Review

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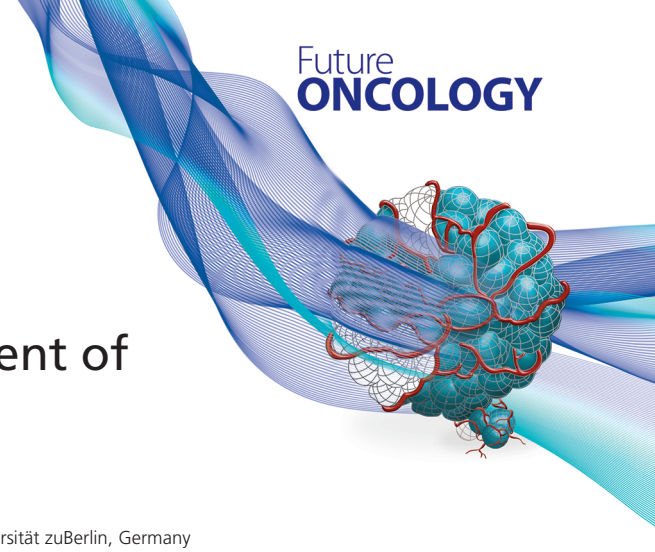

The role of bosutinib in the treatment of chronic myeloid leukemia

Carlo Gambacorti-Passerini*[,1], Philipp le Coutre[2,3] & Rocco Piazza[1]

[1]Department of Medicine & Surgery, University of Milano-Bicocca, Italy

[2]Charité–Universitätsmedizin Berlin, Corporate member of Freie Universität Berlin, Humboldt-Universität zuBerlin, Germany

[3]Berlin Institute of Health, Department of Hematology, Oncology, and Tumor Immunology, Berlin, Germany

*Author for correspondence: carlo.gambacorti@unimib.it

The availability of several *BCR-ABL1* tyrosine kinase inhibitor (TKI) options means physicians and patients can select the most appropriate treatment for a patient with chronic myeloid leukemia (CML). *BCR-ABL* TKI selection as a first- or later-line therapy is dependent on a number of clinical factors. Regular monitoring of patients, patient education, dose optimization and management of treatment-emergent adverse events are key aspects of long-term chronic myeloid leukemia management and contribute to improved clinical outcomes, quality of life, patient adherence and healthcare costs. This review provides an overview of the *BCR-ABL1* TKI bosutinib, its pharmacology and clinical trials; discusses the impact of comorbidities and concomitant medications on bosutinib treatment selection; and suggests strategies for managing adverse events and dose optimization during bosutinib treatment.

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Introduction to chronic myeloid leukemia

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm defined by the presence of the Philadelphia (Ph) chromosome. CML is most frequently diagnosed among people aged 65–74 years, and has a 5-year survival rate of 69.2% [1]. CML can be classified into three stages: chronic phase (CP), accelerated phase (AP) and blast phase (BP) [1–5]. Without treatment, CP CML will progress to AP CML in 3–5 years [3,6].

Until 2000, treatment for CML was limited to hematopoietic stem cell transplant (HSCT) or treatment with busulfan, hydroxyurea or IFN-α. The development of *BCR-ABL1*–targeting tyrosine kinase inhibitors (TKIs) for the treatment of CML has revolutionized the treatment of this disease [2–4,7–10]. Imatinib (Glivec®/Gleevec®) was the first *BCR-ABL1*–targeting TKI, which was approved for CML in 2001 by both the US FDA and the EMA [11,12]. This was followed by dasatinib (Sprycel®), which in 2006 was the first second-generation *BCR-ABL1* TKI approved for CML (by both FDA and EMA) [13,14]. Nilotinib (Tasigna®), another second-generation *BCR-ABL1* TKI, was approved for CML in 2007 (by both FDA and EMA) [15,16], followed by bosutinib (Bosulif®), which received approval in 2012 by the FDA and in 2013 by the EMA [17,18]. A third-generation *BCR-ABL1* TKI, ponatinib (Iclusig®), was also approved for CML in 2012 by the FDA and in 2013 by the EMA [19,20]. The availability of imatinib and other *BCR-ABL1* TKIs allowed the prognosis of patients with CML to progressively ameliorate up to a normal life expectancy [21,22].

Current treatment options for adult patients with newly diagnosed (i.e., first-line) CP Ph+ CML are imatinib, dasatinib, nilotinib and bosutinib [11–18]. Imatinib is also approved for the treatment of patients with Ph+ CML in BP, AP or in patients with CP CML after failure of IFN-α therapy [11,12]. Dasatinib, bosutinib and ponatinib are approved for patients with CP, AP or BP Ph+ CML with resistance or intolerance to prior therapy, including imatinib [13,14,17–20]. Nilotinib is approved for the treatment of patients with CP and AP Ph+ CML who are resistant to or intolerant to prior therapy, including imatinib [15,16].

Given that there are now several *BCR-ABL1* TKI options available for patients with CML, the selection of first- and later-line therapy is dependent on a number of clinical and patient factors. This review discusses the role of bosutinib in the treatment of patients with CML.

Introduction to bosutinib

Bosutinib (also known as SKI-606), has been shown to bind to the kinase domain of *BCR-ABL1*. In murine myeloid cell lines, bosutinib also inhibited 16 of 18 imatinib-resistant forms of *BCR-ABL1* kinase [17,18,23–27]. The Src family kinases Src, Lyn and Hck, as well as platelet-derived growth factor (PDGF) receptor and c-Kit, have also been shown to be inhibitory targets of bosutinib [17,18,23–27].

