NON-INTERVENTIONAL STUDY REPORT ABSTRACT

Title: BOSEVAL: An observational study - Evaluation of efficacy and safety of Bosulif® under real life conditions of use

Date: 30-MAY-2024

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Keywords: Chronic Myeloid Leukemia, TKI, bosutinib, drug-related AE

Rationale and background:

Bosutinib is a TKI indicated in treatment of adult patients with Philadelphia chromosome positive CML (Ph+ CML) in chronic phase (CP), in accelerated phase (AP) or in blast phase (BP), intolerant or resistant to previous TKI therapy. Although Bosutinib's approval was based on phase I to III clinical trials, assessing its safety and effectiveness in real-world conditions of use was imperative.

Research question and objectives: This was an observational study, whose primary objective was to evaluate the rate of treatment discontinuation because of intolerance. Secondary objectives were to evaluate the efficacy and safety of bosutinib.

Study design: This was a national, observational, descriptive, prospective, multicentre study conducted in metropolitan France.

Setting: Patients have been followed prospectively every 3 months over a 3-year period from their enrollment and the initiation of bosutinib.

Subjects and study size, including dropouts: Patient cohort included adult patients treated for chronic myeloid leukemia, intolerant or resistant to previous TKIs therapy.

Variables and data sources: For all patients included baseline characteristics, encompassing demographic details, medical history, comorbidities, and prior treatments, have been recorded. Throughout the follow-up period, efficacy endpoints, including hematological, cytogenetic, and molecular responses to bosutinib (rates, time to response, duration), disease progression, progression-free survival (PFS), overall survival (OS), and time to treatment failure, have been evaluated. Safety data, concerning bosutinib exposure, adverse events (AEs), and biological parameters, have also been analyzed. Furthermore, records of quality of life and treatment adherence have been maintained.

Results: The study conducted from October 15, 2015, to December 19, 2019, aimed to examine the real-world utilization and safety profile of bosutinib in the treatment of chronic myeloid leukemia (CML) patients. A total of 146 patients from 23 medical centers were enrolled.

Concerning baseline characteristics, patients in the Full Analysis Set (FAS) population had an average age of 62.0 ± 13.2 years and were predominantly male (56.1%). The median treatment duration was 2.071 ± 1.217 years. Adverse events (AEs) attributed to bosutinib were documented in 88% of patients, prompting a treatment change in 59.9% of cases. Most patients (84.5%) experienced mild or moderate bosutinib-related AEs (grade 1-2), notably diarrhea affecting 50.7% of patients and nausea in 14.1%, while severe (grade 3-4) bosutinib-related AEs were reported in 31.7% of patients, with grade 3-4 diarrhea observed in only 4.2%. One patient experienced grade 5 drug-related pneumonia. Bostunib-related AEs necessitated permanent discontinuation of treatment for 32.4% of patients with 27.5% for intolerance, mostly diarrhea observed in 11 (7.7%), pleural effusion reported in 7 (4.9%) patients and hepatocellular injury reported in 7 (4.9%) patients.

In terms of efficacy, 91.4% of patients achieved complete hematological response, with a median time to response of 0.24 [0.23-0.25] years. At the data cutoff, 92% of evaluable patients who attained a hematological response maintained it. Most patients (70.5%) achieved a cumulative molecular response, with 15.8% reaching a MR4.5 best response and 29.5% achieving a MR5 best response. The median time to molecular response was 0.28 [0.25-0.45] years, with 86% of patients sustaining their response after three years. Progression-free survival rates at 1 and 2 years were 96% and 95%, respectively, while overall survival rates at 1 and 2 years were 98% and 96%, respectively.

Discussion:

Our results showed that drug-related AEs were mostly mild or moderate and mainly gastrointestinal (diarrhea, nausea, vomiting), like what was recorded in phase I/II/III trials (13, 17-19). Overall, 27.5% of patients had to discontinue due to drug-related intolerance, mainly diarrhea, pleural effusion, and hepatocellular injury. Only 1 patient had a grade 5 drug-related AE, confirming the safety of bosutinib.

Most patients exhibited a hematological and a molecular response in the early phase with 92% and 81% of patients, respectively, still responding at the end of the study. Regarding PFS and OS, at 1 and 2 years, 96% and 95% of patients respectively were progression-free and 98% and 96% of patients respectively, were alive.

Taken together, our data confirmed previous findings showing that bosutinib is effective and tolerable in patients with chronic phase TKI-resistant or intolerant CML.

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