5 Minute JournalClub

Key ASH Presentations
Issue 3, 2011

Bosutinib versus Imatinib in the Initial Management of Chronic-Phase Chronic Myeloid Leukemia (CML-CP)

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CME INFORMATION

OVERVIEW OF ACTIVITY

The annual American Society of Hematology (ASH) meeting is unmatched in its importance with regard to advancements in hematologic cancer and related disorders. It is targeted by many members of the clinical research community as the optimal forum in which to unveil new clinical data. This creates an environment each year in which published results from a plethora of ongoing clinical trials lead to the emergence of many new therapeutic agents and changes in the indications for existing treatments across virtually all malignant and benign hematologic disorders. As online access to posters and plenary presentations is not currently available, a need exists for additional resources to distill the information presented at the ASH annual meeting for those clinicians unable to attend but desiring to remain up to date on the new data released there. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets from the latest ASH meeting, including 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 hematologic cancer.

LEARNING OBJECTIVE

- Compare and contrast the efficacy and safety of bosutinib and imatinib in the initial treatment of CML-CP.

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5 MinuteJournalClub

Key ASH Presentations
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ASH 2010 marked another significant chapter in the decade-long saga that has become a model for molecularly targeted cancer treatment. To that end, **this issue** (click for slides) of *5-Minute Journal Club* focuses on some of the most clinically relevant ASH CML highlights, including:

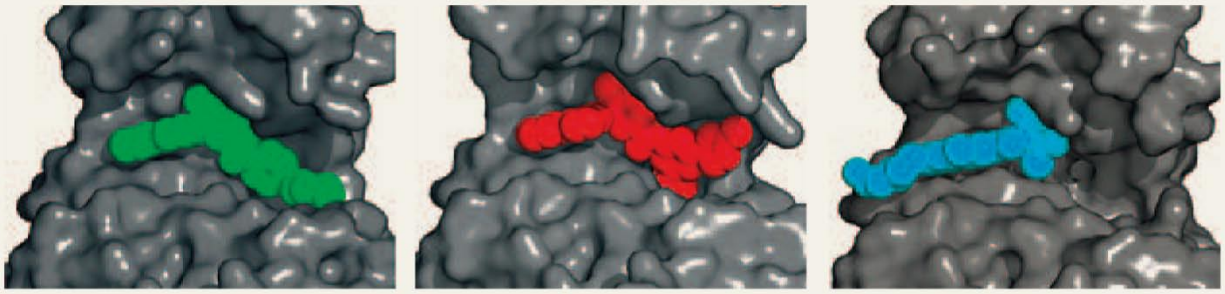
1. **A trial comparing up-front nilotinib to imatinib** and another evaluating a prespecified switch to nilotinib in patients unresponsive to or intolerant of imatinib

The ENESTnd up-front trial, which was first reported at ASH 2009, comparing two doses of nilotinib (400 or 300 mg BID) to imatinib was updated in Orlando. Not surprisingly, the 24-month data continue to demonstrate an advantage to nilotinib in the primary endpoint of major molecular response (MMR). Importantly, progression to accelerated or blast phase was more common with imatinib, yet conversely, while the overall level of side effects was similar between the two agents, rash and serum biochemical abnormalities were more common with nilotinib. A second, very innovative pilot study (TIDEL-II) focused on the use of nilotinib in patients with suboptimal response, loss of response or intolerance to imatinib, which was dose escalated in early molecular nonresponders. Of the 21 patients switched to nilotinib either for poor primary response or intolerance, MMR was observed in 10.

