Original Study

Effects of Bosutinib Treatment on Renal Function in Patients With Philadelphia Chromosome-Positive Leukemias

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Abstract

We evaluated the incidence of renal adverse events and estimated glomerular filtration rate in patients with Philadelphia chromosome-positive leukemias receiving first-line bosutinib (n = 248) or imatinib (n = 251), or second-line or later bosutinib (n = 570). Results show that long-term bosutinib treatment is associated with an apparently reversible decline in renal function with frequency and characteristics similar to those observed with long-term imatinib.

Background: The purpose of the study was to assess renal function in patients with Philadelphia chromosome-positive leukemias receiving bosutinib or imatinib. **Patients and Methods:** Patients received first-line bosutinib (n = 248) or imatinib (n = 251; phase III trial), or second-line or later bosutinib (phase I/II trial; n = 570). Adverse events (AEs) and changes from baseline in estimated glomerular filtration rate (eGFR) and serum creatinine were assessed. **Results:** Time from the last patient's first dose to data cutoff was ≥ 48 months. Renal AEs were reported in 73/570 patients (13%) receiving second-line or later bosutinib, and in 22/248 (9%) and 16/251 (6%) receiving first-line bosutinib and imatinib, respectively. eGFR in patients receiving bosutinib declined over time with more patients developing Grade ≥ 3b eGFR (< 45 mL/min/1.73 m^2 according to the Modification of Diet in Renal Disease method) with second-line or later bosutinib (139/570, 24%) compared with first-line bosutinib (26/248, 10%) and imatinib (25/251, 10%); time to Grade ≥ 3b eGFR was shortest with second-line or later bosutinib. Similar proportions of patients receiving second-line or later bosutinib (74/139, 53%), first-line bosutinib (15/26, 58%), and first-line imatinib (15/25, 60%) improved to ≥ 45 mL/min/1.73 m^2 eGFR as of the last follow-up. In a regression analysis, first-line treatment with bosutinib versus imatinib was not a significant predictor of Grade ≥ 3b eGFR. **Conclusion:** Long-term bosutinib treatment is associated with an apparently reversible decline in renal function with frequency and characteristics similar to renal decline observed with long-term imatinib treatment. Patients with risk factors for Grade ≥ 3b eGFR should be monitored closely.

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Introduction

Although generally well tolerated, tyrosine kinase inhibitors (TKIs) are associated with adverse events (AEs).[1-5] Renal toxicity has been reported during TKI treatment for Philadelphia chromosome-positive (Ph^+) leukemias[2,6-13]; however, information is mostly limited to case reports.[7-9,11-14] Because of the long-term

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nature of TKI therapy and the different kinetics observed, particularly with regard to nonhematologic toxicities, a better understanding of the renal safety profiles of TKIs is important for optimizing patient management.

Bosutinib (Bosulif; SKI-606) is an oral TKI approved in the United States for treatment of Ph^+ chronic phase (CP), accelerated phase (AP), and blast phase (BP) chronic myeloid leukemia (CML) resistant/intolerant to previous TKI therapy and in Europe for treatment of Ph^+ CML in patients previously treated with $\geq$ 1 TKI and for whom other TKIs are not considered appropriate.[2,15] Bosutinib has a manageable safety profile in patients with all phases of CML, with predominantly low-grade gastrointestinal toxicities most commonly reported.[16-21]

Only a small portion (< 4%) of bosutinib is recovered in the urine, and excretion of unchanged bosutinib is low at approximately 1%, indicating minimal renal clearance of the active drug.[22] However, bosutinib administration has been associated with a decline in estimated glomerular filtration rate (eGFR) and dose adjustments are recommended in patients with baseline and treatment-emergent renal impairment.[5] In this study, renal function was comprehensively analyzed in Ph^+ leukemia patients enrolled in 2 large clinical studies[16-18] receiving either bosutinib as first-line treatment (randomized vs. imatinib) or as second-line or later therapy after failure of $\geq$ 1 TKI. The objectives were to assess the extent and time course of renal dysfunction, to identify predictors of Grade $\geq$ 3b eGFR in bosutinib-treated patients, and to evaluate reversibility of treatment-emergent eGFR decline. Additionally, the effect of Grade $\geq$ 3b eGFR on the efficacy of bosutinib across treatment lines was evaluated.

