5 Minute JournalClub

POST-ASH Issue 7, 2013

A Pooled Analysis of Subcutaneous Omacetaxine Mepesuccinate for CML in Blast Crisis

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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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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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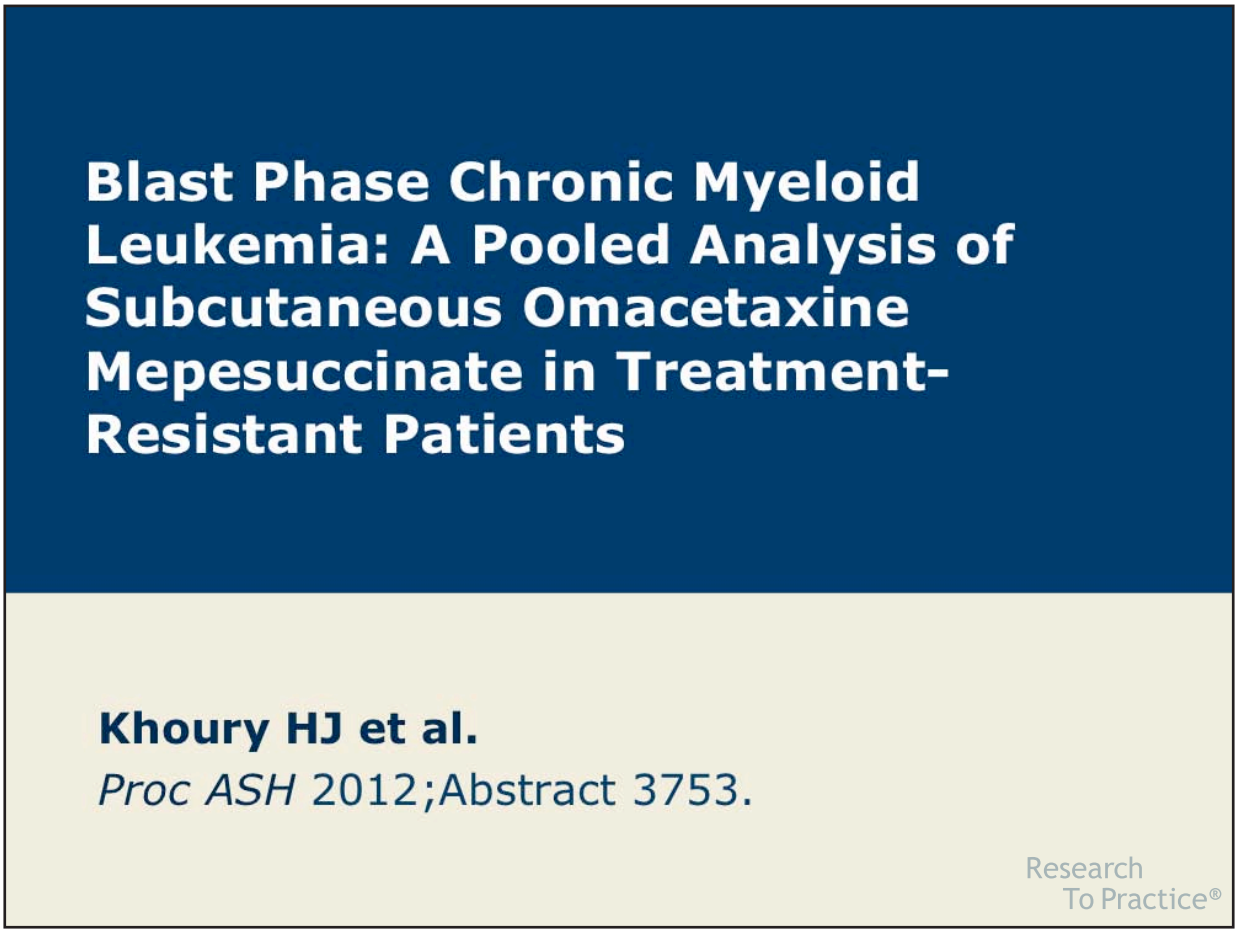
A Pooled Analysis of Subcutaneous Omacetaxine Mepesuccinate for CML in Blast Crisis

Presentation discussed in this issue

Khoury HJ et al. **Blast phase chronic myeloid leukemia: A pooled analysis of subcutaneous omacetaxine mepesuccinate in treatment-resistant patients.** *Proc ASH* 2012;**Abstract 3753**.