In pharmacokinetic studies, bosutinib exhibited dose-proportional increases in area under the plasma concentration–time curve and maximum plasma concentration (C_{max}) over the oral dose range of 200–800 mg [17,18,28,29]. Across different dose groups, median time to C_{max} was 3.0–6.0 h [29]. The absolute bioavailability of a single oral dose of bosutinib 500 mg was 34% in healthy volunteers [17,18,29]. Protein binding of bosutinib was 94% *in vitro* and 96% *ex vivo*, and was independent of concentration [17,18,29]. Following a single intravenous dose of bosutinib 120 mg, the mean (standard deviation [SD]) terminal phase elimination half-life ($t_{1/2}$) was 35.5 (8.5) h and the mean (SD) drug clearance (CL) was 63.6 (14.1) l/h [17,18,29]. Following a single oral dose of bosutinib in patients with CML, the mean (SD) $t_{1/2}$ was 22.5 (1.7) h, and the mean (SD) CL was 189 (48) l/h [17,18,29]. Bosutinib undergoes predominantly hepatic metabolism in humans and is primarily metabolized by cytochrome P450 (CYP) 3A4. More than 90% of bosutinib is excreted in the feces [17,18,29].

In preclinical safety studies, treatment with bosutinib had no effect on respiratory function and blood pressure and no/minimal impact on cardiac function [17,18]. Bosutinib also has not demonstrated any mutagenic, carcinogenic, phototoxic or clastogenic potential [17,18]. Some reproductive and developmental toxicity, as well as fertility impairment, was reported during bosutinib treatment in preclinical animal studies conducted in rats and rabbits [17,18]. In fertility studies, a slight decrease in fertility was observed in male rats; increased embryonic resorptions, and decreases in implantations and viable embryos were observed in female rats [17,18].

Bosutinib 400 mg once daily (QD) is approved for the treatment of patients with newly diagnosed CP Ph+ CML and at 500 mg QD in patients with CP, AP or BP Ph+ CML with resistance or intolerance to prior therapy [17,18].

Bosutinib as a first-line option for the treatment of CML

Bosutinib 400 mg QD is approved as first-line treatment in patients with newly diagnosed CP Ph+ CML [17,18].Two studies, BFORE and BELA, are pivotal Phase III trials of bosutinib in the first-line setting (Table 1). The BFORE trial investigated bosutinib 400 mg QD compared with imatinib 400 mg QD [30,31]. Results showed that patients who received bosutinib had significantly higher rates of major molecular response (MMR) at and complete cytogenetic response (CCyR) by 12 and 24 months, and achieved responses faster, compared with imatinib-treated patients, for example, MMR and CCyR rates at 12 months were 47 versus 37% and 77 versus 66% for bosutinib and imatinib, respectively [30,31]. The BELA trial investigated first-line bosutinib 500 mg QD versus imatinib 400 mg QD [32–35]. The BELA trial did not meet its primary end point of CCyR at 12 months (70 vs 68%), despite a higher MMR rate (41 vs 27%), faster times to CCyR and MMR, and a trend toward fewer on-treatment transformations to AP/BP with bosutinib versus imatinib [32–35]. This negative result was probably due to multiple factors: the higher dose administered, resulting in high rates of dose interruptions (61 vs 42%) and discontinuations (19 vs 6%) in the bosutinib group compared with the imatinib group [32–35]. This was further compounded by a number of centers being relatively inexperienced in administering bosutinib. In both trials, the safety profile of bosutinib was consistent with previous reports and no new safety signals were identified [30–35].

Bosutinib has not been directly compared with IFN-α, dasatinib or nilotinib; however, these agents have been evaluated in comparison with imatinib in Phase III trials in the first-line setting. In the IRIS trial, patients administered imatinib had improved hematologic and cytogenetic responses compared with patients who received IFN-α [36,37]. Both dasatinib 100 mg QD and nilotinib 300 and 400 mg twice-daily doses demonstrated significantly greater CCyR and MMR compared with imatinib 400 mg QD in the DASISION and ENESTnd trials, respectively [38–41]. In terms of safety, although the *BCR-ABL* TKIs share some common class-wide side effects and were generally well tolerated in their respective clinical trials, each agent has a distinct safety profile, discussed later in this review, that should be considered by clinicians during first-line treatment selection [30–41].

Bosutinib in the setting of second- & later-line CML treatment

In patients with CP, AP or BP Ph+ CML with resistance or intolerance to prior therapy, the approved bosutinib dose is 500 mg QD [17,18]. Key trials of bosutinib in the second- and later-line settings include a single-arm, Phase I/II trial and the Phase IV BYOND trial (Table 2). The Phase I/II trial was an open-label, multicenter study that evaluated bosutinib 500 mg QD in patients with imatinib-resistant or -intolerant CML, with separate cohorts for

Table 1. Key trials of bosutinib in the first-line setting of chronic myeloid leukemia.

