5 Minute JournalClub

Key ASCO Presentations
Issue 6, 2010

Safety and Efficacy of Bosutinib in Chronic-Phase Chronic Myeloid Leukemia (CML-CP) After Resistance or Intolerance to Imatinib

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CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians and basic scientists sojourn to the American Society of Clinical Oncology (ASCO) Annual Meeting to learn about recent clinical advances that yield alterations in state-of-the-art management for all tumor types. Attracting tens of thousands of attendees from every corner of the globe to both unveil and digest the latest research, ASCO is unmatched in attendance and clinical relevance. Results presented from ongoing trials lead to the emergence of new therapeutic agents and changes in the indications for existing treatments across all cancer medicine. Despite the importance of the conference, the demands of routine practice often limit the amount of time oncology clinicians can realistically dedicate to travel and learning. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the key presentations from the ASCO Annual Meeting and expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for patients with diverse forms of cancer.

LEARNING OBJECTIVE

- Recall emerging clinical trial data regarding the preliminary safety and efficacy of the dual SRC/ABL tyrosine kinase inhibitor bosutinib for patients with CML-CP who demonstrate intolerance or resistance to imatinib.

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This CME activity contains slides. To receive credit, the participant should review the slide presentation and complete the Educational Assessment and Credit Form located at CME.ResearchToPractice.com.

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FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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Paid Research: Bristol-Myers Squibb Company, Genzyme Corporation, Novartis Pharmaceuticals Corporation.

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To go directly to the slides and commentary, **click here**.

When we launched our *Hematologic Oncology Update* audio series several years ago, one of the first investigators I interviewed was Dr Hagop Kantarjian, and from the moment he began to answer what must have seemed like sophomoric questions, I was transfixed and almost held my breath in anticipation of his every response.

During my most recent chat with this MD Anderson legend, we focused on three groundbreaking ASCO presentations on CML, all of which he coauthored. Two of these studies have been subsequently published in *The New England Journal* (Dr K was first author on one), along with a thought-provoking editorial by Charles Sawyers.

For almost a decade, imatinib has been the pillar of CML treatment, and while the agent produces an approximately 65 percent one-year complete cytogenetic response rate and a major improvement in overall survival, there is room for improvement. This possibility became potentially achievable when significant activity was observed with the more potent second-generation TKIs, nilotinib and dasatinib, in patients with disease progression on imatinib.

In response to these important data, several front-line trials were initiated with these agents. For each of these trials, a key endpoint was major molecular response — defined as a three-log reduction of BCR-ABL from baseline (99.9 percent). The first to report was a study of **nilotinib versus imatinib** unveiled in December at ASH and then updated at ASCO, where **a similar trial comparing dasatinib to imatinib** was also presented. The bottom line is that both of these agents produced superior 12-month complete cytogenetic and major molecular responses along with clinically significant reductions in transformation to accelerated phase or blastic crisis. Dr Kantarjian noted that these impressive findings involve early surrogate endpoints and it will be critical to look at three- to five-year event-free survival. Following closely is yet another TKI, **bosutinib**, which as we heard at ASCO proved to have significant activity in patients with disease progression on TKIs. The Phase III up-front comparison to imatinib is due to report very soon.

Dr Kantarjian agrees with Dr Sawyers' editorial that a key issue moving forward will be the one to two percent a year of patients on TKIs who develop new mutations in the BCR-ABL binding site — particularly T315I lesions, which result in resistance to TKIs.

For these important patients, the key may be to add new agents to the TKIs, and a number are in development.

Next up on 5-Minute Journal Club: Another fascinating example of oncogene addiction and TKIs: EML4-ALK and crizotinib in non-small cell lung cancer... and more.

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Safety and Efficacy of Bosutinib in Chronic-Phase Chronic Myeloid Leukemia (CML-CP) After Resistance or Intolerance to Imatinib

Presentation discussed in this issue

Cortes JE et al. **Safety and efficacy of bosutinib (SKI-606) in patients (pts) with chronic phase (CP) chronic myeloid leukemia (CML) following resistance or intolerance to imatinib (IM).** *Proc ASCO* 2010;**Abstract 6502**.

Slides from a presentation at ASCO 2010 and transcribed comments from a recent interview with Hagop M Kantarjian, MD (6/30/10)

