5 Minute JournalClub

Key ASH Presentations
Issue 3, 2011

Systematic Review and Meta-Analysis of the Relative Efficacy of Treatments for Chronic Myeloid Leukemia (CML)

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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

- Refine or validate your current understanding of the comparative efficacy of BCR-ABL inhibitors in the treatment of newly diagnosed CML-CP.

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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:

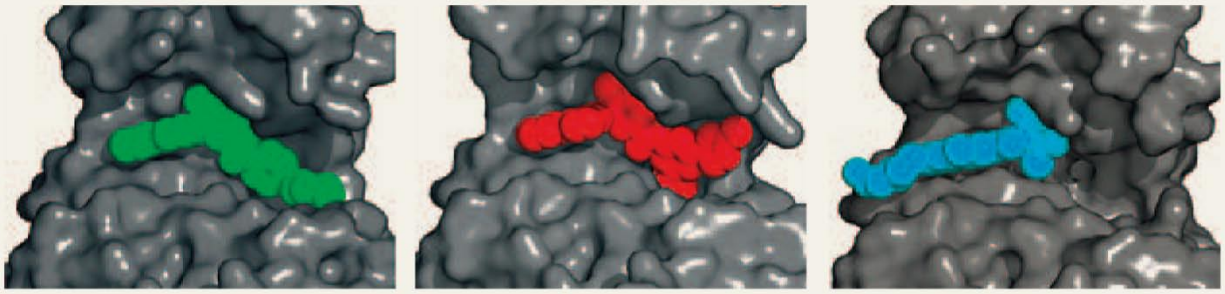
1. **A trial comparing up-front nilotinib to imatinib** and another evaluating a prespecified switch to nilotinib in patients unresponsive to or intolerant of imatinib

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**

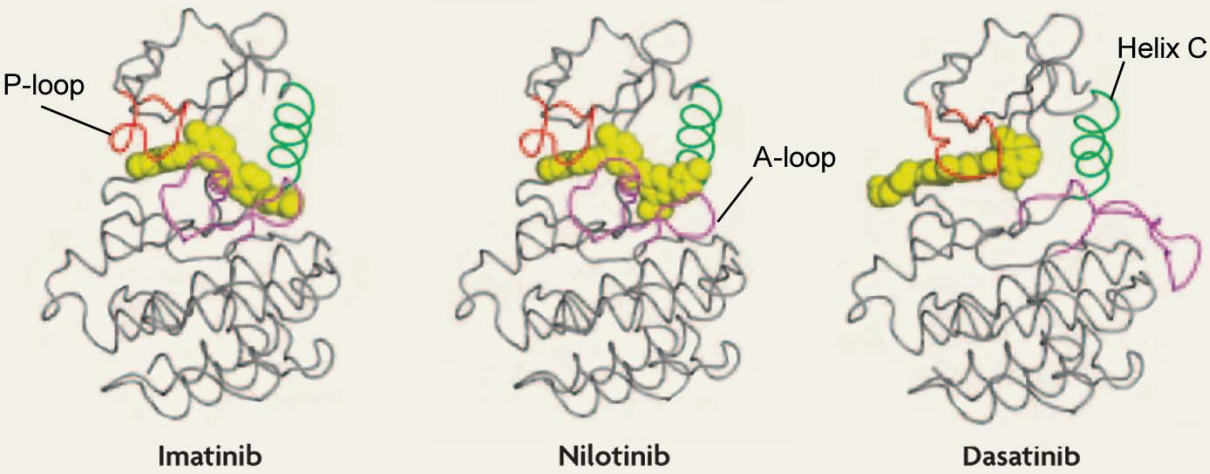
Also at ASH 2009, we heard the first report from the DASISION trial, revealing a higher 12-month confirmed complete cytogenetic response (CCyR) rate with dasatinib than with imatinib. This year, the 18-month update of the study demonstrated continued benefit with this agent, which was first developed 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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Systematic Review and Meta-Analysis of the Relative Efficacy of Treatments for Chronic Myeloid Leukemia (CML)

Presentation discussed in this issue

Mealing S et al. **Comparative efficacy of first-line treatment of chronic myeloid leukemia: A systematic review and meta-analysis.** *Proc ASH* 2010;**Abstract 3436**.

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

Objectives

- Use meta-analysis to evaluate the relative efficacy of the oral BCR-ABL inhibitors imatinib, dasatinib and nilotinib in patients with newly diagnosed chronic-phase CML (CML-CP).
- The analyses were conducted using mixed treatment-comparison meta-analytical techniques.
  - In the absence of randomized head-to-head trials, a Bayesian mixed treatment-comparison meta-analysis provides a means to indirectly estimate the treatment effect of 1 intervention relative to another.

Mealing S et al. *Proc ASH* 2010;Abstract 3436.

