Bosutinib in previously treated CML and in first-line comparison with imatinib

See Commentary on page 103

Bosutinib was recently approved for the treatment of chronic phase (CP), accelerated phase (AP), or blast phase (BP) Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in adult patients with resistance or intolerance to prior therapy. The approval was based on findings in a combined phase 1/2 single-arm trial.[1] The recently reported phase 3 BELA trial compared bosutinib and imatinib as first-line treatments in patients with CP CML and reported no difference in complete cytogenetic response (CCyR) rates at 1 year, but improved major molecular response (MMR) rate and time to response, as well as a distinct safety profile.[2]

Bosutinib is an oral dual SRC/ABL kinase inhibitor that is active against many BCR-ABL mutations associated with imatinib resistance (with the exception of T315I and V299L) and that has reduced activity against nonspecific molecular targets (eg, c-KIT and platelet-derived growth factor receptor) associated with toxicities reported for other second-generation tyrosine kinase inhibitors (TKIs). CML is characterized by a constitutively active BCR-ABL fusion protein, and SRC-family kinases have a critical role in cell adhesion, invasion, proliferation, survival, and angiogenesis. Bosutinib has been found to inhibit growth of experimental tumors that express several imatinib-resistant forms of BCR-ABL.

What's new, what's important

Chronic myelogenous leukemia is the poster child of targeted therapy and more and more targeted drugs continue to evolve for CML. In September 2012, the Food and Drug Administration approved bosutinib tablets for the treatment of chronic, accelerated, or blast phase Philadelphia chromosome-positive CML in adult patients with resistance or intolerance to prior therapy. The approval was based on a single-arm, open-label, multicenter trial for patients with either chronic phase, accelerated phase, or blast phase CML previously treated with at least 1 tyrosine kinase inhibitor. All of the patients had received prior imatinib therapy. In the total patient population, 73% were imatinib resistant and 27% were imatinib intolerant. The recommended dose and schedule for bosutinib is 500 mg orally once daily with food. The treatment is to be continued until disease progression or patient intolerance. The most common side effects were diarrhea, nausea, thrombocytopenia, vomiting, abdominal pain, rash, anemia, pyrexia, and fatigue. It is very exciting to have more treatment options for patients with refractory or resistant CML.

— Jame Abraham, MD

Study in patients with previously treated CML

In a combined phase 1/2 single-arm, open-label, multicenter trial, 546 patients with CP (406 patients) or advanced phase CML (140) who had been previously treated with at least 1 TKI received oral bosutinib 500 mg/d.[1] All of the patients had received prior imatinib, with 73% being imatinib resistant and 27% imatinib intolerant. In all, 53% of patients were men, 65% were white, and 20% were aged 65 years or older. After 396 patients had been enrolled in the trial, patients who were known to harbor the T315I mutation, which confers resistance to both imatinib and bosutinib, were excluded.

The efficacy endpoints for patients with CP CML previously treated with 1 TKI (imatinib) were the major cytogenetic response (MCyR) rate at week 24 and the duration of MCyR. The efficacy endpoints for patients with CP CML previously treated with imatinib and at least 1 additional TKI were the cumulative rate of attaining MCyR by week 24 and the duration of MCyR. The efficacy endpoints for patients with AP and BP CML were confirmed complete hematologic response (CHR) and overall hematologic response (OHR).

In all, 503 patients were evaluable for efficacy. Among 374 evaluable patients with CP CML, 266 had received

Report prepared by Matt Stenger, MS

Commun Oncol 2013;10:105-108
DOI: 10.12788/j.cmonc.0003

How I treat CML

Before treating CML, one needs a complete staging: do a physical exam to establish spleen size and whether there is any hint of extramedullary disease other than hepatospenomegaly, and run a complete blood count with white cell differential, bone marrow aspirate/biopsy, and karyotyping. The goal is to identify the few patients who present with accelerated phase or blastic phase (CML-AP/BC) and to determine the Sokal disease risk score of those with chronic phase (CML-CP). Polymerase chain reaction (PCR) or fluorescence in situ hybridization for BCR-ABL1 is indicated if karyotyping fails to identify a Philadelphia chromosome. Patients who are newly diagnosed with CML-CP have 3 excellent options: imatinib, dasatinib, and nilotinib. Outside of a trial, my therapy selection is influenced by the Sokal risk score, concomitant medical conditions, and the patient's preference. In my opinion, patients with a high Sokal risk are strong candidates for nilitonib or dasatinib; in reality there are no definitive boundaries between high risk CML-CP and CML-AP/BC, so there is not much room for therapeutic compromise. Most patients with low Sokal risk do well on imatinib, so their selection is influenced by considerations that are not directly related to the CML. In reality, there are few absolute contraindications to any of the drugs, but as an example, I would select dasatinib over nilotinib in a badly controlled diabetic and do the opposite in a patient with a history of pleural effusions. All things being equal, the patient's preference trumps everything after he or she has been told about the side effects, dosing schedules, and the long-term experience with the various drugs.