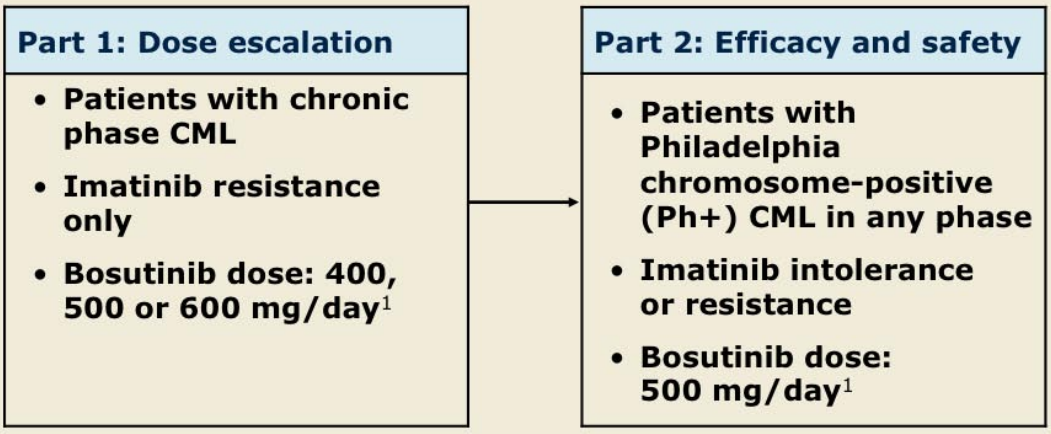
Introduction

- Bosutinib is an orally bioavailable, potent dual SRC/ABL tyrosine kinase inhibitor, with minimal inhibitory activity against PDGFR or c-kit (*Cancer Res* 2006;66:11314).
- Bosutinib inhibits BCR-ABL signaling in chronic myeloid leukemia (CML) cells (*J Cancer Res* 2003;63:375).
- Bosutinib is active against imatinib-resistant mutants of BCR-ABL, except T315I (*Cancer Res* 2006;66:11314).
- **Current study objective:**
  - Investigate the efficacy and safety of bosutinib in patients with imatinib-intolerant or resistant chronic phase (CP) chronic myeloid leukemia (CML).

Cortes JE et al. *Proc ASCO* 2010;Abstract 6502.

Phase I/II Study Design

Accrual: 299 (Closed)



[1] Open label, continuous daily dosing

Cortes JE et al. *Proc ASCO* 2010;Abstract 6502.

Best Response Data

Response	Number of patients (%)
Hematologic[1] (n = 109)[2]	
Overall	102 (94%)
Complete	99 (91%)
Cytogenetic (n = 214)[2]	
Major	136 (64%)
Complete	106 (50%)
Molecular (n = 151)[2]	
Major	79 (52%)
Complete	49 (32%)

[1] Includes patients with unconfirmed hematologic response.
[2] Patients with complete hematologic response, complete cytogenetic response or complete molecular response at baseline (at time of study entry) and those lacking a baseline or post-baseline assessment are considered non-evaluable for the respective response.

Cortes JE et al. *Proc ASCO* 2010;Abstract 6502.

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Efficacy Data

Parameter	Result
Median time to complete cytogenetic response (n = 214)	12.3 months
Median time to major cytogenetic response (n = 214)	6.3 months
Median time to complete hematologic response (n = 109)	0.8 months
Patients progression free at month 24	
Imatinib resistant (n = 202)	77%
Imatinib intolerant (n = 92)	86%
Patients alive at month 24	
Imatinib resistant (n = 202)	92%
Imatinib intolerant (n = 92)	99%

Cortes JE et al. *Proc ASCO* 2010;Abstract 6502.

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Response by BCR-ABL Mutation Status

Mutation type[1]	Complete hematologic response n/n evaluable (%)	Major cytogenetic response n/n evaluable (%)
Any	19/22 (86%)	28/39 (72%)
P-loop	4/4 (100%)	6/9 (67%)
Non-P-loop	15/18 (83%)	22/30 (73%)
No mutation	26/28 (93%)	22/38 (58%)

19 different mutations were identified in 43 of 96 (45%) patients tested.

[1] Patients with complete hematologic, cytogenetic or molecular responses at baseline and patients lacking both a baseline and post-baseline assessment are considered non-evaluable for the respective response.

Cortes JE et al. *Proc ASCO* 2010;Abstract 6502.

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Select Grade 3/4 Adverse Events

Adverse event	Rate
Thrombocytopenia	24%
Neutropenia	16%
Anemia	12%
Diarrhea	9%
Rash	9%
Vomiting	3%
Nausea	2%

Cortes JE et al. *Proc ASCO* 2010;Abstract 6502.

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Conclusions

- Bosutinib is an active agent for patients with CP CML resistant or intolerant to imatinib (complete cytogenetic response 50%).
- Responses occurred across a wide variety of BCR-ABL mutations.
- Duration of response requires further follow-up.
- Bosutinib demonstrated a favorable toxicity profile
  - Self-limiting gastrointestinal adverse events
  - Low rates of hematologic toxicity
  - Minimal fluid retention
- Results of a Phase III randomized trial of bosutinib versus imatinib for patients with newly diagnosed CML are expected at the end of 2010.

Cortes JE et al. *Proc ASCO* 2010;Abstract 6502.

Investigator comment on the results of a Phase I/II study of bosutinib in CML-CP following resistance or intolerance to imatinib

Bosutinib is a highly potent dual Src/Abl inhibitor like dasatinib. It does not inhibit C-kit or PDGFR, so presumably bosutinib will not cause too much myelosuppression or too many pleural effusions.

We have completed both of the salvage studies for patients who became resistant to imatinib, and we observed positive results, with complete cytogenetic response rates of about 50 percent. In August 2010 we will have the data on bosutinib versus imatinib in the front-line setting. We are hoping that these also will be positive and we will have at least three drugs — nilotinib, dasatinib and bosutinib — that could be superior to imatinib and could replace imatinib in the front-line setting.

Surprisingly, bosutinib is associated with fewer adverse events than several of the other drugs. The one problematic issue is diarrhea, typically Grade 1, which is seen in the first one to two weeks and is usually self-limited. The other complications are liver abnormalities — elevations of either the bilirubin or enzymes — which are mostly Grade 1 or 2 and have not been dose limiting in patients on treatment. We did not observe pleural effusions or significant myelosuppression.

Interview with Hagop M Kantarjian, MD, June 30, 2010