5 Minute JournalClub

POST-ASH Issue 7, 2013

Long-Term Follow-Up of Patients with CML Continuing to Receive Omacetaxine Mepesuccinate in 2 Phase II Trials

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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

- Evaluate the efficacy and safety of bosutinib as second-line therapy for patients with chronic-phase chronic myeloid leukemia (CML-CP), including those whose disease is resistant or intolerant to imatinib.
- Compare and contrast response patterns and long-term clinical impact of treatment with nilotinib, imatinib or dasatinib as first-line therapy for CML-CP.
- Describe updated clinical research data on the activity and tolerability of ponatinib from the pivotal Phase II study in patients with CML or Philadelphia chromosome-positive acute lymphoblastic leukemia or those with BCR-ABL T315I mutations, and consider this information when caring for these patients.
- Assess the evolving role of omacetaxine mepesuccinate for patients with treatment-resistant CML, such as those who are in blast crisis.

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Hagop M Kantarjian, MD
Chairman and Professor, Leukemia Department
The University of Texas MD Anderson Cancer Center
Houston, Texas

Consulting Agreement: Novartis Pharmaceuticals Corporation; Paid Research: ARIAD Pharmaceuticals Inc, Bristol-Myers Squibb Company, Novartis Pharmaceuticals Corporation, Pfizer Inc.

Moshe Talpaz, MD
Alexander J Trotman Professor of Leukemia Research
Associate Director of Translational Research
UM Comprehensive Cancer Center
Associate Chief, Division of Hematology/Oncology
Director, Hematologic Malignancies
University of Michigan Medical Center
Ann Arbor, Michigan

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This activity is supported by educational grants from Celgene Corporation, Genentech BioOncology/Biogen Idec, Millennium: The Takeda Oncology Company, Seattle Genetics and Teva Oncology.

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: May 2013
Expiration date: May 2014

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POST-ASH Issue 7, 2013

CML update: A lot going on, as usual

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

With 3 newly approved agents in the past 8 months, chronic myeloid leukemia (CML) is not only the poster child for targeted cancer treatment but also an enormous potential stumbling block for oncologists. So we took a step back after Atlanta, spent some time chatting with investigators and came up with the following CML highlights reel:

1. Selection of an up-front tyrosine kinase inhibitor (TKI)

Unlike ASH in 2010 and 2011, no practice-changing Phase III up-front trials were reported at the 2012 meeting. However, the topic was still center stage in December during a provocative education symposium where Dr David Marin provided a meticulous review that culminated with an interesting conclusion. In Dr Marin's view, for most patients, imatinib is essentially an equivalent clinical option to the second-generation TKIs nilotinib and dasatinib and may become the preferred choice in 2015 because of a cost advantage when its patent expires. He supported his stance by noting that a survival advantage has yet to be demonstrated with the second-generation TKIs and many patients with suboptimal responses to imatinib can be salvaged with other therapies. Of course, this position stands in sharp contrast to the perspectives of most CML investigators, who fully endorse the up-front use of second-generation agents.

2. Ponatinib and bosutinib

At ASH, Dr Jorge Cortes presented yet another impressive data set on ponatinib, the recently approved (12/2012) pan-BCR-ABL TKI and the only one currently known to be effective in cases with T315I gatekeeper mutations. In further follow-up of the **Phase II PACE trial**, major cytogenetic responses were observed in 51% of 203 patients with chronic-phase CML with resistance or intolerance to dasatinib or nilotinib and 70% of 64 patients with chronic-phase CML and T315I mutations. Overall, with a minimum of 12 months of follow-up, 63% of these heavily pretreated patients remain on study. Ponatinib is currently a critical tool in the care of patients who are intolerant to or have suboptimal or no response on other TKIs, and there is considerable excitement about new Phase III trials evaluating this fascinating agent up front.

Another next-generation TKI story is bosutinib, which was approved in September. In Atlanta, we were treated to an **interesting report** looking at 119 patients with chronic-phase CML treated on the Phase I/II trial who had received 2 or 3 prior TKIs. At 2 years most of these individuals had responded and were still on treatment, which was seen as generally tolerable. **Another ASH data set** from the same study demonstrated similarly encouraging efficacy among 285 patients resistant/intolerant to imatinib. Interestingly, this agent previously failed to deliver better outcomes than imatinib up front in a **Phase III trial**, in part because of tolerability issues, resulting in its current positioning as later-line treatment.