When the patient is on therapy, I monitor blood counts weekly until they are stable and metabolic profiles monthly. Response is assessed at 3 months with a bone marrow biopsy that includes cytogenetics. Once a complete cytogenetic response is documented, monitoring continues with quantitative PCR at 3-month intervals. It is important to use a laboratory that reports values on the international scale, otherwise the results are difficult to interpret. As far as response goes, I follow the recommendations of the European LeukemiaNet and National Comprehensive Cancer Network to define optimal response. For example, after 12 months I want to see a complete cytogenetic response. If there is evidence of drug resistance, I first try to rule out nonadherence or drug interactions and then I'll perform a complete resistance work-up that includes complete blood count, bone marrow biopsy with cytogenetics, and BCR-ABL1 kinase domain mutation testing. Drug selection for second-line depends on the patient's previous therapies, the results of mutation screening, and expected side effects, with bosutinib and ponatinib as additional options. In any case, TKI resistance in CML-CP is a very significant diagnosis. It places the disease in a different category and is a trigger for a transplant referral, the same as in patients who present in accelerated or blastic phase.

— Michael Deininger, MD, PhD

prior treatment with only imatinib and 108 had received prior treatment with imatinib followed by either dasatinib and/or nilotinib. All 129 evaluable patients with advanced phase CML (AP, 69 patients; BP, 60) were previously treated with at least imatinib. Median durations of bosutinib treatment were 22 months in patients with CP CML previously treated with imatinib alone, 8 months in patients with CP CML previously treated with imatinib and at least 1 additional TKI, 10 months in patients with AP CML previously treated with at least imatinib, and 3 months in patients with BP CML previously treated with at least imatinib.

Among patients with CP CML who had received prior imatinib alone, 34% achieved MCyR at week 24. Of the 53% of patients who achieved MCyR at any time during the trial, 53% had MCyR lasting at least 18 months. Among the CP CML patients who received prior therapy with imatinib and at least 1 other TKI, 27% achieved MCyR at week 24. Of the 32% who achieved MCyR at any time, 51% had MCyR lasting at least 9 months. Among patients with AP CML, 30% achieved CHR and 55% achieved OHR by week 48. Among patients with BP CML, 15% achieved CHR and 28% achieved OHR by week 48.

In the total patient population, serious adverse reactions included anaphylactic shock, myelosuppression, gastrointestinal toxicity (diarrhea), fluid retention, hepatotoxicity, and rash.

Among the 406 patients with CP CML, the most common adverse events of any grade were diarrhea (84%), nausea (46%), abdominal pain (40%), thrombocytopenia (40%), vomiting (37%), rash (34%), fatigue (26%), anemia (23%), and pyrexia (22%). The most common grade 3 or 4 adverse events (> 5%) were thrombocytopenia (26%), neutropenia (11%), diarrhea (9%), anemia (9%), rash (8%), and increased alanine aminotransferase (ALT; 7%).

The most common grade 3 or 4 laboratory abnormalities were thrombocytopenia (25%), neutropenia (18%), anemia (13%), increased ALT (10%), increased lipase (8%), and low phosphorus (7%).

Among the 140 patients with advanced phase CML, the most common adverse events of any grade were diarrhea (76%), nausea (47%), vomiting (42%), thrombocytopenia (42%), anemia (37%), pyrexia (36%), rash (35%), abdominal pain (29%), and cough (21%). The most common grade 3 or 4 adverse events were thrombocytopenia (37%), anemia (26%), neutropenia (18%), and dyspnea (6%). The most common grade 3 or 4 laboratory abnormalities were thrombocytopenia (57%), neutropenia (37%), anemia (35%), low phosphorus (7%), and increased ALT (6%).

Bosutinib in newly diagnosed CP CML

BELA was an open-label, multinational phase 3 trial of 502 adults with Ph+ CP CML diagnosed within the prior 6 months. In all, 250 patients were randomized to receive bosutinib 500 mg/d and 252 received imatinib 400 mg/d. Patients had received no prior antileukemia treatment apart from 6 months or less of anagrelide or hydroxyurea. An increase in dose of both agents to 600 mg/d was permitted for suboptimal response; patients who could not tolerate a dose of 300 mg/d of either drug were discontinued from the study. The primary endpoint was CCyR rate at 12 months.