Trial	Treatment arms	Main efficacy findings	Main safety findings	Long-term follow-up efficacy data	Long-term follow-up safety data
Phase III BFORE trial in patients with newly diagnosed CP CML [30,31]	• Bosutinib 400 mg QD • Imatinib 400 mg QD	MMR rate at 12 months: • Bosutinib: 47.2% • Imatinib: 36.9% • p = 0.02 CCyR rate by 12 months: • Bosutinib: 77.2% • Imatinib: 66.4% • p = 0.0075 12-month survival rate: • Bosutinib: 99.6% • Imatinib: 97.9% Dose escalations due to suboptimal response: • Bosutinib: 17.2% • Imatinib: 27.5%	Most common AEs with bosutinib: • Diarrhea: 70.1% • Nausea: 35.1% • Thrombocytopenia: 35.1% Most common AEs with imatinib: • Nausea: 38.5% • Diarrhea: 33.6% • Muscle spasms: 26.4% Discontinued treatment: • Bosutinib: 22.0% • Imatinib: 26.8% Dose interruptions and reductions due to AEs: • Bosutinib: 56.3% • Imatinib: 35.8%	MMR by 24 months: • Bosutinib: 67.2% • Imatinib: 57.5% • p = 0.02 Cumulative CCyR: • Bosutinib: 82.5% • Imatinib: 76.8% • p = 0.113 OS at 24 months: • Bosutinib: 99.2% • Imatinib: 97.0% Dose escalations due to suboptimal response: • Bosutinib: 20.1% • Imatinib: 30.9%	AEs related to study drug: • Bosutinib: 16.0% • Imatinib: 9.8% Discontinued treatment: • Bosutinib: 29.1% • Imatinib: 33.6% Dose delay due to AEs: • Bosutinib: 60.4% • Imatinib: 38.9% Dose reductions due to AEs: • Bosutinib: 40.3% • Imatinib: 21.5%
Phase III BELA trial in patients with newly diagnosed CP CML [32–35]	• Bosutinib 500 mg QD • Imatinib 400 mg QD	CCyR rate at 12 months: • Bosutinib: 70% • Imatinib: 68% • p = 0.601 MMR rate at 12 months: • Bosutinib: 41% • Imatinib: 27% • p < 0.001 Confirmed CHR at 12 months: • Bosutinib: 71% • Imatinib: 85% • p > 0.999 OS at 12 months: • Bosutinib: >99% • Imatinib: 97% Dose escalations due to suboptimal response: • Bosutinib: 4% • Imatinib: 12%	Most common AEs with bosutinib: • Anemia: 81% • Diarrhea: 68% • Thrombocytopenia: 66% Most common AEs with imatinib: • Anemia: 84% • Thrombocytopenia: 63% • Hypophosphatemia: 63% Discontinued treatment due to AEs: • Bosutinib: 19% • Imatinib: 6% Dose interruptions due to AEs: • Bosutinib: 61% • Imatinib: 42% Dose reductions due to AEs: • Bosutinib: 39% • Imatinib: 18%	Cumulative CCyR rate by 24 months: • Bosutinib: 79% • Imatinib: 80% MMR rate at 24 mo: • Bosutinib: 47% • Imatinib: 41% Dose escalations due to suboptimal response: • Bosutinib: 6% • Imatinib: 18% 24-month survival rate: • Bosutinib: 97% • Imatinib: 95%	Discontinued treatment due to AEs: • Bosutinib: 25% • Imatinib: 9% Dose interruptions due to AEs: • Bosutinib: 66% • Imatinib: 45% Dose reductions due to AEs: • Bosutinib: 43% • Imatinib: 21%

AE: Adverse event; CCyR: Complete cytogenetic response; CHR: Complete hematologic response; CML: Chronic myeloid leukemia; MMR: Major molecular response; OS: Overall survival; QD: Once daily.

CP, AP and BP CML [42–47]. In this trial, bosutinib demonstrated durable efficacy and a manageable safety profile in patients with CML treated for up to 5 years [42–47]. The Phase IV BYOND trial of bosutinib 500 mg QD included patients with CML after failure of prior TKI treatment and those who are otherwise not appropriate for treatment with other TKIs [48]. Patients treated with bosutinib showed high rates of cytogenetic and molecular responses, including a large proportion of patients who achieved deep molecular responses; in patients with CP Ph+ CML, 81.3% achieved CCyR and 71.8% achieved MMR [48]. In both the Phase I/II trial and BYOND, treatment with bosutinib was tolerable and manageable; diarrhea and nausea were the most common adverse events (AEs) in both trials [42–48].

In patients with imatinib-resistant or -intolerant CP CML, both dasatinib (Phase III trial, CA180-034) and nilotinib (Phase II trial) have reported long-term efficacy and acceptable safety profiles [49,50]. In the Phase II PACE trial, ponatinib demonstrated durable and clinically meaningful efficacy and acceptable tolerability in patients with imatinib-resistant or -intolerant CP CML [51]. There are no comparative trials for these *BCR-ABL1* TKIs in the second- and later-line settings; however, in a matching-adjusted indirect comparison analysis in patients in second-line treatment of CP CML, both progression-free survival and overall survival were longer with bosutinib compared with either dasatinib or nilotinib [52]. Dasatinib and nilotinib reported numerically greater responses versus bosutinib for major cytogenetic response (MCyR) [52].

Table 2. Key trials of bosutinib in the second- and later-line settings of chronic myeloid leukemia.

Trial	Treatment arms	Main efficacy findings	Main safety findings	Long-term follow-up efficacy data	Long-term follow-up safety data
Phase I/II open-label, multicenter trial in patients with imatinib-resistant or imatinib-intolerant CP CML [42,47]	• Bosutinib 500 mg QD	MCyR at 24 wk: • All patients: 31% • Imatinib-resistant: 33% • Imatinib-intolerant: 27% Achieved MCyR during the study: 53% Achieved CCyR during the study: 41% OS at 1 yr: 97% OS at 2 yr: 92%	Most common non-hematologic AEs: • Diarrhea: 84% • Nausea: 44% • Rash: 44% Discontinued treatment due to AEs: 21% Most common AEs leading to discontinuation: • Thrombocytopenia: 4% • Increased ALT: 2% • Increased AST: 2% • Diarrhea: 2% Dose interruptions due to AEs: • All patients: 66% • Imatinib-resistant: 61% • Imatinib-intolerant: 77% Dose reductions due to AEs: • All patients: 47% • Imatinib-resistant: 43% • Imatinib-intolerant: 56%	Cumulative MCyR rate: • Week 12: 35% • Year 2: 58% • Year 5: 60% Cumulative CCyR rate: • Week 12: 22% • Year 2: 46% • Year 5: 50% Cumulative MMR rate: 42% Probability of OS at year 2: 91% Probability of OS at year 5: 84% Discontinued treatment: • By year 2: 46% • Years 3–5: 13%	Discontinued treatment due to AEs: 24% Most common hematologic AEs: • Thrombocytopenia: 42% • Anemia: 29% • Neutropenia: 16% Most common non-hematologic AEs: • Diarrhea: 86% • Nausea: 46% • Vomiting: 37%
Phase IV BYOND trial in patients with CML and resistance/intolerance to prior treatment [48]	• Bosutinib 500 mg QD	Cumulative confirmed MCyR by 1 year in patients with CP Ph+ CML: 75.8% Cumulative confirmed OHR response by 1 year in patients with AP CML: 75.0% Cumulative CCyR in patients with CP Ph+ CML: 81.3% Cumulative MMR in patients with CP Ph+ CML: 71.8% OS in patients with CP Ph+ CML: At 1 year: 98.0% At 2 year 96.0%	Discontinued treatment due to AEs in patients with CP Ph+ CML: 25.0% Most common AEs in the overall patient population: • Diarrhea: 87.7% • Nausea: 39.9% • Vomiting: 32.5% Grade 3/4 AEs occurring in >10% of patients in the overall patient population: • Diarrhea: 16.0% • Increased ALT: 14.1% Dose reductions due to AEs in patients with CP Ph+ CML: 78.2% Dose delays due to AEs in patients with CP Ph+ CML: 75.6%	Ongoing	Ongoing