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



Background

- Subcutaneous omacetaxine mepesuccinate has demonstrated clinical activity and adequate tolerability in 2 Phase II international multicenter studies for patients with
  - A history of T315I mutations who experienced failure of prior imatinib therapy (*Blood* 2012;120:2573)
  - Resistance or intolerance to ≥2 tyrosine kinase inhibitors (TKIs) (*Am J Hematol* 2013;88:350)
- **Current study objective:** To evaluate the safety and efficacy of omacetaxine for patients with CML in the blast phase (CML-BP) from the 2 Phase II trials through a pooled analysis.

Khoury HJ et al. *Proc ASH* 2012;Abstract 3753.

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Methods (Abstract Only)

- Pooled analysis of patients (N = 44) with CML-BP from 2 Phase II studies
- Patients received omacetaxine 1.25 mg/m^2 subcutaneously twice daily for up to 14 consecutive days every 28 days for induction.
- Patients received the same dosage for up to 7 days every 28 days as maintenance therapy.
- The number of consecutive days of dosing could be adjusted as clinically indicated.
- Primary outcomes:
  - Major hematologic response (MaHR)
  - Major cytogenetic response (MCyR)

Khoury HJ et al. *Proc ASH* 2012;Abstract 3753.

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Prior TKI Therapy and Primary Response Endpoints (Abstract Only)

Number of prior TKIs

1	11%
2	45%
3	43%

Efficacy endpoints	
MaHR	9%
Median duration of MaHR	1.7 months
MCyR	0%
Median OS	3.5 months
Median OS with MaHR	Not yet reached as of >1 year follow-up
Median OS without MaHR	3.5 months
Median PFS	2.2 months

OS = overall survival; PFS = progression-free survival

Khoury HJ et al. *Proc ASH* 2012;Abstract 3753.

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Grade 3 and 4 Adverse Events (Abstract Only)

Grade 3 or 4 adverse events	
Thrombocytopenia	98%
Anemia	82%
Neutropenia	82%
Leukopenia	66%

Two patients discontinued treatment because of AEs.
One treatment-related death (sepsis) was recorded.

Khoury HJ et al. *Proc ASH* 2012;Abstract 3753.

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Author Conclusions

- Among heavily pretreated patients with CML-BP who had experienced failure of prior TKI therapy, omacetaxine demonstrated limited activity:
  - 13% of patients experienced hematologic improvement.
  - 2 patients experienced responses with a duration exceeding 1 year.
- Most Grade 3 and 4 adverse events were hematologic.
- Grade 3 or 4 nonhematologic events were uncommon.

Khoury HJ et al. *Proc ASH* 2012;Abstract 3753.

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Investigator Commentary: Omacetaxine in Patients with Treatment-Resistant CML in Blast Crisis

I was involved in the early studies of omacetaxine in the 1990s, and I have not used it frequently. Omacetaxine can be effective for patients with longstanding disease that is resistant to all our other treatments. I don't view it as being useful in "pushing" for cytogenetic responses. Rather, it can be used to maintain hematologic remission in some patients whose disease is still in the chronic or accelerated phase and is resistant to our other treatments. I don't believe it has much of a role in blast crisis.

Interview with Moshe Talpaz, MD, February 20, 2013

We conducted the pivotal trials in CML that led to the recent FDA approval of omacetaxine. I believe that the role of this agent could be broader than its current indication. I can envision omacetaxine potentially being used with TKIs in the stage of minimal molecular disease to produce durable complete molecular responses — the final step to possibly curing CML and stopping therapy.

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

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