5 Minute JournalClub

Key ASH Presentations
Issue 8, 2012

Prediction of Risk of Disease Progression and Death in CML After Imatinib Treatment

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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 and new information 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, hematologists and hematology-oncology fellows in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- Apply emerging clinical trial data to the rational selection of treatment with targeted tyrosine kinase inhibitors for patients with refractory or relapsed chronic myeloid leukemia.
- Assess the risks of molecular relapse after the discontinuation of treatment with targeted tyrosine kinase inhibitors in patients with chronic myeloid leukemia.
- Communicate the benefits and risks of therapy with multitargeted tyrosine kinase inhibitors for patients with newly diagnosed, relapsed or refractory chronic myeloid leukemia in chronic, accelerated or blast phase.
- Compare and contrast the benefits and adverse effects of continuous therapy with different targeted tyrosine kinase inhibitors in the treatment of chronic myeloid leukemia.

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No real or apparent conflicts of interest to disclose.

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To go directly to slides and commentary for this issue, **click here**.

The 2009 ASH meeting marked a high point in the amazing and continuing evolution of the management of chronic phase chronic myelogenous leukemia (CML-CP) with the sudden appearance of several convincing Phase III data sets demonstrating that the second-generation BCR-ABL TKIs nilotinib and dasatinib resulted in improvements in a number of major short-term endpoints and were equally or better tolerated compared to imatinib. These and other recent findings also put into sharp focus the fact that despite the impressive steps forward during the last decade there is room for improvement in CML-related outcomes, including survival. For this issue of our series we briefly review 8 new ASH data sets addressing the following important CML questions:

1. What is the role of second-generation TKIs?

The weight of evidence for the newer agents continues to mount, and at ASH another round of related data sets was reported.

More follow-up on up-front nilotinib versus imatinib

The landmark IRIS trial that established the role of imatinib demonstrated that most disease progression events occurred within 3 years, and as such similar follow-up with the newer TKIs is critical. At ASH, 3-year data from the ENESTnd trial of nilotinib versus imatinib revealed continued separation of the curves for major and deeper molecular response. Importantly, in the imatinib arm a 6% rate of progression to accelerated phase and blast crisis (AP/BC) was observed compared to only 0.7% with 300 mg BID of nilotinib.

Switching TKIs at 1 year

Many/most investigators currently prefer nilotinib or dasatinib as first-line therapy, but any imatinib holdouts will be forced to strongly consider the compelling preliminary results from the ENESTcmr Phase III trial assessing the benefit of switching therapy for individuals who do not achieve complete molecular response (CMR) after treatment with imatinib. In the study, 207 patients in complete cytogenetic response (CCyR) but with detectable BCR-ABL less than 2 years after starting imatinib were randomly assigned

to either continue therapy or switch to nilotinib 400 mg BID. At 12 months of follow-up, the rate of confirmed CMR was 5.8% with imatinib compared to 12.5% for nilotinib.

Nilotinib 400 mg BID

The ENESTnd extension trial reported at ASH evaluated the higher 400-mg BID dose of nilotinib in patients with suboptimal response or treatment failure on imatinib or nilotinib at 300 mg BID. The findings illustrate clear-cut efficacy in patients treated with prior imatinib — even after dose escalation — and also point to a benefit in those escalated to the higher nilotinib dose. Currently, 300 mg BID is still the recommended starting dose up front.

2. Are there even newer TKIs with significant supportive trial data?

Ponatinib

Ponatinib has been previously shown to have notable activity in tumors with otherwise problematic T315I mutations, and the clinical impact of this agent in resistant or intolerant disease was once again displayed in an impressive Phase II trial of 403 patients reported at ASH.

