Bosutinib finds its place in the CML treatment paradigm

Michael Deininger, MD, PhD

University of Utah, Huntsman Cancer Institute, Salt Lake City, Utah

See Community Translations on page 105

Drug therapy of chronic myeloid leukemia (CML) used to be simple. Or rather, it was narrow and not very effective. For a long time all we had was interferon alpha (IFN-alpha) and hydoxyurea, which failed to protect most patients from progression to the blastic phase. As a result, allotransplant, although associated with high mortality, was the treatment of choice for all eligible patients. Then imatinib came along and replaced a simple but poor choice with a simple but good choice for drug therapy. Now, 12 years later, the drug therapy space for CML is populated by 5 different tyrosine kinase inhibitors (TKIs; imatinib, dasatinib, nilotinib, bosutinib, and ponatinib) and omacetaxine (previously known as homoharringtonine) in addition to IFN-alpha and hydoxyurea. Navigating this space is a challenge, especially for hematologists and oncologists who don't have the privilege of specializing.

The drug at issue is bosutinib, which has been approved for treating adults "with chronic, accelerated, or blast phase Philadelphia chromosome-positive (Ph+) CML with resistance or intolerance to prior therapy," but it has not received approval for frontline therapy. A combined phase 1/2 study demonstrated a 41% cumulative rate of complete cytogenetic response (CCyR) in patients with chronic phase CML with resistance to or intolerance of imatinib who were treated with bosutinib; progression-free and overall survival at 2 years were 79% and 92%, respectively, with better results for patients with intolerance compared with patients with resistance. The results are quite comparable with those of nilotinib or dasatinib in the same setting.[1-3] In contrast, only 24% of patients on bosutinib achieved CCyR if they had prior exposure to dasatinib or nilotinib in addition to imatinib, which is also similar to the results with dasatinib or nilotinib in the third line,[4] although follow-up is shorter. Only 2 BCR-ABL1 kinase mutations confer resistance to bosutinib: the multiresistant T315I mutations and V299L.[5]

Correspondence Michael Deininger, MD, PhD, University of Utah, Huntsman Cancer Institute, 2000 Circle of Hope, Room 4280, Salt Lake City, UT 84112-5550 (michael.deininger@hci.utah.edu).

Disclosures The author has no disclosures.

Despite these promising results, bosutinib failed in the phase 3 (BELA) trial in which it was compared with imatinib. The design of the BELA trial was practically identical to the design of the DASISION study of dasatinib and imatinib,[6] with CCyR at 12 months as the primary endpoint, but response rates were identical (70% for bosutinib and 68% for imatinib).[7] The lack of a difference is explicable by the high drop-out rate in the experimental arm (19% for bosutinib vs 6% for imatinib) that obliterated a possible CCyR difference in an intention-to-treat analysis. The leading and distinguishing adverse event with bosutinib was diarrhea (11% grade 3 or 4 for bosutinib vs 2% for imatnib), which turned out to be mostly manageable and transient in patients who stayed on the drug. However, the damage was done, and neither the higher rate of major molecular response (41% for bosutinib vs 27% for imatinib at 12 months) nor the hint at a lower rate of progression to accelerated or blastic phase (2% vs 4%) was sufficient to obtain approval for frontline therapy, although these results are comparable with those of dasatinib or nilotinib in the same setting.[8,9]

Where does bosutinib fit in the treatment paradigm? As far as efficacy is concerned, bosutinib is comparable with nilotinib and dasatinib in patients with imatinib resistance; thus, TKI selection in this situation can take into account expected side effects. Diarrhea on bosutinib is frequent and sometimes severe, but it is quite amenable to supportive care measures and usually self-limited. In contrast, bosutinib's efficacy after treatment with nilotinib or dasatinib is less impressive, which emphasizes the general theme that resistance to 1 second-line TKI does not bode well for a durable response to another agent from that same group. Ponatinib, the recently approved third-line TKI (with activity also against the T315I mutant) holds much more therapeutic promise in this situation and maybe also in the second line; however, this superior efficacy must be balanced against liver toxicity and arterial thrombosis, which led to a black box warning.[10] To make things even more complicated, omacetaxine has been

Commun Oncol 2013;10:103-104
DOI: 10.12788/j.cmonc.0002

approved for patients who failed 2 or more TKIs and may have a role in the small subset of patients who are resistant to all TKIs and despite inhibition of BCR-ABL1.[11] At this point, it seems fair to say that bosutinib has clearly enriched the therapeutic armamentarium for CML. The drug's distinct side effect profile has added to our ability to select drugs based on disease characteristics as well as side effect profiles to achieve disease control while maintaining a high quality of life.

References

1. Cortes JE, Kantarjian HM, Brummendorf TH, et al. Safety and efficacy of bosutinib (SKI-606) in chronic phase Philadelphia chromosome-positive chronic myeloid leukemia patients with resistance or intolerance to imatinib. *Blood*. 2011;118:4567-4576.
2. Hochhaus A, Kantarjian HM, Baccarani M, et al. Dasatinib induces notable hematologic and cytogenetic responses in chronic phase chronic myeloid leukemia after failure of imatinib therapy [published correction appears in *Blood*. 2007;110:1438]. *Blood*. 2007;109:2303-2309.
3. Kantarjian HM, Giles F, Gattermann N, et al. Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is effective in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase following imatinib resistance and intolerance. *Blood*. 2007;110:3540-3546.
4. Garg RJ, Kantarjian H, O'Brien S, et al. The use of nilotinib or dasatinib after failure to 2 prior tyrosine kinase inhibitors: long-term follow-up. *Blood*. 2009;114:4361-4368.
5. Redaelli S, Piazza R, Rostagno R, et al. Activity of bosutinib, dasatinib, and nilotinib against 18 imatinib-resistant BCR/ABL mutants. *J Clin Oncol*. 2009;27:469-471.
6. Kantarjian HM, Shah NP, Cortes JE, et al. Dasatinib or imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: 2-year follow-up from a randomized phase 3 trial (DASISION). *Blood*. 2012;119:1123-1129.
7. 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.
8. Saglio G, Kim DW, Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N Engl J Med*. 2010;362:2251-2259.
9. Kantarjian H, Shah NP, Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med*. 2010;362:2260-2270.
10. Cortes JE, Kantarjian H, Shah NP, et al. Ponatinib in refractory Philadelphia chromosome-positive leukemias. *N Engl J Med*. 2012;367:2075-2088.
11. Cortes J, Lipton JH, Rea D, et al. Phase 2 study of subcutaneous omacetaxine mepesuccinate after TKI failure in patients with chronic-phase CML with T315I mutation. *Blood*. 2012;120:2573-2580.