2. **Two trials comparing up-front dasatinib to imatinib**

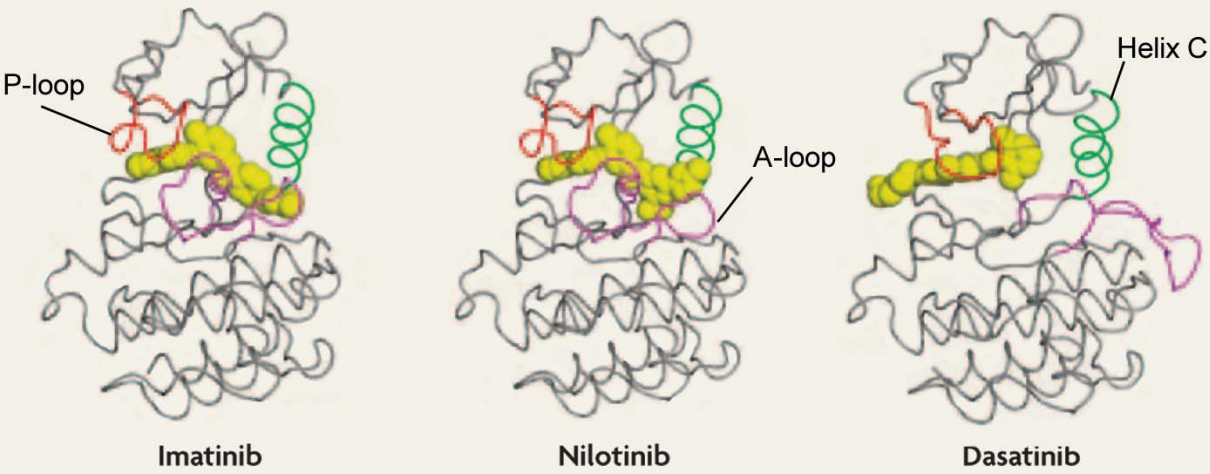
Also at ASH 2009, we heard the first report from the DASISION trial, revealing a higher 12-month confirmed complete cytogenetic response (CCyR) rate with dasatinib than with imatinib. This year, the 18-month update of the study demonstrated continued benefit with this agent, which was first developed as an Src kinase inhibitor and interacts with the BCR protein quite differently than imatinib or nilotinib. In this most recent data set we again witnessed higher rates of both CCyR and MMR with dasatinib and, as with ENESTnd, fewer patients with accelerated or blast phase. As was seen previously, the side effects of dasatinib were of similar frequency but were different from those of imatinib and included pleural effusion (which may be PDGF related) in 31 patients (12 percent), usually requiring treatment interruption or dose modification. A second, smaller Phase II study with a similar randomization reported by the SWOG/ Intergroup demonstrated a 12-month MMR advantage with dasatinib.

Surface representations of crystal structures of ABL kinase in complex with TKIs



Imatinib Nilotinib Dasatinib

Comparison of the different binding modes of three ABL inhibitors



Imatinib Nilotinib Dasatinib

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The aforementioned data sets are helping to fuel extensive debate on the optimal up-front CML chronic phase treatment, and a **mini-metaanalysis** also presented at ASH suggested that a similar early advantage exists for both dasatinib and nilotinib. That being said, most investigators I have spoken with agree that imatinib remains a very reasonable tried and true option.

3. **A trial comparing up-front bosutinib to imatinib** that did not meet the primary endpoint (12-month CCyR)

Apparently not all TKIs are created equal, and a key issue with bosutinib was that while fewer patients experienced treatment failure, 19 percent discontinued the drug due to toxicity (mainly GI) compared to only five percent with imatinib.

For all the fascinating new ASH data, my personal CML highlight from the meeting was a spectacular review of the field by Jerald Radich from the "Hutch." During his discussion, Dr Radich touched on amazing new translational strategies, including mass spectrometry to instantly differentiate 31 clinically relevant mutations and a dizzying

array of serum assays to detect remnants of the nemesis BCR-ABL. The astonishing pace of this research made me think about the many investigators in solid tumors who complain that CML is an anomaly with few analogies to their genomically complicated diseases, but I disagree. Dr Radich's talk (click **here** to order the ASH DVD) makes it abundantly clear that "we have the technology" — the question is whether we have the will, leadership, skills and wisdom to use these powerful tools and concepts to make the dream of a cancer-free world a reality.

Next up on this ASH highlights series: Perhaps the most important ASH paper on lymphoma — the stunning impact of the immunoconjugate brentuximab vedotin in Hodgkin lymphoma.

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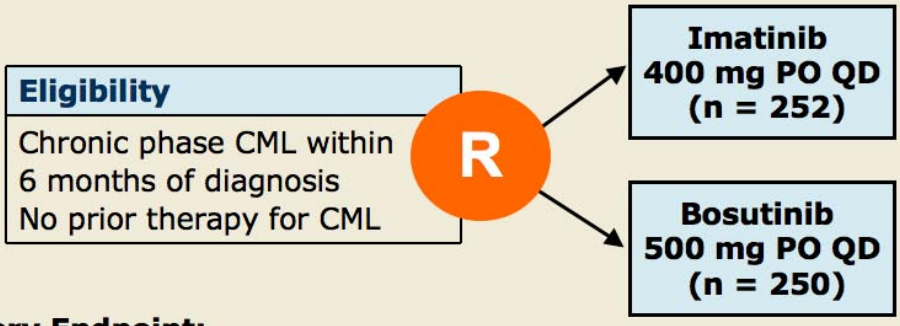
Bosutinib versus Imatinib in the Initial Management of Chronic-Phase Chronic Myeloid Leukemia (CML-CP)

Presentation discussed in this issue

Gambacorti-Passerini C et al. **An ongoing phase 3 study of bosutinib (SKI-606) versus imatinib in patients with newly diagnosed chronic phase chronic myeloid leukemia.** *Proc ASH* 2010;**Abstract 208**.

Slides from a presentation at ASH 2010 and transcribed comments from recent interviews with Susan M O'Brien, MD (1/4/11) and Neil P Shah, MD, PhD (1/4/11)

BELA Study Schema



Primary Endpoint:
Complete cytogenetic response (CCyR) rate at 12 months

Other Key Endpoints:
Major molecular response (MMR) rate at 12 months
Duration of CCyR, MMR and complete hematologic response (CHR)
Time to and rate of progression to accelerated/blast phase (AP/BP)
Safety and tolerability

Gambacorti-Passerini C et al. *Proc ASH* 2010;Abstract 208.