AE: Adverse event; ALT: Alanine aminotransferase; AP: Accelerated phase; AST: Aspartate aminotransferase; CCyR: Complete cytogenetic response; CHR: Complete hematologic response; CML: Chronic myeloid leukemia; CP: Chronic phase; MCyR: Major cytogenetic response; MMR: Major molecular response; OS: Overall survival; Ph: Philadelphia chromosome; QD: Once daily.

General considerations for bosutinib treatment selection in CML

Disease risk

Disease risk status is a consideration for treatment selection in newly diagnosed patients with CP CML. Currently, there are three prognostic scoring systems utilized in clinical practice: Sokal, Hasford (Euro) and European Treatment and Outcome Study (EUTOS) [2–4,9,53–56]. These scoring systems use clinical parameters to predict outcomes, for example, the EUTOS score is based on spleen size and the percentage of basophils in the blood, whereas the Sokal and Hasford scores include a number of factors, such as spleen size, age, peripheral blood blasts and platelet count [2–4,9,53–56]. Patients with low-risk scores are likely to respond to treatment with any *BCR-ABL1* TKI, whereas a second-generation TKI, such as bosutinib, dasatinib or nilotinib, might be preferable in patients with intermediate or high-risk scores [2–4,9,53–56]. However, no controlled study has demonstrated a significant decrease in progression to AP/BP in patients receiving a second-generation *BCR-ABL1* TKI compared with imatinib [57].

Comorbidities & concomitant medications

The number of patients with comorbid conditions in clinical trials is typically low and/or patients with certain conditions are excluded from entering the trial. This is in contrast to clinical practice, where many patients will present with comorbid conditions and receive concomitant medications; conditions may also arise during their therapy plan that require supportive care to manage the disease. These factors can have a large impact on the selection of treatments for first-, second- and later-line CML, including treatment with bosutinib (Table 3) [2–4,9,58–61].

In patients with a low number of cardiovascular risk factors, any *BCR-ABL1* TKI can be administered. Bosutinib, as well as imatinib and dasatinib, is generally recommended in patients with a higher number of cardiac or vascular risk factors or comorbidities, for example, patients with history of arrhythmias, poorly controlled hypertension, peripheral arterial occlusive disease or heart disease [2,3,8,9,58,60,62–65,67–70]. However, bosutinib should be used with caution in patients receiving agents that have the potential to prolong the corrected QT (QTc) interval, for example, anti-arrhythmic medications or others such as chloroquine, clarithromycin, domperidone and methadone [17,18].

In patients with pulmonary comorbidities or a history of lung disease, such as chronic obstructive pulmonary disease, bosutinib is generally associated with a lower risk of pulmonary AEs compared with dasatinib; therefore, bosutinib is recommended, as are imatinib, nilotinib and ponatinib, in these patients [2,3,8,9,60,63,65]. Additionally, bosutinib may also be preferable in patients at risk of developing pleural effusions, pulmonary arterial hypertension or pneumonitis [2,3,8,9,60,63,65]. However, fluid retention has been reported, although rarely, during bosutinib treatment, and may manifest as pericardial effusion, pleural effusion, pulmonary edema and/or peripheral edema; therefore, patients should be monitored for these symptoms and managed using supportive care and/or modification to a bosutinib therapy plan, where necessary [17,18].

In patients with diabetes or hyperglycemia, bosutinib is recommended, as are imatinib and dasatinib, but should be used with caution in patients with pancreatitis or a history of pancreatitis [3,8,17,18,60,63,65]. Elevations in serum transaminases have been reported during treatment with bosutinib; therefore, bosutinib should be used with caution in patients with hepatic comorbidities. All *BCR-ABL1* TKIs are predominantly metabolized via the CYP system; therefore, concomitant administration of bosutinib with CYP3A4 inhibitors and inducers should be avoided, where possible [3,8,17,18,63,65]. In patients with hepatic or renal impairment, bosutinib dose reductions are recommended, as well as periodic monitoring during treatment [17,18].

Bosutinib should be used with caution in patients with gastrointestinal comorbidities, in particular patients with diarrhea, chronic inflammatory bowel disease or gastric ulcer [3,8,17,18,63,65]. Common AEs during treatment with bosutinib include diarrhea, nausea, vomiting and abdominal pain; therefore, patients should be regularly monitored and supportive care administered, where necessary. Additionally, concomitant administration of bosutinib with proton pump inhibitors (PPIs) decreased bosutinib exposure compared with bosutinib alone, and may lead to reduced efficacy. Therefore, co-administration of bosutinib with PPIs should be avoided, and replaced with short-acting antacids or H2 antagonists. The administration times of short-acting antacids/H2 antagonists and bosutinib should also be separated, where possible [3,8,17,18,58,63,65].