3. Early assessment of response

In his highly informative **ASH CML wrap-up**, Dr Steve O'Brien ranks as the number 1 meeting theme this year "the 10% thing" — referring to the rapid proliferation of papers demonstrating that failure to achieve a PCR BCR-ABL/ABL level of less than 10% at 3 or 6 months puts patients in a group at higher risk of disease progression or developing early resistance.

One of the key ASH papers in this regard evaluated 483 patients who received treatment at MD Anderson with nilotinib, dasatinib or high- or normal-dose imatinib. In this data set, deep cytogenetic and molecular response at 3 and 6 months was **predictive of outcome with all 4 modalities**, and based on these and similar findings in other studies there is now considerable interest in new trials that randomize between continuing or switching therapy in patients with suboptimal early response.

4. Can CML be "cured"?

While most patients nowadays can expect to achieve and maintain clinical remission, lifelong therapy is required. At ASH we saw **more data on treatment discontinuation** in specific situations — usually CMR (defined as >5 log reduction) for 2 or more years after a total of 3 years of treatment. Using these criteria, perhaps 40% of patients receiving imatinib and 60% receiving nilotinib or dasatinib fare well off therapy. The problem is that currently we have no way to identify patients who will or won't experience relapse, and therefore physicians are universally encouraged to consider discontinuation only within the context of a clinical trial.

Related to this issue, perhaps my favorite ASH CML moment came during **Dr Susan Branford's education session presentation** when she showed serial PCR analyses from several patients who received up to 12 years of imatinib. In one case, a 22-year-old man had an undetectable BCR-ABL for 8 years when a major blip appeared on his PCR curve.

Was this some new mutated, resistant clone? In fact, it was discovered that the patient had recently stopped treatment, essentially replicating the classic discontinuation trials like STIM and CML8 in which patients who experienced disease progression off treatment did so fairly quickly. Dr Branford noted that the first question to ask any

patient with a PCR spike is, "Are you taking your medicine?" Careful assessment of side effects and adherence is particularly important in younger patients who may be less accepting of indefinite treatment.

5. Something non-TKI related

In a previous issue of this series we profiled a fascinating Phase III effort out of China evaluating the subcutaneously administered cephalotaxine, omacetaxine mepesuccinate, in patients with AML. Also known as homoharringtonine, this agent — which inhibits protein synthesis via a mechanism independent of BCR-ABL — was approved in October for CML, and at ASH we saw updated data from **2 Phase II studies**. These findings further illustrate the effectiveness of this agent in later-line disease, including among **patients with T315I mutations**.

That does it for this year's ASH highlights series. Stay tuned for our next hem-onc email program, as we explore the therapeutic revolution in myelofibrosis by providing you with the perspectives and practice patterns of 8 investigators with extensive experience with this complex disease.

