ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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Bosutinib in the Treatment of Chronic Myelogenous Leukemia

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H&O What is bosutinib (Bosulif, Pfizer), and what is its mechanism of action?

JC Bosutinib is a new, second-generation tyrosine kinase inhibitor (TKI). It inhibits the *BCR-ABL* tyrosine kinase that promotes chronic myelogenous leukemia (CML). It is also an inhibitor of Src-family kinases (including Src, Lyn, and Hck), which play a crucial role in cell adhesion, invasion, proliferation, survival, and angiogenesis during tumor development. Specifically, bosutinib has been shown to inhibit 16 of 18 imatinib (Gleevec, Novartis)-resistant forms of *BCR-ABL* expressed in murine myeloid cell lines, with no observed inhibition of *T315I*- and *V299L*-mutant cells. In distinction to other similar inhibitors, bosutinib does not inhibit the platelet-derived growth factor (PDGF) receptor or c-kit. It has been suggested that this could help minimize some of the off-target effects associated with therapy with TKIs.

H&O In which patients is bosutinib currently indicated?

JC On September 4, 2012, bosutinib was approved by the US Food and Drug Administration (FDA) for the treatment of chronic phase, accelerated phase, or blast phase Philadelphia chromosome–positive CML in adult patients with resistance or intolerance to prior therapy.

H&O What study led to the approval of bosutinib?

JC The study that led to the approval of bosutinib was a single-arm, open-label, multicenter, phase I/II trial involving 546 patients (503 patients evaluable for efficacy) with chronic phase-, accelerated phase-, or blast phase-CML who were previously treated with imatinib; 73% of patients were imatinib-resistant and 27% were imatinib-intolerant. This study showed that bosutinib could induce major cytogenetic responses in 54% of patients with imatinib resistance and 49% of patients with imatinib intolerance. The complete cytogenetic response rates were 41% in both groups. These responses have been durable, with a 2-year progression-free survival rate of 79%. The study was later amended to include patients who had received additional TKIs. This portion of the study showed that, even in this subset of heavily treated patients, bosutinib induced major cytogenetic responses in 29–37% of patients and complete cytogenetic responses in up to 34% of patients. Table 1 summarizes the efficacy results at week 24.

H&O How has bosutinib been studied in the frontline setting?

JC Another important area of study is the use of bosutinib as initial therapy for CML. The Bosutinib Efficacy and Safety in Newly Diagnosed Chronic Myeloid Leukemia (BELA) trial was a randomized trial of patients with newly diagnosed disease who were randomized to receive either bosutinib or imatinib. The study was very interesting because the primary endpoint, the achievement of complete cytogenetic response at 12 months, was not met. However, after all patients had been followed for at least 24 months, the major molecular response rate was significantly higher among patients who received

Table 1. Efficacy Results of Bosutinib in Evaluable Patients With Ph+ CP CML With Resistance or Intolerance to Imatinib

	Prior Treatment With Imatinib Only (n=266) n (%) at 24 Weeks	Prior Treatment With Imatinib and Dasatinib or Nilotinib (n=108) n (%) by 24 Weeks
Week 24 MCyR (95% CI)	90 (33.8) (28.2–39.9)	29 (26.9) (18.8–36.2)

CI=confidence interval; CML=chronic myelogenous leukemia; CP=chronic phase; MCyR=major cytogenetic response; Ph+=Philadelphia chromosome–positive.

Data from the US Food and Drug Administration. Highlights of Prescribing Information for Bosulif. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203341lbl.pdf. Accessed October 23, 2012.

bosutinib. Notably, the rates of transformations, treatment failures, and deaths were all significantly lower in the bosutinib arm. Even though the primary endpoint was not met, bosutinib demonstrated beneficial results. Part of the reason that the primary endpoint was not met was because of toxicity, which most commonly included grade 1/2 diarrhea. As such, many patients were taken off therapy very early and were not assessed for a cytogenetic response. To summarize, patients who received bosutinib had better responses and a better rate of transformation, which are key components in preventing the disease from transforming to an accelerated phase or blast phase. Table 2 summarizes efficacy data of the BELA trial at 30 months.

H&O How does bosutinib compare to imatinib?

JC In the laboratory, bosutinib can overcome most of the mutations that are commonly seen after resistance to imatinib. This has been confirmed in the clinic, where responses were observed in patients with most of the mutations commonly seen after imatinib resistance. It is also more potent than imatinib, which likely explains the improved responses seen in the frontline setting in the BELA trial.

H&O What are the biggest remaining challenges?

JC Ideally, we would like to have bosutinib available for the initial treatment of patients with CML; however, this may not happen, certainly not in the near future. We need to better understand the mechanisms of resistance to TKIs, including those that are not associated with mutations.

Table 2. Efficacy of Bosutinib and Imatinib at 30 Months

	Bosutinib (n=250)	Imatinib (n=252)
CCyR, n (%)		
At 30 months	140 (56)	153 (61)
Cumulative by 30 months	197 (79)	204 (81)
MMR, n (%)		
At 30 months	113 (45)	107 (43)
Cumulative by 30 months	153 (61)	132 (52)
Median EFS at 30 months, % (95% CI)	88 (82–92)	86 (80–90)
Median OS at 30 months, % (95% CI)	97 (94–99)	95 (91–97)
Transformation to AP/BP CML, n	8	15

AP/BP=accelerated phase/blast phase; CCyR=complete cytogenetic response; CI=confidence interval; CML=chronic myelogenous leukemia; EFS=event-free survival; MMR=major molecular response; OS=overall survival.

Data from Gambacorti-Passerini C et al. BELA trial update: bosutinib (BOS) versus imatinib (IM) in patients (pts) with newly diagnosed chronic phase chronic myeloid leukemia (CP CML) after 30 months of follow-up. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2012;30: Abstract 6512.

H&O What does the future hold?

JC Bosutinib will certainly be a valuable option for patients who develop resistance to other TKIs. Overall, it is a very exciting time in CML. We do not appear to be reaching the end of the development of new drugs. We continue to develop drugs that have advantages over the previous ones, and this is great news for patients with CML. It is also of utmost importance that we adequately diagnose and stage patients, monitor them closely, and employ treatments properly. Seeing patients with CML essentially live a normal life and not die from this disease is certainly on the horizon.

Suggested Readings

Cortes JE, Kim DW, 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.

Khoury HJ, Cortes JE, Kantarjian HM, et al. Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib and/or nilotinib therapy failure. *Blood*. 2012;119:3403-3412.

Gambacorti-Passerini C, Lipton JH, Tee GY, et al. BELA trial update: bosutinib (BOS) versus imatinib (IM) in patients (pts) with newly diagnosed chronic phase chronic myeloid leukemia (CP CML) after 30 months of follow-up. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2012;30: Abstract 6512.

US Food and Drug Administration. Highlights of Prescribing Information for Bosulif. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203341lbl.pdf. Accessed October 23, 2012.