In preclinical studies, congenital abnormalities and reproductive toxicity were reported during bosutinib treatment in female animals. There were also reports of a risk in decreased fertility in male animals [17,18]. However, a review of pregnancy outcomes in patients with CML treated with bosutinib reported the number of spontaneous abortions and malformations were within the range for normal pregnancies, and that there were no specific bosutinib-induced abnormalities [71]. However, treatment with bosutinib is not recommended at any time during pregnancy [17,18]. It is not yet known if bosutinib and/or its metabolites are excreted in human milk, and breastfeeding should be discontinued during treatment with bosutinib [17,18]. Prior to starting bosutinib treatment, female patients with CML should receive a pregnancy test. Contraceptive use is recommended for female patients during treatment and for $\geq$1 month after the last dose of bosutinib. There are currently no restrictions for male patients with CML; however, males and their female partners should be made aware of the potential risks associated with bosutinib during pregnancy [17,18].

Management of AEs

The introduction of *BCR-ABL1* TKIs has led to a shift in the treatment goals for CML. In many cases, CP CML has transformed from a terminal disease to a long-term chronic condition. Therefore, one of the biggest challenges in long-term therapy plans is monitoring and managing treatment-emergent AEs [2,8,72,73]. Effective AE monitoring and management can lead to improved clinical outcomes, quality of life and treatment adherence [3,56,65,70,72,74]. Careful consideration of the patient's medical history, risk factors, pre-existing comorbidities and concomitant

Table 3. Summary of bosutinib use in patients with concomitant medications, comorbidities or other special populations.

Parameter	Use of bosutinib
Dosing and administration	• 400 mg QD with food in newly diagnosed patients with CP Ph+ CML • 500 mg QD with food in CP, AP or BP Ph+ CML with resistance or intolerance to prior therapy
Concomitant medications	
Antacids, H2 antagonists, PPIs	• Use short-acting antacids or H2 antagonists as alternative to PPIs • Separate administration times, i.e., take bosutinib in the morning and antacids/H2 antagonists in the evening, whenever possible
CYP substrates, inhibitors and inducers	• Co-administration of CYP3A4 inhibitors and inducers should be avoided • If concomitant use of CYP3A4 inhibitors and inducers is necessary, consider dose reductions or interruptions
QTc prolonging agents	• Use with caution in patients taking anti-arrhythmic medications or products such as chloroquine, clarithromycin, domperidone, halofantrine, haloperidol, methadone and moxifloxacin
Comorbidities and other special populations	
CV comorbidities	• Generally lower risk of CV AEs; therefore, recommended alongside imatinib and dasatinib • However, CV risk factors should be assessed and a baseline ECG performed prior to treatment initiation • Correct hypokalemia or hypomagnesemia prior to treatment and regularly monitor during treatment
Pulmonary comorbidities	• Generally lower risk of pulmonary AEs; therefore, recommendable alongside imatinib, nilotinib and ponatinib • Fluid retention may manifest as pleural effusion and/or pulmonary edema • In cases of pleural effusion and/or pulmonary edema, monitor patients and manage using standard of care treatment. Consider withholding bosutinib, or dose reductions or discontinuations
Pancreatitis and diabetes	• In patients with diabetes, bosutinib is recommended, as is imatinib and dasatinib • In patients with pancreatitis or a history of pancreatitis, bosutinib should be used with caution
Gastrointestinal comorbidities	• Diarrhea, nausea, vomiting and abdominal pain have been reported during bosutinib treatment • Bosutinib should be used with caution in patients with diarrhea, chronic inflammatory bowel disease or gastric ulcer • Monitor and manage patients, as necessary, using standards of care • Consider dose reductions or discontinuations
Hepatic comorbidities	• Elevations in serum transaminases have been reported during bosutinib treatment • In patients with liver disease or a history of liver disease, bosutinib should be used with caution • Monitor liver enzymes at least monthly for the first 3 months and where necessary • Consider withholding bosutinib, or dose reductions or discontinuations
Hepatic impairment	In newly diagnosed patients with CP Ph+ CML or CP, AP or BP Ph+ CML with resistance or intolerance to prior therapy: • Mild (Child-Pugh A), moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment: dose reduction to 200 mg QD
Fluid retention	• Fluid retention has been reported during bosutinib treatment, and may manifest as pericardial effusion, pleural effusion, pulmonary edema and/or peripheral edema • Monitor patients and manage using standard of care treatment • Consider withholding bosutinib, or dose reductions or discontinuations
Renal impairment	• Monitor renal function at baseline and during treatment with bosutinib, in particular, for those patients who have pre-existing renal impairment or risk factors for renal dysfunction, including concomitant use of medications with the potential for nephrotoxicity, e.g., diuretics, ACE inhibitors, angiotensin receptor blockers and NSAIDs Newly diagnosed patients with CP Ph+ CML: • Cr_{CL}: 30–50 mL/min: dose reduction to 300 mg QD • Cr_{CL}: <30 mL/min: dose reduction to 200 mg QD CP, AP, or BP Ph+ CML with resistance or intolerance to prior therapy: • Cr_{CL}: 30–50 mL/min: dose reduction to 400 mg QD • Cr_{CL}: <30 mL/min: dose reduction to 300 mg QD
Pregnancy	• Female patients should receive a pregnancy test prior to starting bosutinib treatment, and use contraception during treatment and for ≥1 month after the last dose • There are currently no restrictions for male patients • If pregnancy occurs, both male and female patients should be warned of the potential hazard to the fetus and to discuss risks versus benefits with the healthcare provider

ACE: Angiotensin-converting enzyme; AE: Adverse event; AP: Accelerated phase; BP: Blast phase; CML: Chronic myeloid leukemia; CP: Chronic phase; Cr_{CL}: Creatinine clearance; CV: Cardiovascular; CYP: Cytochrome P450; ECG: Electrocardiogram; H2: Histamine 2 receptor; NSAID: Nonsteroidal anti-inflammatory drug; Ph: Philadelphia chromosome; PPI: Proton pump inhibitor; QD: Once daily; QTc: Corrected QT interval.
Data taken from [2,3,7,9,17,18,56,59,60,62–66].

