



*POST-ASH* Issue 2, 2014

# **Dose Interruption/Reduction of TKIs in the First 3 Months of CML Treatment**

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## CME INFORMATION

### OVERVIEW OF ACTIVITY

Each year, thousands of clinicians, basic scientists and other industry professionals sojourn to major international oncology conferences, like the American Society of Hematology (ASH) annual meeting, to hone their skills, network with colleagues and learn about recent advances altering state-of-the-art management in hematologic oncology. As such, these events have become global stages where exciting science, cutting-edge concepts and practice-changing data emerge on a truly grand scale. This massive outpouring of information has enormous benefits for the hematologic oncology community, but the truth is it also creates a major challenge for practicing oncologists and hematologists.

Although original data are consistently being presented and published, the flood of information unveiled during a major academic conference is unprecedented and leaves in its wake an enormous volume of new knowledge that practicing oncologists must try to sift through, evaluate and consider applying. Unfortunately and quite commonly, time constraints and an inability to access these data sets leave many oncologists struggling to ensure that they're aware of crucial practice-altering findings. This creates an almost insurmountable obstacle for clinicians in community practice because they are not only confronted almost overnight with thousands of new presentations and data sets to consider but they are also severely restricted in their ability to review and interrogate the raw findings.

To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets on the management of chronic myeloid leukemia (CML) from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts may be applied to routine clinical care. This activity will assist medical oncologists, hematologists, hematology-oncology fellows and other healthcare professionals in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

### LEARNING OBJECTIVES

- Evaluate the impact of early molecular response or dose interruption of tyrosine kinase inhibitors (TKIs) on the prognosis of patients with CML.
- Compare and contrast the benefits and risks of nilotinib versus imatinib therapy in patients with newly diagnosed chronic-phase CML.
- Appraise recent clinical data on the effect of switching to nilotinib in patients with a suboptimal response to imatinib therapy versus continuation of imatinib at a higher dose.
- Analyze the outcomes of the STIM1 and STIM2 studies of discontinuation of imatinib in patients with a deep molecular response, and consider these results in the management of CML.
- Assess the efficacy and safety of ponatinib as initial therapy and in patients with TKI-resistant CML.

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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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Consulting Agreements: Bristol-Myers Squibb Company, Genentech BioOncology, Lilly, Novartis Pharmaceuticals Corporation, Pfizer Inc, Sanofi; Contracted Research: Bristol-Myers Squibb Company, Celgene Corporation, Novartis Pharmaceuticals Corporation, Pfizer Inc, Sanofi.

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No real or apparent conflicts of interest to disclose.

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Hardware/Software Requirements:

A high-speed Internet connection  
A monitor set to 1280 x 1024 pixels or more  
Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari 3.0 or later  
Adobe Flash Player 10.2 plug-in or later  
Adobe Acrobat Reader  
(Optional) Sound card and speakers for audio

Last review date: February 2014

Expiration date: February 2015

To go directly to slides and commentary for this issue, [click here](#).

Sometimes I have to pinch myself to see if this is a dream or if I really have a job listening to and learning from the great minds in our chosen field. Last week was a perfect reminder of just how cool “work” can be when within the space of a few days my calendar included extensive interviews with Drs Jorge Cortes and then Hagop Kantarjian. As deputy chair and chair of MD Anderson’s Department of Leukemia, respectively, these 2 investigators lead a unique clinical and research powerhouse that has contributed perhaps as much to the care of patients with these and other related hematologic disorders as any other institution in the world.



**Jorge E Cortes, MD**

To get a sense of just how prolific they are, peruse the 2013 ASH abstracts and you will find that Drs Cortes and Kantarjian helped author 103 oral presentations and posters, including 30 on chronic myelogenous leukemia (CML) alone. As such, and not surprisingly, each of these conversations focused heavily on that disease — which has become the poster child for targeted oncologic treatment — and below find the bottom line on their thoughts about how the data sets from New Orleans helped address the following important questions in CML.



**Hagop M Kantarjian, MD**

**1. What are the key early markers of response, and when should consideration be given to switching to another tyrosine kinase inhibitor (TKI)?**

Another MD Anderson leukemia maven and chair of the NCCN CML guidelines committee, Dr Susan O’Brien frequently reinforces the important concept that although there are many reasons to seek deep molecular responses (DMR), the classic and most important endpoint is complete cytogenetic response (CCyR) — a milestone that is achieved faster and more frequently with the second-generation agents, nilotinib and dasatinib. The question of whether suboptimal molecular response should trigger a switch to another TKI ties directly into the issue of selection of up-front therapy and whether long-term outcomes are compromised when residual disease is present.