Neil Love, MD
Research To Practice
Miami, Florida

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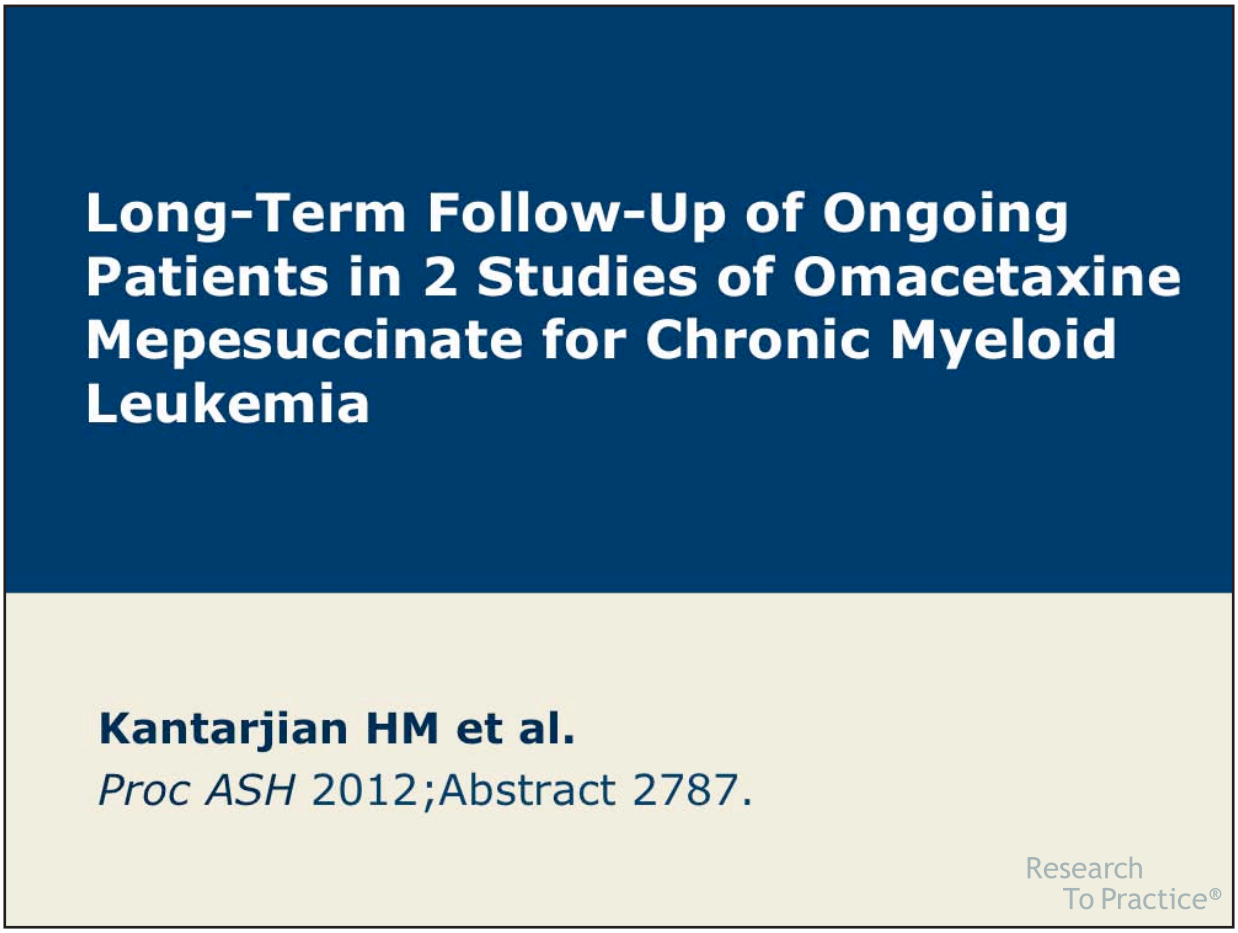
Long-Term Follow-Up of Patients with CML Continuing to Receive Omacetaxine Mepesuccinate in 2 Phase II Trials

Presentation discussed in this issue

Kantarjian HM et al. **Long-term follow-up of ongoing patients in 2 studies of omacetaxine mepesuccinate for chronic myeloid leukemia.** *Proc ASH* 2012;**Abstract 2787**.

Slides from a presentation at ASH 2012 and transcribed comments from a recent interview with Hagop M Kantarjian, MD (2/20/13)



Background

- Omacetaxine mepesuccinate is a semisynthetic, highly purified homoharringtonine compound that recently received approval for the treatment of chronic myeloid leukemia (CML).
- Omacetaxine reduces levels of multiple oncoproteins, including BCR-ABL, and induces apoptosis in leukemic stem cells.
- In 2 separate Phase II trials, it has demonstrated
  - Clinical activity and tolerability in patients with chronic-phase CML (CML-CP) with T315I BCR-ABL mutation (*Blood* 2012;120:2573).
  - Efficacy in patients with resistance or intolerance to ≥2 approved tyrosine kinase inhibitors (*Am J Hematol* 2013;88:350).
- **Study objective:** To report updated efficacy and safety results for patients continuing to receive omacetaxine as of March 2012 in these 2 Phase II studies.

Kantarjian HM et al. *Proc ASH* 2012;Abstract 2787.