Bosutinib

Another data set presented at ASH came from the Phase III BELA trial comparing bosutinib to imatinib in patients with newly diagnosed CML-CP. The study did not meet its primary endpoint of CCyR at 12 months partly due to early treatment discontinuation in about a quarter of the patients related to bosutinib-associated adverse effects, particularly GI toxicity (diarrhea). However, other endpoints favored the new TKI bosutinib — including a lower rate of progression to AP/BC — and the future role of the agent is still up for debate.

3. How early can suboptimal response be identified?

The answer just might be 3 months, based on findings from an ASH presentation showing that patients on imatinib with >10% BCR-ABL levels or >35% Ph+ cells at the 3-month time point had a 5-year survival rate of only 87%. Ongoing trials are evaluating an early switch to another TKI in these patients.

4. Can TKI treatment ever be stopped?

Although disease control is everyone's primary concern, lifelong TKI use introduces quality of life and financial constraints, and as such many have wondered if it is safe to stop therapy at some point. At ASH we saw results from the STIM study evaluating treatment discontinuation in 100 patients who received imatinib and experienced a CMR for at least 2 years. Interestingly, 61% of patients experienced molecular relapse upon

stopping therapy (almost all within 7 months). However, most went back into CMR with re-treatment. The ability to stay off the drug seemed to correlate with disease biology (Sokal score) and duration of therapy. Another ASH report of 25 patients who stopped either nilotinib or dasatinib seemed to reflect a similar conclusion, and indefinite treatment is still recommended outside a trial setting.

Next, our final ASH report: More data and perspectives on non-Hodgkin lymphoma and chronic lymphocytic leukemia.

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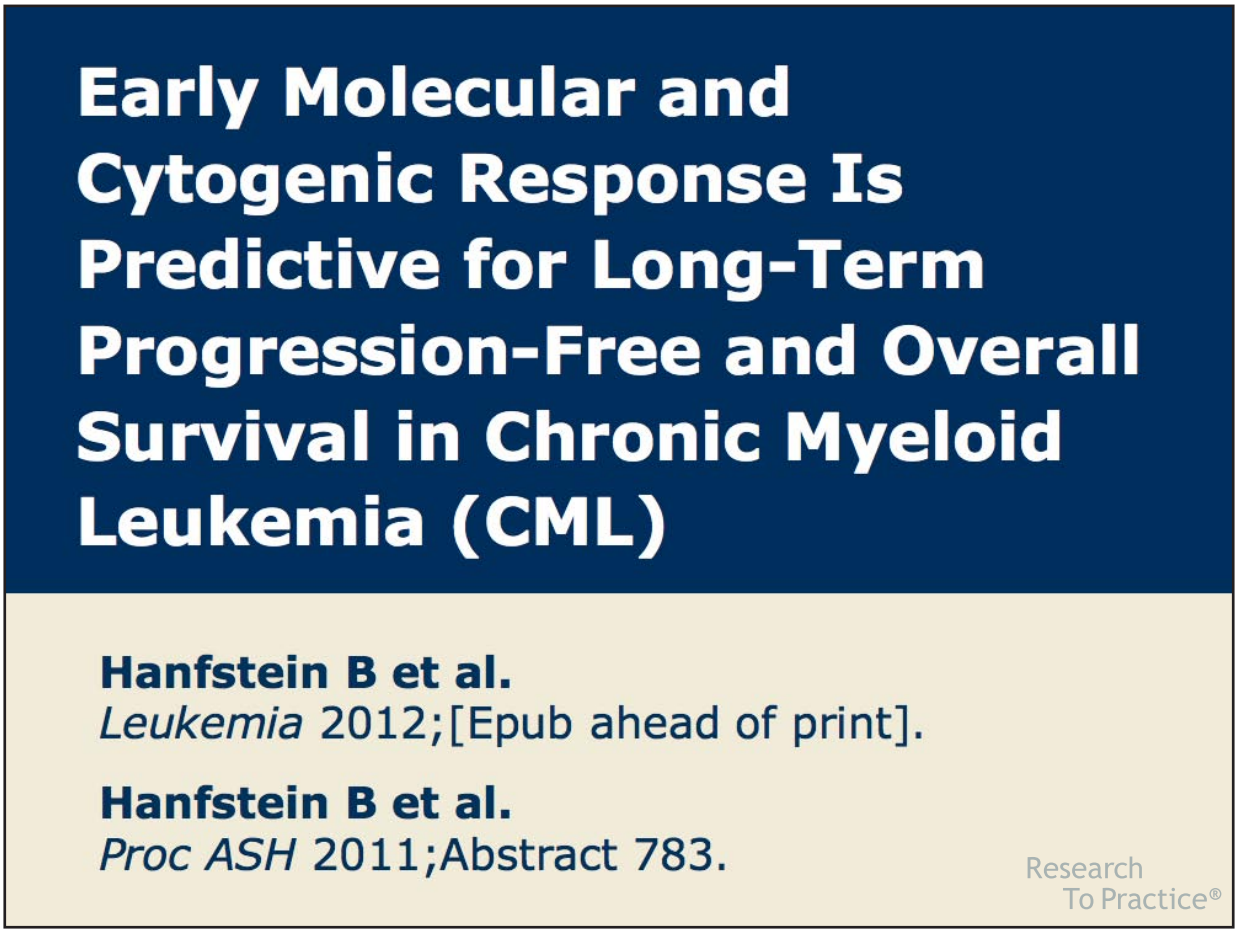
Prediction of Risk of Disease Progression and Death in CML After Imatinib Treatment