Equally relevant and looming in the background is a fascinating question of “quality” and cost associated with oncology care. Specifically, imatinib is due to go off patent in January 2015, and it is expected that this will dramatically lower the annual tab (about \$90,000 with imatinib, and with nilotinib and dasatinib closer to \$100,000). With a current prevalence of about 100,000 CML cases in the United States alone — a number that will likely double in the next 3 decades before plateauing — researchers, clinicians and policy makers will almost certainly continue the debate about the value of starting with imatinib (the soon-to-be less costly and perhaps slightly less effective agent) and reserving second-generation treatment for patients with higher-risk disease and those with suboptimal initial responses to imatinib. How these potential resource savings stack up against others in oncology related to, for example, futile care and unnecessary imaging will be discussed extensively, and more globally Dr Kantarjian has taken a leadership role in organizing a group of “CML experts” (including Dr Cortes) who have been on a dedicated and major offensive attacking the current CML cost structure.

At ASH we witnessed a number of related papers that tie in to the issue of imatinib versus the rest, including the **36-month update** of the ENESTcmr study. This landmark Phase III effort demonstrated that among patients in CCyR but with detectable BCR-ABL transcripts, those randomly assigned to switch to nilotinib achieved more DMRs compared to those continuing on imatinib (47% with nilotinib versus 33% with imatinib at 36 months). This benefit came with greater toxicity, which may in part be attributable to the trial design in that patients who transitioned to nilotinib were already tolerating imatinib well.

On a similar note, an ASH data set presented by Dr Cortes from the Phase III **LASOR trial** revealed that switching to nilotinib versus escalating the dose of imatinib in patients who experienced suboptimal response resulted in a better rate of CCyR at 6 months (49% versus 42%, respectively), although the findings were not statistically significant ( $p = 0.3844$ ).

Finally, a **retrospective analysis** of 3- and 6-month responses in early trials of imatinib demonstrated that some patients who achieve an optimal response by 6 instead of 3 months have long-term outcomes comparable to those who achieved an optimal response at 3 months, suggesting that waiting a few additional months before considering a change in treatment is a rational approach.

Proponents of using imatinib as initial treatment in standard-risk situations often point out that so far, no survival benefit has been demonstrated using the second-generation agents — possibly because these drugs also effectively rescue patients experiencing disease progression on imatinib. Thus, although DMR is an intuitively appealing goal, until further research identifies more accurately who can cease TKI treatment (now there’s a cost saving!), there will be debate and controversy about what to start with and when and if to make a switch. This is particularly true as more follow-up occurs

with the landmark second-generation trials, some of which are documenting more long-term complications, such as the 5-year update of the [ENESTnd trial](#) presented at ASH that now shows not only deeper molecular responses with nilotinib but also an increasing number of cardiovascular events.

## **2. Are there situations in which it is safe to discontinue TKI treatment?**

At ASH we saw more data from [2 French studies](#) (STIM 1 and 2) attempting to define the outcomes of patients with prolonged (more than 2 years) DMRs who discontinued treatment. These studies and others have documented that when taken off therapy more than half the patients experience relapse — usually quickly — and the remainder fare well off treatment. Importantly, although most patients experiencing relapse can be effectively salvaged with the same or a different TKI, at this point there is no way to pick who will do well without treatment and therefore neither professor employs this approach outside a trial setting, although Dr Kantarjian notes that if ongoing research shows how to identify these patients, both long-term toxicity and financial costs can be avoided.

Interestingly, Dr Cortes commented on one situation in which a variation of this stopping strategy is often a consideration — specifically, in women with CML who wish to become pregnant — and so far he has managed about 2 dozen carefully selected patients, most of whom have not required retreatment until after childbirth.

Another fascinating and somewhat [related ASH report](#) documented that in a major Phase III trial of dasatinib versus imatinib patients starting treatment who missed doses due to toxicities like cytopenias had significantly worse 3-month outcomes. Importantly, this effect appears to occur when missing even 1 dose (in the case of imatinib) and increases with the number of doses missed.

## **3. What is the current role of ponatinib?**

In December 2012 this pan-BCR-ABL “super TKI” was approved by the FDA, but last October it was pulled off the market due to toxicity concerns, mainly arteriothrombotic events. By December ponatinib was once again available, accompanied by a new black box warning and a Risk Evaluation and Mitigation Strategy program designed to help clinicians more effectively evaluate the risks and benefits of using the agent.

In discussing ponatinib, Dr Kantarjian noted that the approved daily dose of 45 mg not uncommonly leads to toxicities such as hypertension, vasospastic reactions, pancreatitis and skin rashes that are not acceptable in the up-front setting, where safer effective choices exist. In this regard an MD Anderson single-arm [pilot study](#) of 51 patients presented at ASH was amended to include a starting dose of 30 mg daily. Regardless, accrual was suspended in October, as in another major Phase III up-front study comparing ponatinib to imatinib.