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Study Methods

- Patients with CML-CP, accelerated-phase CML (CML-AP) and blast-phase CML (CML-BP) were enrolled in both Phase II trials (n = 203).
- Patients (n = 11) received omacetaxine 1.25 mg/m^2 BID (SC):
  - Induction: Up to 14 consecutive days/cycle (28-day cycles)
  - Maintenance: Up to 7 days/28-day cycle
- Patients with CML-CP (n = 9) and CML-AP (n = 2) continued to receive omacetaxine as of March 2012.
- Primary efficacy measures differed by disease phase:
  - CML-CP: Complete hematologic response (CHR) for ≥8 weeks and major cytogenetic response (MCyR)
  - CML-AP and CML-BP: Major hematologic response or return to CML-CP, lasting for ≥4 weeks

Kantarjian HM et al. *Proc ASH* 2012;Abstract 2787.

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Baseline Characteristics

Characteristic	CML-CP (n = 9)	CML-AP (n = 2)
Median age	61.0 years	57.5 years
Median number of Tx cycles	35	19 and 22
Gender (male)	78%	100%
ECOG PS 0 1	78% 22%	50% 50%
CHR at baseline	66.7%	0%
Mutational status BCR-ABL T3151 Other None	 56% 22% 22%	 0% 50% 50%

Kantarjian HM et al. *Proc ASH* 2012;Abstract 2787.

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Best Responses

Response rate, n (%)	CML-CP (n = 9)	CML-AP (n = 2)
MCyR	7 (77.8%)	0%
CHR at ≥8 weeks	6 (66.7%)	0%
CHR within 3 months of Tx	3 (33.3%)	1 (50%)

- For patients with CML-CP
  - Median time to onset of MCyR was 4.5 months.
  - Median duration of CHR was 24.4 months.
  - Median duration of response was 14.1 months.
- For patients with CML-AP
  - Duration of CHR at <3 months was ongoing at time of analysis (11.4 months).

Kantarjian HM et al. *Proc ASH* 2012;Abstract 2787.

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Select Adverse Events (AEs)

Nonhematologic AEs (all grades)	CML-CP (n = 9)	CML-AP (n = 2)
Upper respiratory infection	55.6%	100%
Nausea	77.8%	Not reported (NR)
Diarrhea	55.6%	NR
Fatigue	55.6%	NR
Headache	44.4%	NR
Peripheral edema	44.4%	NR

- No Grade 3 or 4 nonhematologic AEs reported in ≥2 patients
- Treatment-related blast crisis was reported in 1 patient with CML-AP; treatment was discontinued for this patient
- Grade 3 and 4 laboratory hematologic and nonhematologic AEs were common in early cycles but less frequent as treatment progressed for patients with CML-CP

Kantarjian HM et al. *Proc ASH* 2012;Abstract 2787.

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Author Conclusions

- A subset of heavily pretreated patients with CML-CP or CML-AP who participated in 2 Phase II studies of omacetaxine were able to continue treatment for up to 53 cycles.
- Seven out of 9 patients with CML-CP experienced a durable MCyR, and all 9 patients maintained a CHR.
- One of 2 patients with CML-AP experienced a durable CHR.
- Grade 3 and 4 adverse events were primarily hematologic, and these results were consistent with the known safety profile of omacetaxine.

Kantarjian HM et al. *Proc ASH* 2012;Abstract 2787.

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Investigator Commentary: Long-Term Follow-Up of Patients Continuing to Receive Omacetaxine in 2 Phase II Trials

With omacetaxine we observe quite a bit of clinical activity in patients who have CML refractory to several lines of therapy — major cytogenetic responses in about 20% of patients. Aside from the potential for combining this agent with TKIs, which is currently being explored in a pilot study, I believe omacetaxine may also have a role for elderly patients with acute myeloid leukemia (AML) and as consolidation therapy in younger patients with AML as part of a combination regimen.

I have administered this agent to patients for up to 4 years and have achieved long-term disease control. However, if we stop therapy the disease will relapse. There are no long-term side effects that we know of, and the main toxicity observed is myelosuppression, which can be managed by adjusting the number of days of administration anywhere from 1 to 7 days, depending on the degree of myelosuppression with each course.

Interview with Hagop M Kantarjian, MD, February 20, 2013

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