Table 4. Summary of common adverse events associated with bosutinib treatment and management strategies.

Common AEs	AE management strategies
Gastrointestinal toxicities: • Nausea • Diarrhea • Vomiting	• Take with food and/or water per label instructions • Concomitant administration of anti-nausea, anti-diarrheal, anti-emetic medications and/or fluid replacement • Avoid large meals, alcohol, caffeine, lactose-containing products, laxatives/stool softeners, raw fruits and vegetables, and sweet, spicy or fatty foods • Avoid concomitant use of PPIs • Consider withholding bosutinib, dose reductions or discontinuations • For grade 3–4 diarrhea (≥7 stools/day versus baseline/pre-treatment), withhold bosutinib until recovery to grade ≤1, then resume at 400 mg QD
Myelosuppression: • Neutropenia • Thrombocytopenia	• Regular blood monitoring weekly for the first month of therapy and then monthly thereafter, or as clinically indicated • Advise patients to report any possible signs or symptoms as soon as possible, e.g., fever, signs of infection, easy bruising, unexpected bleeding or blood in urine or stool • Consider withholding bosutinib, dose adjustments or interruptions • Concomitant administration of growth factors for resistant neutropenia and thrombocytopenia For ANC less than 1000×10^6/l or platelets less than $50{,}000 \times 10^6$/l: • Withhold bosutinib until ANC ≥1000×10^6/l and platelets ≥$50{,}000 \times 10^6$/l • Resume treatment with bosutinib at the same dose if recovery occurs within 2 weeks. If blood counts remain low for >2 weeks, upon recovery, reduce dose by 100 mg and resume treatment • If cytopenia recurs, reduce dose by an additional 100 mg upon recovery and resume treatment
Elevated liver function tests: • ALT increased • AST increased	• Monitor liver enzymes at least monthly for the first 3 months, and where necessary • Advise patients to report any possible signs or symptoms as soon as possible, e.g., 'tea-colored' urine or jaundice • Avoid other hepatotoxic agents, where possible, and excessive consumption of alcohol • No supportive care therapies; however, some clinical trials have used essential phospholipids, glycyrrhizic acid, milk thistle extract, ursodiol, steroids and S-adenosylmethionine • Consider withholding bosutinib, or dose reductions or discontinuations • Increased transaminases >5 × ULN: withhold bosutinib until ≤2.5 × ULN and resume at 400 mg QD thereafter. If recovery takes longer than 4 weeks, discontinue bosutinib treatment • Increased transaminases ≥3 × ULN plus increased bilirubin >2 × ULN and alkaline phosphatase <2 × ULN: discontinue bosutinib treatment
Dermatologic toxicities: • Rash	• Concomitant administration of hypoallergenic moisturizing creams, topical steroids, topical antiseptics, topical antibiotics and/or antihistamines • In severe cases, use systemic antibiotics and/or short-term systemic steroids • Consider other potential causes for rash • Consider consulting a dermatologist • Avoid prolonged bathing, hot water when washing/showering and tight clothing • Consider dose reductions and/or interruptions
Fluid retention	• Regular monitoring of signs and symptoms, and may manifest as pericardial effusion, pleural effusion, pulmonary edema and/or peripheral edema • Concomitant administration of diuretics and supportive care • Consider withholding bosutinib, or dose reductions or discontinuations
Renal dysfunction	• Monitor renal function at baseline and during treatment with bosutinib • Advise patients to report any possible signs or symptoms as soon as possible, e.g., changes in urinary frequency, oliguria or polyuria • Review of concomitant medications or other nephrotoxic agents • Consider withholding bosutinib, or dose reductions or discontinuations – see Table 3 for renal impairment

AE: Adverse event; ANC: Absolute neutrophil count; PPI: Proton pump inhibitor; QD: Once daily; ULN: Upper limit of normal.
Data taken from [3,17,18,63,65,70,74,76].

medications prior to treatment selection and initiation is critical to mitigating the risk of developing treatment-emergent AEs. However, there are also a number of strategies to manage AEs that may arise during a therapy plan with bosutinib (Table 4), the most important is the availability of a clinic dedicated to CML [75].

One of the most common side effects with bosutinib treatment is gastrointestinal AEs, such as diarrhea, nausea and vomiting. Median time to onset of diarrhea was 2–3 days and median duration of diarrhea was 2–3 days [17,18]. Pharmacologic strategies include supportive care with anti-diarrheal, anti-emetic or anti-nausea medications; bosutinib dose reductions or interruptions; and avoidance of concomitant use with PPIs [3,17,18,65,70,74,76]. Nonpharmacologic strategies to manage these AEs include taking bosutinib with food and water; eating smaller meals; keeping well hydrated, for example, sports drinks to replenish electrolytes, although care should be taken to consider the mineral content of these drinks, in other words, the levels of sodium chloride versus glucose; and avoiding certain foods and drinks, such as caffeine and spicy food, that may exacerbate these AEs. Ensuring that patients are educated in the identification and alleviation of these symptoms and are provided dietary advice prior to and throughout bosutinib treatment are important for managing these gastrointestinal AEs [3,17,18,65,70,74,76].

Patient education is also critical to the management of treatment-emergent rash. Behavioral changes, for example, avoiding tight clothing and prolonged exposure to hot water and baths, are important nonpharmacologic strategies for dermatologic toxicities [3,17,18,65,70,74,76]. In addition to bosutinib dose modifications, patients can be administered supportive care therapies, such as hypoallergenic moisturizing creams, topical steroids, topical antiseptics, topical antibiotics and/or antihistamines. In severe cases, consultation with a dermatologist or administration of systemic antibiotics and/or short-term systemic steroids could be considered for treatment-emergent rash [3,17,18,65,70,74,76].

