MANAGEMENT OF ADVERSE EVENTS ASSOCIATED WITH BOSUTINIB TREATMENT OF CHRONIC-PHASE CHRONIC MYELOID LEUKEMIA: EXPERT PANEL REVIEW

Cortes JE, Apperley JF, DeAngelo DJ, Deininger MW, Kota VK, Rousselot P, Gambacorti-Passerini C. *J Hematol Oncol*. 2018;11(1):143.

The FDA has not reviewed the recommendations contained in this reprint.

METHODOLOGY[1]

- An expert panel of 7 hematologists from the United States and Europe convened to discuss treatment management and guidelines, dosing strategies they apply in practice, patient characteristics that influence their decisions, and their management of adverse events (AEs) when using BOSULIF® (bosutinib) in patients with chronic-phase chronic myeloid leukemia (CP-CML)
- To reach a consensus during the meeting, the expert group reviewed and discussed the responses to a number of premeeting questions on dosing strategies and management of AEs with BOSULIF

INDICATIONS

BOSULIF is indicated for the treatment of adult patients with

- Newly diagnosed chronic phase (CP) Ph+ chronic myelogenous leukemia (CML). This indication is approved under accelerated approval based on molecular and cytogenetic response rates. Continued approval for this indication may be contingent upon verification and confirmation of clinical benefit in an ongoing long-term follow-up trial
- Chronic, accelerated, or blast phase Ph+ CML with resistance or intolerance to prior therapy

IMPORTANT SAFETY INFORMATION

Contraindication: History of hypersensitivity to BOSULIF. Reactions have included anaphylaxis. Anaphylactic shock occurred in less than 0.2% of treated patients in single-agent cancer studies with BOSULIF.

Gastrointestinal Toxicity: Diarrhea, nausea, vomiting, and abdominal pain occur with BOSULIF. In the study of patients with newly diagnosed CP Ph+ CML, the median time to onset for diarrhea (all grades) was 3 days and the median duration per event was 3 days. In the study of patients with CML who were resistant or intolerant to prior therapy, median time to onset of diarrhea (all grades) was 2 days, median duration was 2 days, and the median number of episodes per patient was 3 (range 1-268). Monitor and manage patients using standards of care, including antidiarrheals, antiemetics, and/or fluid replacement. Withhold, dose reduce, or discontinue BOSULIF as necessary.

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KEY TAKEAWAYS[1,2]

The consensus recommendations include a number of strategies to consider to reduce issues with tolerability, with the ultimate aim of adherence to the maximum tolerated dose.

- **Differences from label:** The panel provided clinical considerations and recommendations for the management of specific AEs before and during BOSULIF® (bosutinib) treatment of CP-CML. Information around dosing strategies, patient counseling, and AE rates and management differ from the approved labeling
- **Balancing efficacy and tolerability:** The recommendations for the dosing strategies discussed are based on management of AEs, but it is important to consider the broader clinical setting. The ability to monitor and manage a patient closely following initiation of treatment is an important consideration regarding starting at the approved dose versus a lower dose
- **Importance of patient education:** Across the commonly occurring AEs, the panel highlighted the importance of education and communication with patients about anticipated AEs
- **Limitations:** The recommendations are based on the expert panel's clinical experience, pharmacokinetic studies, and secondary analyses from pivotal studies. No formal studies have been conducted to confirm the minimum effective dose of BOSULIF for CP-CML in first line or later settings

IMPORTANT SAFETY INFORMATION (cont'd)

Myelosuppression: Thrombocytopenia, anemia, and neutropenia occur with BOSULIF. Perform complete blood counts weekly for the first month and then monthly thereafter, or as clinically indicated. Withhold, dose reduce, or discontinue BOSULIF as necessary.

Hepatic Toxicity: BOSULIF may cause elevations in serum transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]). In a study of BOSULIF in combination with letrozole, one drug-induced liver injury occurred without alternative causes. In the study of patients with newly diagnosed CP Ph+ CML, the incidence of ALT/AST elevations was 31% and 23%, respectively.