Presentation discussed in this issue

Hanfstein B et al. **Molecular and cytogenetic response after 3 months of imatinib treatment is predictive for the risk of disease progression and death in newly diagnosed chronic myeloid leukemia patients — A follow-up analysis of the German CML study IV.** *Proc ASH* 2011;**Abstract 783**.

Slides from a presentation at ASH 2011 and transcribed comments from a recent interview with Srdan Verstovsek, MD, PhD (1/25/12)



Background

- The advent of second-generation tyrosine kinase inhibitors (TKIs) in the front-line treatment setting of chronic myeloid leukemia (CML) has prompted a closer evaluation of the response to imatinib (*N Engl J Med* 2010;362:2251, 2260).
- Early assessment of response markers might identify slow responders harboring a BCR-ABL positive clone with an inferior susceptibility to TKIs.
- Slow responders could benefit from an early dose escalation or a change of treatment to a second-generation TKI, thus avoiding the risk of disease progression.
- **Current study objective**: Evaluate the impact of molecular and cytogenetic response levels after 3 months of an imatinib-based treatment on the course of CML.

Hanfstein B et al. *Leukemia* 2012;[Epub ahead of print].

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CML Study IV Methods

- Patients with CML treated with imatinib (n = 1,303).
- Patients were randomly assigned to receive:
  - Imatinib 400 mg/d
  - Imatinib 400 mg/d + interferon alpha (IFN)
  - Imatinib 400 mg/d + low-dose cytarabine (arm closed 2005)
  - Imatinib 400 mg/d after IFN failure (arm closed 2005)
  - Imatinib 800 mg/d
- Molecular and cytogenetic responses analyzed at 3 months and 6 months.
- BCR-ABL and total ABL transcript levels were measured by quantitative RT-PCR, standardized according to international scale (BCR-ABL^{IS}).
- Cytogenetic response was determined by conventional metaphase analyses with standard G-banding or fluorescence R-banding techniques.
- Endpoints include progression-free survival (PFS) and overall survival (OS).

Hanfstein B et al. *Leukemia* 2012;[Epub ahead of print].

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PFS by Molecular Response

BCR-ABL^{IS} at 3 months	Five-year PFS	*p*-value	
≤1% (n = 218)	96%	NS	—
>1%-10% (n = 281)	92%		0.037
>10% (n = 189)	87%	—	
BCR-ABL^{IS} at 6 months	**Five-year PFS**	***p*-value**	
≤1% (n = 498)	96%	0.006	—
>1%-10% (n = 194)	89%		NS
>10% (n = 91)	86%	—	

NS = not significant

- PFS was defined as the absence of accelerated phase, blast crisis and death.
- Probability of PFS was calculated from the Kaplan-Meier plot and compared by log-rank statistics.