For the bosutinib and imatinib groups, respectively, median ages were 48 and 47 years, 60% and 54% were men, 64% and 65% were white, median times since diagnosis were 23 and 22 days, and 74% and 72% had ECOG performance status of 0. The Sokal disease risk score was low in 35% of patients in each group, intermediate in 47%, and high in 18%. Median duration of treatment for both groups was 13.8 months. Median dose intensities were 489 mg/d (range, 115-542 mg/d) for bosutinib and 400 mg/d (range, 201-542 mg/d) for imatinib. A total of 4% of bosutinib patients and 12% of imatinib patients had their dose increased to 600 mg/d.

On intent-to-treat analysis, CCyR rates were 70% in the bosutinib group and 68% in the imatinib group at 12 months ($P = .601$). Median time to CCyR was significantly reduced with bosutinib treatment (12.9 vs 24.6 weeks; $P < .001$), and the bosutinib group had significantly higher CCyR rates at 3, 6, and 9 months. Cumulative CCyR rates by 12 months were similar in the 2 groups (79% vs 75%). The MMR rate at 12 months was significantly higher with bosutinib treatment than with imatinib (41% vs 27%; $P < .001$); MMR rates were also significantly higher with bosutinib at 3, 6, and 9 months. The median time to MMR was significantly reduced with bosutinib treatment (37.1 vs 72.3 weeks; $P < .001$), and the cumulative rate of MMR was significantly increased (47% vs 32%; $P < .001$). The rate of complete molecular response at 12 months was also significantly higher with bosutinib (12% vs 3%; $P < .001$).

There were no significant differences between the bosutinib and imatinib groups in CCyR rates at 12 months, in Sokal low-risk groups (78% vs 75%), intermediate-risk (69% vs 67%), or high-risk (56% vs 56%). The MMR rate was significantly higher with bosutinib in the low-risk group (53% vs 28%; $P < .001$), with rates being similar for bosutinib and imatinib patients in the intermediate group (31% vs 24%) and high-risk (33% vs 28%) groups.

On-treatment event-free survival (EFS) events occurred in fewer bosutinib patients (4% vs 7%), and fewer bosutinib patients had on-treatment progression to AP or BP CML (2% vs 4%). In EFS analysis including death at any time or on-treatment progression to AP or BP as events, events were less common in bosutinib patients (2% vs 6%). Estimated 12-month overall survival was greater than 99% in the bosutinib group and 97% in the imatinib group, and estimated 12-month EFS was 94% and 93%, respectively.

The most common adverse events of any grade (≥ 20%) were diarrhea, vomiting, nausea, and rash in bosutinib patients and edema, nausea, diarrhea, and muscle cramps in imatinib patients. Diarrhea (68% vs 21%, respectively), vomiting (32% vs 13%), and abdominal pain (11% vs 5%) were more common with bosutinib, whereas edema (11% vs 38%), bone pain (4% vs 10%), and muscle cramps (2% vs 20%) were more common with imatinib. Grade 3 or 4 adverse events occurred in 64% of bosutinib patients and in 48% of imatinib patients ($P < .001$). The most common in bosutinib patients were diarrhea (11%) and vomiting (3%).

Among grade 3 or 4 laboratory abnormalities, liver aminotransferase elevations were more common in bosutinib patients and neutropenia and hypophosphatemia were more common in imatinib patients. The most common grade 3 or 4 laboratory abnormalities were elevated ALT (22%), thrombocytopenia (14%), elevated aspartate aminotransferase (11%), neutropenia (11%), elevated lipase (9%), and anemia (6%) in bosutinib patients and neutropenia (24%), hypophosphatemia (15%), thrombocytopenia (14%), anemia (7%), and elevated lipase (5%) in imatinib patients. Drug-related cardiac adverse events occurred in 4% of bosutinib patients and in 3% of imatinib patients.

Study treatment was discontinued due to adverse events in 48 bosutinib patients (19%) and 14 imatinib patients (6%); 15 (31%) of the 48 bosutinib patients discontinued treatment before the first postbaseline

assessment at month 3. Treatment interruptions due to adverse events occurred in 61% of bosutinib patients and 42% of imatinib patients, and dose reduction due to adverse events occurred in 39% of patients compared with 18%, respectively. Fewer bosutinib patients died, and fewer died from CML-related causes. Of 4 deaths in the bosutinib group, 3 were owing to CML-related causes and 1 was due to mesenteric embolism/intestinal necrosis. Of 10 deaths in the imatinib group, 8 were owing to CML-related causes, 1 was due to cardiovascular disease, and 1 was due to lung embolism. None of the deaths was considered related to study treatment.

References

1. Bosulif (bosutinib) tablets prescribing information. Pfizer Inc, September 2012. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203341lbl.pdf. Accessed November 16, 2012.
2. Cortes JE, Kim D-W, Kantarjian HM, et al. Bosutinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: results from the BELA trial. *J Clin Oncol*. 2012;30:3486-3492.