5 Minute JournalClub

POST-ASH Issue 2, 2014

Results of the STIM1 and STIM2 Studies of Imatinib Cessation for Patients in Deep Molecular Response

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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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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

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POST-ASH Issue 2, 2014

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

Jorge E Cortes, MD

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.

Hagop M Kantarjian, 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.

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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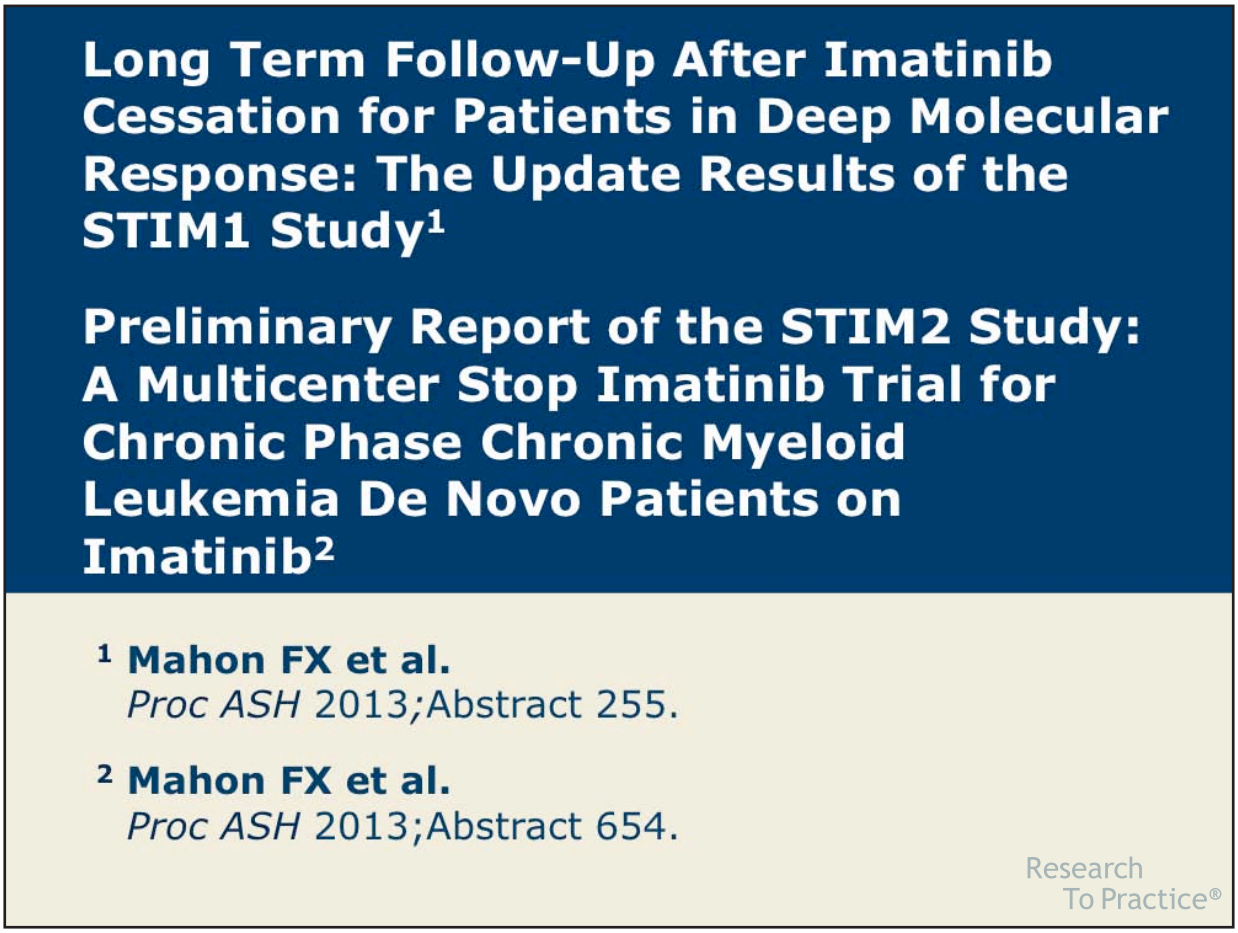
Results of the STIM1 and STIM2 Studies of Imatinib Cessation for Patients in Deep Molecular Response

Presentations discussed in this issue

Mahon FX et al. **Long term follow-up after imatinib cessation for patients in deep molecular response: The update results of the STIM1 study.** *Proc ASH* 2013;**Abstract 255**.