Regular monitoring and patient reporting of signs and symptoms are critical to identifying treatment-emergent myelosuppression and/or elevated serum transaminases – both of which have been reported during treatment with bosutinib [3,17,18,65,70,74,76]. Bosutinib dose modifications or interruptions in line with the product label is one of the most common treatment strategies to manage these AEs; however, these AEs have also been reported to spontaneously improve or return to normal after a few weeks [3,17,18,65,70,74,76]. Therefore, periodic assessment of and communication with the patient is important to identify and manage these treatment-emergent AEs, particularly in the first few months after initiating bosutinib therapy.

Other AE management strategies include monitoring renal function at baseline and throughout bosutinib treatment for signs of renal dysfunction, and the use of concomitant diuretics and supportive care for the treatment of fluid retention. As in all cases of treatment-emergent AEs, bosutinib dose reductions or interruptions should also be considered, where necessary [3,17,18,65,70,74,76].

Intensive management of CML

In line with European Leukemia Net (ELN) and National Comprehensive Cancer Network (NCCN) guidelines, regular monitoring of response is essential to the achievement of therapeutic milestones and the management of CML [3,4]. Achievement of early molecular responses during first-line treatment is indicative of long-term survival and positive clinical outcomes [2–4,9,72,73,77–82]. In the BELA trial, early response (*BCR-ABL1*/ABL1 $\leq$10% at 3 months) was associated with better CCyR by and MMR rates at 12 and 24 months in patients treated with first-line bosutinib or imatinib [34]. In the Phase I/II trial, early attainment or maintenance of MCyR by month 3 in patients treated with second-line bosutinib was associated with better overall survival. In patients treated with bosutinib following failure of $\geq$2 TKIs, association with long-term outcomes was borderline for MCyR by month 3, but significant for MCyR by months 6, 9 and 12 [77,78]. Most importantly, early and regular monitoring can lead to improved treatment adherence and management of side effects, as well as help to identify the most appropriate therapy for an individual patient [2–4,9,72,73]. Patients receiving *BCR-ABL1* TKIs can be readily assessed for potential drug–drug interactions and AEs, thus allowing dose modifications to be made earlier and/or co-administering supportive care or concomitant medications. Furthermore, periodic monitoring ensures that patients who are inadequately responding to first-line treatment can be identified, and steps can be taken to adjust their therapy plan appropriately [2–4,9,72,73].

BCR-ABL1 kinase domain mutational status

In the second- and later-line setting, resistance to prior *BCR-ABL1* TKI therapy is a particularly important consideration in treatment selection [3,4,58,66]. Mutations in the *BCR-ABL1* kinase domain are a frequent cause of resistance to *BCR-ABL1* TKI therapy and all patients should undergo *BCR-ABL1* mutational profile testing in order to guide TKI selection. Patients harboring V299L, T315A and F317L/V/I/C mutations are resistant to dasatinib; therefore, nilotinib is a recommended TKI for these patients. Y253H, E255K/V and F359V/C/I mutations convey resistance to nilotinib, and so dasatinib is a recommended TKI in this subset of patients. It is also recommended that patients harboring G250A, Y253H, E255K/V, F359V/C/I, T315A and F317L/V/I/C mutations be treated with bosutinib. However, a V299L mutation conveys resistance to bosutinib. Patients harboring T315I mutations should be treated with ponatinib, as this mutational profile is resistant to all other *BCR-ABL1* TKIs [3,4,58,66].

Other considerations for treatment selection

Additional considerations for treatment selection in patients with CML include the impact of treatment adherence on clinical outcomes, for example, nonadherence to treatment has been associated with poorer response rates, deteriorations in quality of life and increased healthcare costs [56,58,72,83–87]. Factors that contribute to a lack of adherence to medication include AEs, drug–drug interactions and a lack of patient support and education. Therefore, it is critical to patient adherence that patients are prescribed the optimum *BCR-ABL* TKI based on

medical history, risk factors, pre-existing comorbidities and concomitant medications, as well as have regular monitoring and communications regarding AEs, continued assessment of the treatment plan, and ongoing patient education [56,58,72].

Allogenic HSCT is a potentially curative option in patients with CML resistant or intolerant to all *BCR-ABL1* TKIs or BP CML, or who had progressed to AP or BP during *BCR-ABL1* TKI treatment [3,4,66]. Existing evidence has shown that *BCR-ABL1* TKIs do not impact outcomes post allogenic HSCT or lead to an increase in transplant-related toxicity [3]. Additionally, *BCR-ABL1* TKI monotherapy or in combination with chemotherapy could be considered for patients who are not candidates for transplant, or as a bridge and debulking option prior to allogenic HSCT [66].

Dose optimization of bosutinib in the treatment of CML

Following the selection of a *BCR-ABL1* TKI for the treatment of CML, it is important that patients are regularly and closely monitored to ensure that they are achieving the required therapeutic milestones, and that they are receiving appropriate supportive care for any treatment-emergent AEs, drug–drug interactions or worsening of comorbidities or quality of life [3,4]. Another consideration that is central to the management of CML is dose optimization of *BCR-ABL1* TKIs.

Per the product label, patients can initiate bosutinib at starting doses at less than the recommended dose in the case of comorbidities, such as hepatic and renal impairment [17,18]. The aim is to incrementally increase the bosutinib dose to the standard dose for the indication, where possible, and depending on patient tolerability [76]. In patients with suboptimal cytogenetic, hematologic or molecular response, and who do not have any grade 3 or higher AEs, incremental bosutinib dose escalations up to 600 mg QD are permitted [17,18]. In the first-line setting, bosutinib dose escalations due to suboptimal response occurred in approximately 20% of patients in the BFORE trial (starting dose 400 mg QD) and in <10% of patients in the BELA trial (starting dose 500 mg QD) [30–35].