However, in discussing the updated ASH results from the pivotal **[PACE trial](#)** in relapsed disease, Dr Kantarjian reiterated that ponatinib, when used in that indicated setting, can be a life-altering therapy, particularly for those with BCR-ABL T315I mutations. He also pointed out that the vaso-occlusive reactions that have been observed with this drug occur infrequently with the other TKIs.

Next on this series, we provide an update on ASH reports in lymphoma, including encouraging data sets on the nonchemotherapy combination of lenalidomide and rituximab, the antibody-drug conjugate brentuximab vedotin and a fascinating paper on crizotinib in ALK-positive lymphoma.

Neil Love, MD

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Miami, Florida

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# **Dose Interruption/Reduction of TKIs in the First 3 Months of CML Treatment**

## **Presentation discussed in this issue**

Apperley JF et al. **Dose interruption/reduction of tyrosine kinase inhibitors in the first 3 months of treatment of CML is associated with inferior early molecular responses and predicts for an increased likelihood of discontinuation of the 1st line agent.** *Proc ASH 2013*; **Abstract 93**.

**Slides from a presentation at ASH 2013 and transcribed comments from recent interviews with Jorge E Cortes, MD (1/24/14) and Hagop M Kantarjian, MD (1/29/14)**

**Dose Interruption/Reduction of Tyrosine Kinase Inhibitors in the First 3 Months of Treatment of CML Is Associated with Inferior Early Molecular Responses and Predicts for an Increased Likelihood of Discontinuation of the 1<sup>st</sup> Line Agent**

**Apperley JF et al.**

*Proc ASH 2013*; Abstract 93.

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## Background

- In chronic myeloid leukemia (CML), rapid reductions in tumor load, defined by  $\leq 65\%$  Philadelphia chromosome negativity and/or BCR-ABL<sup>IS</sup>  $< 10\%$  at 3 months, are associated with an improved probability of complete cytogenetic response (CCyR) and better progression-free survival (PFS) and overall survival (OS).
- However, about 15% to 20% of patients experience cytopenias shortly after starting tyrosine kinase inhibitor (TKI) treatment and receive drug interruptions and/or dose reduction.
- It is unclear whether these early periods of altered treatment should be considered in the interpretation of the results of BCR-ABL<sup>IS</sup>  $< 10\%$  at 3 months.
- **Study objective:** To investigate the effects of therapy interruptions and dose reduction during the first 3 months of therapy on the achievement of BCR-ABL<sup>IS</sup>  $< 10\%$  at 3 months, CCyR rate at 12 months and ability to remain on study.

Apperley JF et al. *Proc ASH* 2013;Abstract 93.

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## Study Methods

- This was a randomized Phase III trial of imatinib (IM) versus dasatinib (DA) for patients with newly diagnosed CML.
- Quantitative real-time PCR (qRT-PCR) results of BCR-ABL<sup>IS</sup> levels at 3 months were available for 585 of 632 patients who completed 3 months of therapy:
  - IM (n = 292)
  - DA (n = 293)
- Patients were divided according to the agent assigned on randomization and the amount missed:
  - Patients who did not miss Tx (IM0, DA0): IM0 (n = 243); DA0 (n = 211)
  - Patients who missed 1-14 days of Tx (IM1-14, DA1-14): IM1-14 (n = 38); DA1-14 (n = 37)
  - Patients who missed  $> 14$  days of Tx (IM $>14$ , DA $>14$ ): IM $>14$  (n = 11); DA $>14$  (n = 45)

Apperley JF et al. *Proc ASH* 2013;Abstract 93.

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## Achievement of BCR-ABL<sup>IS</sup> <10% at 3 Months

Outcome	IM0	IM1-14	IM>14
BCR-ABL <sup>IS</sup> <10%	78.6%	63.2%	63.5%
<i>p</i> -value	0.033		
	DA0	DA1-14	DA>14
BCR-ABL <sup>IS</sup> <10%	93.8%	91.9%	77.8%
<i>p</i> -value	0.001		

- More patients who received DA missed days of dosing (28%) than patients who received IM (17%); *p* = 0.008:
  - Median number of missed days for DA = 16 (range 1-62)
  - Median number of missed days for IM = 12.5 (range 1-42)
- Predictably, the likelihood of a qRT-PCR level of BCR-ABL<sup>IS</sup> <10% at 3 months is higher with DA than with IM, but DA is less well tolerated in the early months.

Apperley JF et al. *Proc ASH* 2013;Abstract 93 (abstract only).