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Methods

- Abstracts were independently reviewed by 2 members of the project team for inclusion in the network meta-analysis (NMA).
- Criteria for inclusion of study data in the NMA:
  - English-language, randomized controlled trials that included adult patients (>18 years of age) with newly diagnosed CML-CP
    - Evaluated dasatinib, imatinib, nilotinib, interferon alpha* or hydroxyurea*
    - Major molecular response (MMR), complete cytogenetic response (CCyR), partial cytogenetic response, minor cytogenetic response, no cytogenetic response, and overall and progression-free survival outcomes data

*Non-BCR-ABL inhibitors were also included to increase the available data network.

Mealing S et al. *Proc ASH* 2010;Abstract 3436.

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Trials Included in the NMA

Citation	Study Design	Treatments (N)
N Engl J Med 2010;362:2260-70	R, MC, phIII	Dasatinib 100 mg QD (n=259) Imatinib 400 mg QD (n=260)
Blood 2009;113:4497-504	P, R	Imatinib 400 mg QD (n=108) Imatinib 800 mg QD (n=108)
N Engl J Med 2010;362:2251-9	MC, R, phIII	Nilotinib 300 mg BID (n=282) Nilotinib 400 mg BID (n=281) Imatinib 400 mg QD (n=283)

R = randomized; MC = multicenter; phIII = Phase III;
P = prospective

Mealing S et al. *Proc ASH* 2010;Abstract 3436.

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Data Used in the NMA

Citation	Treatments	CCyR 6 mo (%)	CCyR 12 mo (%)	MMR 12 mo (%)
N Engl J Med 2010;362:2260-70	Dasatinib 100 mg QD Imatinib 400 mg QD	73.0 59.2 (P=NR)	83.4 71.5 (P=0.0011)	45.9 28.1 (P<0.0001)
Blood 2009;113:4497-504	Imatinib 400 mg QD Imatinib 800 mg QD	50.0 51.9 (P=NS)	58.3 63.9 (P=0.435)	33.3 39.8 (P=NS)
N Engl J Med 2010;362:2251-9	Nilotinib 300 mg BID Nilotinib 400 mg BID Imatinib 400 mg QD	67.0 63.0 44.9 (P=NR)	80.1 77.9 65.0 (P<0.001)*	44.0 43.1 21.9 (P<0.001)*

*P-value is for both nilotinib arms vs imatinib. NR = not reported; NS = not significant

Mealing S et al. *Proc ASH* 2010;Abstract 3436.

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Relative Treatment Effects: CCyR at 12 Months

	Imatinib 400 mg QD OR (95% CI*)	Dasatinib 100 mg QD OR (95% CI*)	Nilotinib 300 mg BID OR (95% CI*)	Nilotinib 400 mg BID OR (95% CI*)
Imatinib 400 mg QD	—	0.51 (0.33, 0.76)	0.47 (0.31, 0.67)	0.53 (0.36, 0.76)
Dasatinib 100 mg QD	2.06 (1.31, 3.06)	—	0.96 (0.52, 1.63)	1.10 (0.60, 1.85)
Nilotinib 300 mg BID	2.22 (1.49, 3.21)	1.13 (0.61, 1.93)	—	1.17 (0.76, 1.71)
Nilotinib 400 mg BID	1.94 (1.31, 2.78)	0.99 (0.54, 1.67)	0.89 (0.58, 1.31)	—

**95% CI = Bayesian equivalent of a 95% confidence interval*

Mealing S et al. *Proc ASH* 2010;Abstract 3436.

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Efficacy Results

- The evaluation of efficacy using 6-month and 12-month CCyR and 12-month MMR:
  - Significantly higher responses in the dasatinib 100 mg QD and nilotinib 300 mg BID groups compared with imatinib 400 mg QD ($P<0.05$).
  - Response odds for dasatinib 100 mg QD and nilotinib 300 mg BID were >2-fold higher than those of imatinib 400 mg QD
- Indirect comparisons of dasatinib vs nilotinib showed no significant differences in relative efficacy.
- Evidence networks could not be constructed for survival endpoints due to a paucity of events in the publications.

Mealing S et al. *Proc ASH* 2010;Abstract 3436.

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Conclusions

- Dasatinib and nilotinib were associated with significant improvements in CCyR and MMR compared with imatinib 400 mg QD.
- Using the CCyR at 6 and 12 months and the MMR at 12 months, there were no significant differences in the relative efficacy of dasatinib and nilotinib.
- CCyR at 18 months, survival and safety-related outcomes could not be evaluated in this study.
- The addition of data from future randomized controlled trials will strengthen the present meta-analysis.

Mealing S et al. *Proc ASH* 2010;Abstract 3436.

Investigator comment on the meta-analysis and systematic review of the comparative efficacy of first-line treatment of CML

This review tells us something that we already knew from the two randomized trials of second generation TKIs published earlier this year in the *New England Journal of Medicine.* Both the controlled trials had primary endpoints at 12 months of treatment, though the well-established endpoint with imatinib is complete cytogenetic response at 18 months. With the earlier endpoints at 12 months, the second-generation TKIs looked better.

We currently do not know if these earlier endpoints are going to be associated with better event-free or overall survival in the long run.

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

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