In order to manage treatment-emergent AEs, bosutinib dose can be reduced and interrupted per the product label, and then resumed either at the starting dose or lower upon resolution of the AE [17,18]. In patients with newly diagnosed CP CML in the BFORE trial, bosutinib dose reduction down to 300 or 200 mg QD improved tolerability and enabled patients to continue treatment [88]. A secondary analyses of the first-line BFORE and second-/later-line Phase I/II trial demonstrated that patients who had their dose reduced due to AEs were still able to achieve and/or maintain cytogenetic responses, even with bosutinib 200 mg QD, and appeared to experience fewer gastrointestinal AEs [76,88,89]. In the BYOND study in patients with CP CML resistant or intolerant to prior TKIs, bosutinib dose reduction improved tolerability [90]. In the same study, patients who were TKI-resistant generally tolerated higher doses of bosutinib than TKI-intolerant patients. Additionally, individualized treatment allowed patients to remain on bosutinib and manage treatment-emergent AEs while maintaining efficacy, with some patients achieving a first response after dose reduction [90].

Long-term treatment plans will vary depending on patient age, as older patients may be more likely to present with comorbidities and concomitant medications, and younger patients may be more focused on achieving treatment-free remission [56]. Therefore, optimization of bosutinib dose is an important aspect of ongoing and long-term CML management and can be individualized depending on the patient's medical circumstances and treatment preferences. Dose adjustments are also important for patient adherence to treatment, and thus will have a positive impact on clinical outcomes, quality of life and healthcare costs [56,58,72,83–87].

Conclusion & future perspective

The availability of several *BCR-ABL1* TKI options for patients with CML means that physicians and patients can select the most appropriate treatment for an individual patient. Second-generation *BCR-ABL1* TKIs have been compared with imatinib in clinical trials; however, further studies are needed to directly compare bosutinib, dasatinib and nilotinib. Bosutinib is a suitable treatment option for both patients with newly diagnosed (i.e., first-line) CML and those with CML resistant or intolerant to prior (i.e., second-line) therapies. Bosutinib has fewer severe AEs than other *BCR-ABL1* TKIs, such as nilotinib and dasatinib, while maintaining similar anti-leukemic efficacy, as well as activity against CML with dasatinib- and nilotinib-resistant mutations. However, the selection of bosutinib as a first- or later-line therapy is dependent on a number of factors, such as patient comorbidities, concomitant medications and risk factors. Additional information is needed to establish those patient subgroups that would benefit most from treatment with bosutinib, as well as the optimum bosutinib doses for patient subgroups. This is particularly important for long-term efficacy and safety outcomes. Regular monitoring of patients and patient

education are key aspects of long-term CML management and contribute to improved clinical outcomes, quality of life, patient adherence and healthcare costs. Finally, treatment-free remission is becoming an increasing possibility in patients with CML and further studies are warranted to establish if particular patient subgroups and *BCR-ABL1* TKI combinations would lead to an increased likelihood and maintenance of treatment-free remission.

Executive summary

Introduction to chronic myeloid leukemia

- *BCR-ABL1*-targeting tyrosine kinase inhibitors (TKIs) have revolutionized the treatment of chronic myeloid leukemia (CML).
- Current *BCR-ABL1* TKI treatment options for CML are imatinib, dasatinib, nilotinib, ponatinib and bosutinib.

Introduction to bosutinib

- Bosutinib exhibited dose proportional pharmacokinetics over the oral dose range of 200–800 mg.
- Bosutinib is primarily metabolized by cytochrome P450 3A4.

Bosutinib as a first-line option for the treatment of CML

- Bosutinib 400 mg once daily (QD) is approved for patients with newly diagnosed chronic phase (CP) Philadelphia chromosome positive (Ph+) CML.
- In the BFORE trial, significantly higher rates of major molecular response (MMR) and complete cytogenetic response (CCyR) were observed for bosutinib 400 mg QD versus imatinib 400 mg QD.
- In the BELA trial, CCyR at 12 months was not met with bosutinib, despite a higher MMR rate, faster times to CCyR and MMR, and fewer on-treatment transformations to accelerated phase (AP)/blast phase (BP) with bosutinib 500 mg QD versus imatinib 400 mg QD.
- In both the BFORE and BELA trials, the safety profile of bosutinib was consistent with previous reports.

Bosutinib in the setting of second- & later-line CML treatment

- Bosutinib 500 mg QD is approved for patients with CP, AP or BP Ph+ CML resistant/intolerant to prior therapy.
- In a Phase I/II open-label trial, bosutinib 500 mg QD demonstrated durable efficacy and had a manageable safety profile for up to 5 years in patients with imatinib-resistant/intolerant CML.
- In the BYOND trial, bosutinib 500 mg QD showed high rates of cytogenetic and molecular responses, including in a large proportion of patients who achieved deep molecular responses.
- In both the Phase I/II trial and BYOND, treatment with bosutinib was tolerable and manageable.

General considerations for bosutinib treatment selection in CML

- Key considerations for bosutinib treatment selection include patient medical history, disease risk, comorbidities and concomitant medications.
- Effective adverse event (AE) monitoring and management can lead to improvements in clinical outcomes, quality of life and treatment adherence.
- Strategies for managing AEs include regular monitoring, supportive care, dose reductions and patient education.
- Additional considerations include early response monitoring and mutational status.

Dose optimization of bosutinib in the treatment of CML

- Patients can initiate bosutinib at starting doses less than the recommended dose in cases of certain comorbidities.
- Bosutinib dose can be escalated incrementally in patients with suboptimal response.
- Bosutinib dose can be reduced to improve tolerability and to manage AEs, without a loss in efficacy.

Author contributions

All authors participated equally in discussions and development of the manuscript, contributed to correcting the draft manuscript, provided additional recommendations and have read and approved the final manuscript.

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