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## Summary of BCR-ABL<sup>IS</sup> <10% Results at 3 Months

- Of patients who received >95% of the standard doses, BCR-ABL<sup>IS</sup> <10% at 3 months occurred in 78.7% (IM) versus 93.8% (DA).
- In contrast, of patients who missed >20% of the prescribed doses, BCR-ABL<sup>IS</sup> <10% at 3 months occurred in 60% (IM) versus 84% (DA).
- Thus, drug interruptions and dose reductions are associated with a reduced probability of achieving BCR-ABL<sup>IS</sup> <10% at 3 months.
  - This effect is not observed among patients missing <14 days of DA.
  - It is less marked for reduced average dosing of DA.
  - These results suggest that the higher potency of DA compensates for dose reduction or a few missed days of therapy.

Apperley JF et al. *Proc ASH* 2013;Abstract 93 (abstract only).

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## BCR-ABL<sup>IS</sup> <1% (MR2) as a Surrogate for CCyR

Outcome	IM0	IM1-14	IM>14
12-month MR2 rate	78%	78%	90%
<i>p</i> -value	0.5		
	DA0	DA1-14	DA>14
12-month MR2 rate	96%	88.6%	79.5%
<i>p</i> -value	0.026		

- 107/632 (17%) of patients had discontinued the study by 12 months, and qRT-PCR results were available for all remaining patients.
- These results confirm the superiority of DA over IM for MR2 and the potential impact of missing early doses of DA.
- However, it is not yet clear whether these results are related to inadequate dosing or whether failure to tolerate the recommended dose is indicative of higher-risk disease.

Apperley JF et al. *Proc ASH* 2013;Abstract 93 (abstract only).

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## Treatment Continuation and Discontinuation Rates

Proportion of patients	IM0/DA0	IM1-14/ DA1-14	IM>14/ DA>14
Able to receive Tx consistently through months 3-12	91%	71%	57%
	IM0	IM1-14	IM>14
Who discontinued Tx	12.5%	38.1%	35.7%
	DA0	DA1-14	DA>14
Who discontinued Tx	4.4%	12.8%	18.8%

- Thus, tolerance of the daily drug in the first 3 months predicts future tolerability and efficacy during the subsequent 9 months and long-term compliance with the first-line therapy.

Apperley JF et al. *Proc ASH* 2013;Abstract 93 (abstract only).

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## BCR-ABL<sup>IS</sup> <0.1% (MR3) Rates with Respect to Average Dosing During the First 3 Months

Treatment	Prescribed dose completed		
	>95%	80%-95%	<80%
<b>IM</b>	50%	52.8%	54.9%
<i>p</i> -value	0.17		
<b>DA</b>	68.1%	59.4%	53.1%
<i>p</i> -value	0.038		

- Because long-term qRT-PCR monitoring was provided for all patients entered into the study irrespective of their continuation in the study, it was possible to study the achievement of MR3 at 12 months in an intention-to-treat analysis with all patients.

Apperley JF et al. *Proc ASH* 2013;Abstract 93 (abstract only).

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## Author Conclusions

- Similar results were obtained using the number of days of missed drug (data not shown), suggesting that early failure to tolerate IM as first-line therapy does not affect subsequent responses because effective alternative therapy is available for the majority of patients.
- In contrast, failure to tolerate DA is associated with a reduced chance of MR3 at 12 months.
- Patients who experience cessation or reduction of either agent in the first 3 months are less likely to achieve BCR-ABL<sup>IS</sup> <10% at 3 months and are more likely to require a change of drug in the longer term.
  - Therefore, these patients require close observation during the first year.

Apperley JF et al. *Proc ASH* 2013;Abstract 93.

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### **Investigator Commentary: Interruption or Reduction of TKIs in the First 3 Months After Diagnosis of CML**

In this study, the investigators examined the important question of treatment continuation during the first 3 months after CML diagnosis and evaluated how this affects the probability of getting the best response at 3 months. They found that patients who undergo any treatment interruption, even for only a day, already have a diminished probability of a good response at 3 months. The more treatment the patient misses, the higher the probability that the patient's disease will progress or undergo transformation.

***Interview with Jorge E Cortes, MD, January 24, 2014***

Different reasons exist for dose interruptions, and each of them probably carries a different implication for long-term prognosis. If the interruption is due to nonmyelosuppressive toxicity, then the dose can be reduced or changed to a different TKI, and I believe the prognosis will be unchanged. Noncompliance and myelosuppression carry a different meaning because you expect these patients in the long run to have a lower incidence of CCyR or major molecular response and probably more adverse events such as transformation.

***Interview with Hagop M Kantarjian, MD, January 29, 2014***