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DOSING GUIDANCE IN THE US PRESCRIBING INFORMATION FOR BOSULIF® (bosutinib)[2]

- For patients with normal renal and hepatic function, the recommended starting dose in the product labeling is 400 mg orally once daily with food for newly diagnosed CP Ph+ CML, and 500 mg orally once daily with food for chronic, accelerated, or blast phase Ph+ CML resistant or intolerant to prior therapy
  - Lower starting doses are recommended for renal or hepatic impairment
- The labeling also provides dose modification guidance, including withholding, dose reduction, or discontinuation of drug, if necessary, for elevated liver transaminases, diarrhea, fluid retention, other clinically significant nonhematologic toxicities, or myelosuppression
- Doses less than 300 mg/day have been used in patients; however, efficacy has not been established

FUNDING

- Pfizer funded the meeting for discussion of BOSULIF treatment and provided a formal review of the publication, including for medical accuracy, but the authors had final authority, including choice of journal. The experts were compensated for expenses for their attendance at the meeting but were not compensated for manuscript preparation

IMPORTANT SAFETY INFORMATION (cont'd)

Hepatic Toxicity (cont'd)**:** In patients with CML who were resistant or intolerant to prior therapy, the incidence of ALT/AST elevations was 18% and 15%, respectively. Twenty percent of the patients resistant or intolerant to prior therapy experienced an increase in either ALT or AST. Perform hepatic enzyme tests at least monthly for the first 3 months and as clinically indicated. In patients with transaminase elevations, monitor liver enzymes more frequently. Withhold, dose reduce, or discontinue BOSULIF as necessary. In patients with mild, moderate, or severe hepatic impairment, the recommended starting dose is 200 mg daily.

IMPORTANT SAFETY INFORMATION (cont'd)

Cardiac Failure: Cardiac failure and left ventricular dysfunction have been reported in patients taking BOSULIF® (bosutinib). These events occurred more frequently in previously treated patients than in patients with newly diagnosed CML and were more frequent in patients with advanced age or risk factors, including previous medical history of cardiac failure. In a randomized study with newly diagnosed CML, cardiac failure occurred in 1.5% of patients treated with BOSULIF compared to 0.8% of patients treated with imatinib. In a single-arm study in patients with CML who were resistant or intolerant to prior therapy, cardiac failure was observed in 5.3% of patients treated with BOSULIF. Monitor patients for signs and symptoms consistent with cardiac failure and treat as clinically indicated. Interrupt, dose reduce, or discontinue BOSULIF as necessary.

Fluid Retention: Fluid retention occurs with BOSULIF and may cause pericardial effusion, pleural effusion, pulmonary edema, and/or peripheral edema. Monitor and manage patients using standards of care. Interrupt, dose reduce, or discontinue BOSULIF as necessary.

Renal Toxicity: An on-treatment decline in estimated glomerular filtration rate has occurred in patients treated with BOSULIF. Monitor renal function at baseline and during therapy, with particular attention to patients with preexisting renal impairment or risk factors for renal dysfunction. Lower starting doses are recommended for patients with renal impairment. For patients who have declining renal function while on BOSULIF or who cannot tolerate the starting dose, follow dose adjustment recommendations for toxicity.

Embryofetal Toxicity: BOSULIF can cause fetal harm. Women of childbearing potential should be advised of the potential hazard to the fetus and to use effective contraceptive measures while on treatment and for at least 2 weeks after the final dose.

Adverse Reactions: The most common adverse reactions observed in greater than or equal to 20% of patients with newly diagnosed CML were diarrhea, nausea, thrombocytopenia, rash, increased ALT, abdominal pain, and increased AST. The most common Grade 3/4 adverse reactions and laboratory abnormalities observed in greater than 10% of newly diagnosed CML patients were increased ALT and thrombocytopenia. The most common adverse reactions observed in greater than or equal to 20% of patients with CML who were resistant or intolerant to prior therapy were diarrhea, nausea, abdominal pain, rash, thrombocytopenia, vomiting, anemia, fatigue, pyrexia, cough, headache, increased ALT, and edema. The most common Grade 3/4 adverse reactions and laboratory abnormalities observed in greater than 10% of patients who were resistant or intolerant to prior therapy were thrombocytopenia, neutropenia, and anemia.

CYP3A Inhibitors and Inducers: Avoid concurrent use with strong or moderate CYP3A inhibitors or strong CYP3A inducers.

Proton Pump Inhibitors (PPIs): Consider using short-acting antacids or H2 blockers instead of PPIs to avoid a reduction in BOSULIF exposure. Separate antacid or H2 blocker dosing and BOSULIF dosing by more than 2 hours.

Lactation: Because of the potential for serious adverse reactions in a nursing child, breastfeeding is not recommended during treatment with BOSULIF and for at least 2 weeks after the last dose.

Please see additional Important Safety Information throughout.
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References: 1. Cortes JE, Apperley JF, DeAngelo DJ, et al. Management of adverse events associated with bosutinib treatment of chronic-phase chronic myeloid leukemia: expert panel review. *J Hematol Oncol.* 2018;11(1):143. **2.** BOSULIF Prescribing Information. New York, NY: Pfizer Inc.

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