Mahon FX et al. **Preliminary report of the STIM2 study: A multicenter stop imatinib trial for chronic phase chronic myeloid leukemia *de novo* patients on imatinib.** *Proc ASH* 2013;**Abstract 654**.

Slides from presentations at ASH 2013 and transcribed comments from a recent interview with Hagop M Kantarjian, MD (1/29/14)



Long Term Follow-Up After Imatinib Cessation for Patients in Deep Molecular Response: The Update Results of the STIM1 Study

Mahon FX et al.

Proc ASH 2013;Abstract 255.

Background

- Imatinib treatment significantly improves survival in patients with chronic myeloid leukemia (CML) (*J Clin Oncol* 2011;29:2514).
- The STIM study previously demonstrated that imatinib can be safely discontinued in patients with a deep molecular response (DMR), ie, with undetectable minimal residual disease (UMRD) for at least 2 years (*Lancet Oncol* 2010;11:1029).
- Around 40% of patients with CML with stable DMR on imatinib for at least 2 years are likely to remain in a prolonged treatment-free remission after treatment is stopped.
  - This rate was safely confirmed by the recent TWISTER study (*Blood* 2013;122:515).
- **Study objective:** To assess the risk of molecular relapse after imatinib discontinuation after a median follow-up of 50 months.

STIM1 Study Methods

- Eligibility (N = 100):
  - Patients with CML who had discontinued imatinib (>2 years duration)
  - Sustained DMR for at least 2 years
  - Patients who had received immunomodulatory treatment (other than IFN-α), treatment for other malignancies or allogeneic hematopoietic stem cell transplantation were excluded
- Rate of relapse was assessed by quantitative RT-PCR:
  - Molecular relapse was defined as positivity of BCR-ABL transcript levels, confirmed by a second analysis point indicating the increase of 1 log in relation to the first analysis point, at 2 successive assessments or loss of major molecular response at 1 point.

Mahon FX et al. *Proc ASH* 2013;Abstract 255; *Lancet Oncol* 2010;11(11):1029-35.

STIM1 Study Methods (Continued)

- Quantitative RT-PCR analysis using peripheral blood samples was performed every month for the first year, every 2 months for the second year and every 3 months thereafter.
- Beyond 2 years, the treating physician was recommended to reintroduce therapy with a tyrosine kinase inhibitor (TKI) in case of molecular relapse.

Mahon FX et al. *Proc ASH* 2013;Abstract 255; *Lancet Oncol* 2010;11(11):1029-35.

Response After Imatinib Discontinuation and Rechallenge

- Molecular relapse: 61 patients
  - 58 relapses during first 7 months
  - 3 relapses at 19, 20 and 22 months
- Cumulative incidence of molecular relapse: 60%
- All 58 surviving patients were sensitive to TKI rechallenge and underwent re-treatment with
  - Imatinib (n = 48), nilotinib (n = 5), dasatinib (n = 5)
  - 1 patient had to discontinue therapy because of side effects
- Second attempt of TKI discontinuation was proposed for 15 patients in sustained DMR, and 5 cases of molecular relapse were reported at the last update after this second attempt at TKI cessation

Mahon FX et al. *Proc ASH* 2013;Abstract 255 (abstract only).

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Deaths Due to Adverse Events

- Extrahematologic deaths observed (n = 4)
  - 1 case in DMR after 9 months of imatinib cessation
    - Due to myocardial infarction
  - 3 cases in the group of patients with molecular relapse
    - Due to stroke, mesothelioma and gastric carcinoma

Mahon FX et al. *Proc ASH* 2013;Abstract 255 (abstract only).

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Author Conclusions

- Imatinib can be safely discontinued in patients with a DMR of at least 2 years duration.
- Discontinuation should be proposed only in clinical trials with close molecular monitoring.
- Although no other molecular relapses beyond 2 years were observed, a long-term follow-up of the different cessation studies will be necessary to affirm cure.
- Because the life expectancy of patients with de novo CML is now close to that of the healthy population, long-term medical costs and quality of life have become important and depend on the possibility of safely ceasing TKI therapy in the long term.