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Efficacy Outcomes

	Imatinib	Bosutinib	*p*-value
CCyR at 12 months			
ITT population (n = 252; 250)	68%	70%	0.601
Evaluable population (n = 241; 219)	68%	78%	0.026
MMR at 12 months			
ITT population (n = 252; 250)	26%	39%	0.002
Evaluable population (n = 241; 219)	27%	43%	<0.001
Median time to CCyR	24.6 weeks	12.9 weeks	<0.0001
Median time to MMR	72.3 weeks	37.1 weeks	<0.0001
Transformation to AP/BP (n = 252; 250)	4%	2%	0.053
CML-related deaths (n = 252; 250)	3%	1%	0.056

Gambacorti-Passerini C et al. *Proc ASH* 2010;Abstract 208.

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Nonhematologic Safety Events

	Imatinib (n = 251)		Bosutinib (n = 248)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Diarrhea	21%	1%	68%	10%
Vomiting	13%	0%	32%	3%
Bone pain	10%	1%	4%	0%
Muscle cramps	20%	0%	2%	0%
Peri-orbital edema	14%	0%	<1%	0%
Increased ALT	Not Reported	3.2%	Not Reported	20.6%
Increased AST	Not Reported	2.8%	Not Reported	10.1%

Gambacorti-Passerini C et al. *Proc ASH* 2010;Abstract 208.

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Hematologic Adverse Events

	Imatinib (n = 251)	Bosutinib (n = 248)
Grade ≥3 anemia	6.4%	6.0%
Grade ≥3 neutropenia	22.7%	8.9%
Grade ≥3 thrombocytopenia	13.1%	12.5%

Gambacorti-Passerini C et al. *Proc ASH* 2010;Abstract 208.

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Treatment Summary: Dose Interruption, Reduction, Discontinuation

Parameter	Imatinib (n = 251)	Bosutinib (n = 248)
Dose interruption secondary to adverse event	42%	61%
Dose reduction secondary to adverse event	18%	39%
Discontinued patients (total)	20%	29%
Discontinuation secondary to adverse event	5%	19%
Discontinuation secondary to treatment failure	10%	3%

Gambacorti-Passerini C et al. *Proc ASH* 2010;Abstract 208.

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Author's Conclusions

- Bosutinib did not demonstrate a superior rate of CCyR at 12 months based on the ITT population, but was higher based on the evaluable population.
- Bosutinib treatment did result in a superior rate of MMR at 12 months compared to imatinib based on the ITT and evaluable populations.
- Patients on bosutinib appear to have lower rates of deaths due to CML progression, transformation to AP/BP and discontinuations due to treatment failure compared to those on imatinib.

Gambacorti-Passerini C et al. *Proc ASH* 2010;Abstract 208.

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Investigator comment on the Phase III study of bosutinib versus imatinib in CML

This was a study comparing another second-generation TKI, bosutinib, to imatinib in the up-front management of CML. Bosutinib is an interesting drug because the putative advantage of this drug is that it doesn't interfere with the PDGF receptor or with c-Kit. The hypothesis has been that one of the reasons dasatinib causes pleural effusions is by interfering with PDGF receptor signaling, and all the currently available TKIs cause myelosuppression by inhibiting c-Kit. Thus there was a theoretical rationale that bosutinib might cause fewer pleural effusions and less myelosuppression.

The general expectation was that this would be another positive randomized trial of a second-generation TKI in first-line chronic phase CML. Unfortunately, the results were rather disappointing as the complete cytogenetic responses were similar in both arms in the intent-to-treat analysis. Additionally, a high percentage of patients came off study because of toxicity in response to bosutinib.

Interview with Susan M O'Brien, MD, January 4, 2011

Investigator comment on the Phase III study of bosutinib versus imatinib in CML

The primary endpoint of this study was complete cytogenetic response (CCyR), and in viewing the intent-to-treat population at 12 months no significant difference was observed in the CCyR rate between the two arms. Seventy percent of patients receiving bosutinib versus 68 percent receiving imatinib achieved CCyR. The major molecular response rate seemed to be superior for bosutinib at 39 percent versus 26 percent, but this was not the primary endpoint.

One of the most important observations of this trial was that 19 percent of patients discontinued bosutinib due to adverse events compared to only five percent of patients receiving imatinib. The most common cause for discontinuation of imatinib was treatment failure, at 10 percent compared to three percent with bosutinib.

So this study, unfortunately, missed its primary endpoint. I believe this agent has significant activity. However, whether it will obtain approval in the front-line setting, now that nilotinib and dasatinib have already established a high bar, remains to be seen.

Interview with Neil P Shah, MD, PhD, January 4, 2011