Patients and Methods

Study Design and Patients

This retrospective analysis included data from 2 open-label, multinational studies. The first is a 2-part, phase I/II study of bosutinib (starting dose, 500 mg/d [part 2]) in patients with Ph^+ CP CML resistant/intolerant to $\geq$ 1 previous TKI (n = 403 [n = 284 second-line and n = 119 third- or fourth-line]), or AP CML (n = 79), BP CML (n = 64), or acute lymphoblastic leukemia (n = 24) after previous TKI therapy.[16] The second is a phase III study of patients with newly diagnosed Ph^+ CP CML treated with bosutinib 500 mg/d (n = 248) or imatinib 400 mg/d (n = 251).[17] Data are from unlocked trial databases with data cutoff dates of May 23, 2014 (phase I/II study) and November 21, 2013 (phase III; applied to the March 14, 2014 snapshot).

Patients were required to have adequate renal function (creatinine $\leq$ 1.5 times the upper limit of normal [ULN]); those with significant preexisting conditions were excluded.[16,17]

Renal Toxicity Assessments

Renal toxicity was assessed on the basis of treatment-emergent AEs (TEAEs) and laboratory parameters reported at each visit and for 28 days (phase III study) or 30 days (phase I/II study) after the last dose of study drug (for details, see the Supplemental Methods section of the Supplemental Material in the online version). Laboratory end points included serum creatinine and eGFR (calculated using the Modification of Diet in Renal Disease formula and graded on the basis of the Kidney Disease Improving Global Outcomes criteria).[23] Normal/high eGFR and mildly to moderately decreased eGFR encompassed Grades $\leq$ 3a ($\geq$ 45 mL/min/1.73 m^2); moderately to severely decreased eGFR included Grades $\geq$ 3b (< 45 mL/min/1.73 m^2).[24-26]

Renal Safety and Efficacy Analyses and Statistical Methods

Treatment-emergent AEs are reported descriptively according to disease stage (CP vs. advanced) for the phase I/II study and according to treatment (bosutinib vs. imatinib) for the phase III study; baseline characteristics are described in patients with and without Grade $\geq$ 3b eGFR. Changes from baseline in eGFR and serum creatinine levels are reported for the safety population (received $\geq$ 1 dose of study treatment) and for patients whose bosutinib dose was reduced (400 mg/d) or escalated (600 mg/d). The effect of dose reductions/escalations on changes from baseline in eGFR were compared with that in matched control participants who received 500 mg/d during their entire course of treatment. Matching was on the basis of age (within 10 years), baseline eGFR category (Grades 1-5), and treatment duration (within 6 months). On-treatment changes in creatinine levels were assessed in bosutinib-treated patients (combined studies) with baseline creatinine levels > ULN versus $\leq$ ULN (as specified by the local laboratory).

Baseline and on-treatment time-dependent predictors of time to Grade $\geq$ 3b eGFR were assessed using forward selection from Cox proportional hazard regression models. Forward entry criteria was $P = .20$. Two analyses were performed, one combining all bosutinib data from CP CML patients in both studies, and another from patients receiving only first-line bosutinib and imatinib. P values were not adjusted for multiple testing.

Response was assessed in patients before and after first Grade $\geq$ 3b eGFR and for patients who did not experience Grade $\geq$ 3b eGFR. Complete cytogenetic response (CCyR) and major cytogenetic response (MCyR) were determined using standard cytogenetics with $\geq$ 20 metaphases counted for postbaseline assessments. If < 20 metaphases were available postbaseline, fluorescence in situ hybridization analysis of bone marrow aspirate or peripheral blood with $\geq$ 200 cells for the presence of breakpoint cluster region-Abelson kinase 1 fusion gene was used.

Results

Patients

Demographic and baseline clinical characteristics are presented in Table 1. Of 56 bosutinib-treated patients with baseline creatinine levels > ULN, only 4 were newly diagnosed with CML. Median (range) treatment duration in the phase I/II trial was 18.1 (0.2-94.9) months for CP CML patients and 3.95 (0.03-89.2) months for advanced patients (AP CML: 10.2 [0.1-88.6], BP CML: 2.8 [0.03-55.9], acute lymphoblastic leukemia: 0.97 [0.3-89.2] months). Treatment duration was longer for second- versus third- and fourth-line CP CML patients (25.6 [0.16-94.9] months vs. 8.6 [0.23-87.7] months). In the phase III study, the median (range) duration of first-line bosutinib and imatinib treatment was 54.4 (0.03-69.1) and 49.5 (0.5-62.6) months, respectively. Time from the last patient's first dose to data cutoff was $\geq$ 48 months (both studies).