Mahon FX et al. *Proc ASH* 2013;Abstract 255 (abstract only).

Preliminary Report of the STIM2 Study: A Multicenter Stop Imatinib Trial for Chronic Phase Chronic Myeloid Leukemia De Novo Patients on Imatinib

Mahon FX et al.

Proc ASH 2013;Abstract 654.

Background

- The STIM1 trial previously demonstrated that imatinib could be safely discontinued in patients with a sustained deep molecular response (DMR) (undetectable BCR-ABL transcripts [UMRD] for at least 2 years) (*Lancet Oncol* 2010;11:1029).
- These results were recently confirmed by the TWISTER study using criteria for imatinib cessation similar to those used in the STIM1 study (*Blood* 2013;122:515).
- However, in both of these studies, half of the patients had previously received IFN, leading to a nonhomogenous cohort of patients.
- **Study objective:** To conduct a prospective second trial in which cessation of imatinib treatment was proposed for patients in sustained DMR who had received only imatinib.

Mahon FX et al. *Proc ASH* 2013;Abstract 654.

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STIM2 Study Methods

- Eligibility (N = 124):
  - Same criteria as those reported previously for the STIM1 trial:
    - Patients with CML who had discontinued imatinib (>2 years duration)
    - Sustained DMR for at least 2 years
- Rate of relapse was assessed by quantitative RT-PCR:
  - Same definition of molecular relapse as in the STIM1 trial
- Quantitative RT-PCR analysis using peripheral blood samples was performed every month for the first year, every 2 months for the second year and every 3 months thereafter.

Mahon FX et al. *Proc ASH* 2013;Abstract 654; www.clinicaltrials.gov, accessed February 2014.

Response After Imatinib Discontinuation and Rechallenge

- Molecular relapse: 48 patients
  - 45 relapses during first 6 months
  - 3 relapses between 6 and 12 months
- Patients free of treatment at the last update with DMR (n = 76)
  - 41 experienced a BCR-ABL quantitative RT-PCR fluctuation without clear molecular relapse
  - BCR-ABL reappearance does not automatically mean clinical relapse
- All patients in molecular relapse were sensitive to TKI rechallenge and underwent re-treatment with:
  - Imatinib (n = 33), nilotinib (n = 5), dasatinib (n = 3)
- Median time to achieve a DMR again from the molecular relapse was 7 months (range 4-16 months) and median time from reinitiation of TKI was 4 months (range 2-14)

Mahon FX et al. *Proc ASH* 2013;Abstract 654 (abstract only).

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Author Conclusions

- STIM2 confirms that imatinib can be safely and prospectively discontinued in patients with DMR of at least 2 years duration who received only imatinib.
- The complete eradication of residual leukemic stem cells may not be required to discontinue treatment because positive fluctuation PCR results do not lead to CML relapse or progression.
- These intriguing results, even for patients who received imatinib only since disease onset (already observed after IFN therapy), are comparable to those reported with the more sensitive PCR on DNA in the TWISTER study and are currently under investigation.

Mahon FX et al. *Proc ASH* 2013;Abstract 654 (abstract only).

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Investigator Commentary: Discontinuation of Imatinib Therapy in Patients with CML

These are important studies because everyone is concerned not only about the long-term cost of TKIs but also about the potential long-term toxicities at 5 or 10 years into treatment. STIM1 and STIM2 investigators stopped the TKI in patients who had complete molecular responses for more than 2 years and reported that about 40% to 50% of those patients continue to be in a complete molecular response, suggesting that perhaps these patients may never require TKI therapy in the future.

Although we found in these studies that most of the molecular responses occurred in the first 12 months, I'm concerned that patients might experience a sudden transformation at 8 or 10 years, after we've discontinued therapy and become more relaxed about follow-up. These are important studies, however, in terms of trying to limit the cost and potential long-term side effects of TKIs, but discontinuation should not be routine in everyday practice. These patients should be entered on clinical trials so that they can be monitored over the long run.

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

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