15

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

papular, and pruritic rash, acne, allergic dermatitis, folliculitis, or skin exfoliation, occur in 22% of patients. Overall 90% of these rashes are grades 1/2, are often easily managed with topical supportive care, such as diphenhydramine or hydrocortisone, and resolve with time, and without discontinuation of BOS. Other less common adverse events include fluid retention (15%), pleural effusions (8%), arthralgias (14%), constipation (13%), and dyspnea (12%). Only 2% of these events are severe (grades 3/4).

The most common laboratory adverse event is elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) that are reported in 10–13% and is most often (90%) grades 1/2. These ALT and AST elevations occur early after initiation of BOS (in the first month), resolve 10–15 days after holding the drug, and led to dose reductions, interruptions or discontinuation in 1–3% in the phase I/II trial [Cortes *et al.* 2011]. When rechallenged with BOS, the majority of patients (90%) do not experience recurrence of ALT/AST elevations.

Similar to what has been seen in other TKIs, myelosuppression (anemia, neutropenia, and thrombocytopenia) are frequently reported during BOS treatment. Thrombocytopenia is common, with 25% experiencing grades 3/4 toxicity. Grades 3/4 neutropenia and anemia occur in 19% and 8%, respectively [Khoury *et al.* 2012]. Myelosuppression is transient, and is effectively managed with dose-reductions or interruptions. Only 6% of patients on clinical trials permanently discontinued BOS treatment due to myelosuppression.

Conclusions

BOS is an effective, safe, and relatively well-tolerated addition to the therapeutic arsenal against CML. BOS has shown activity in all phases of CML regardless of the presence or not of ABL-kinase domain mutations, with the exception of *T315I* and *V299L*. BOS demonstrates a distinct toxicity profile, the most common of which are gastrointestinal toxicities that are transient and manageable with prophylactic and/or concomitant medications. In the absence of the detection of *T315I* and *V299L* mutations, there are no contraindications for the use of BOS. With the increasing therapeutic options in CML, healthcare providers have the luxury to select a TKI based on factors such as age, comorbidities, schedule of administration, toxicities of previous TKI therapy, as well as patient/family member and physician preference in order to individualize treatment options and plan of care.

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Conflict of interest statement

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