Hanfstein B et al. *Leukemia* 2012;[Epub ahead of print].

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PFS by Cytogenetic Response

Ph+ at 3 months	Five-year PFS	*p*-value
≤35% (n = 336)	94%	0.016
>35% (n = 122)	87%	
Ph+ at 6 months	**Five-year PFS**	***p*-value**
0% (n = 319)	97%	0.014
>0% (n = 160)	91%	

- Median proportion of Philadelphia chromosome-positive metaphases (Ph+) = 8%

Hanfstein B et al. *Leukemia* 2012;[Epub ahead of print].

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OS by Molecular Response

BCR-ABL^{IS} at 3 months	Five-year OS	*p*-value	
≤1% (n = 218)	97%	NS	—
>1%-10% (n = 283)	94%		0.012
>10% (n = 191)	87%	—	
BCR-ABL^{IS} at 6 months	**Five-year OS**	***p*-value**	
≤1% (n = 498)	97%	0.002	—
>1%-10% (n = 196)	90%		NS
>10% (n = 95)	88%	—	

- OS was defined as the absence of death from any cause.
- Probability of OS was calculated from the Kaplan-Meier plot and compared by log-rank statistics.

Hanfstein B et al. *Leukemia* 2012;[Epub ahead of print].

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OS by Cytogenetic Response

Ph+ at 3 months	Five-year OS	*p*-value
≤35% (n = 336)	95%	0.036
>35% (n = 124)	87%	
Ph+ at 6 months	**Five-year OS**	***p*-value**
0% (n = 320)	97%	0.015
>0% (n = 162)	91%	

Hanfstein B et al. *Leukemia* 2012;[Epub ahead of print].

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Author Conclusions

- The levels of molecular or cytogenetic response at 3 months of imatinib treatment allow for a risk stratification of patient outcome in terms of PFS and OS.
- Patients (28%) who failed to achieve 10% BCR-ABL^{IS} level at 3 months had a 5-year OS of only 87%.
- Survival rates were significantly better for patients with >1% to 10% and ≤1% BCR-ABL^{IS}. However, there was no significant difference between the >1% to 10% and ≤1% BCR-ABL^{IS} groups.
- Therefore, missing the 10% BCR-ABL^{IS} landmark at 3 months predicts inferior survival.
- A similar risk group is defined by failure to achieve the 35% Ph+ landmark at 3 months:
  - 5-year OS with Ph+ >35% at 3 months is 87%.
- Treatment optimization is suggested for patients missing these landmarks.

Hanfstein B et al. *Leukemia* 2012;[Epub ahead of print].

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Investigator Commentary: Molecular and Cytogenetic Response After 3 Months of Imatinib Treatment Predicts Survival in CML

This study reported a significant difference in outcome for patients with CML depending on molecular and cytogenetic responses after 3 months of imatinib treatment. After 3 months of therapy, it is possible to predict the risk of disease progression and death.

Results from this study raised the question as to whether a patient's treatment should be changed early on, depending on the response after 3 months of imatinib therapy. Clinical studies have already been initiated based on these results, in which early use of a different TKI has been attempted to improve outcomes in patients with CML in chronic phase. Second-generation TKIs like dasatinib and nilotinib have received FDA approval in the front-line setting for CML. Although this study suggests the administration of a different second-generation TKI as first-line therapy for patients who will not fare well on imatinib, the question of how such patients will be predefined remains unanswered.

Overall, monitoring of molecular and cytogenetic responses to therapy early on may help community oncologists in treatment decision-making.

Interview with Srdan Verstovsek, MD, PhD, January 25, 2012