



POST-ASH Issue 3, 2013

**Phase III Trial of
Homoharringtonine-Based
Induction Regimens for
De Novo AML**

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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

- Appraise recent clinical research findings on the long-term efficacy and safety of ruxolitinib for patients with myelofibrosis, and apply this information to clinical practice.
- Evaluate the efficacy and dose-finding studies of ruxolitinib in patients with myelofibrosis who have low platelet counts.
- Compare and contrast the benefits and risks of homoharringtonine-based induction regimens for patients with de novo acute myeloid leukemia.
- Evaluate the efficacy and safety of quizartinib for patients with FLT3-ITD-positive or negative acute myeloid leukemia.

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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:

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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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: March 2013

Expiration date: March 2014

Does the JAK1/2 inhibitor ruxolitinib benefit patients with myelofibrosis without JAK2 mutations?...and more

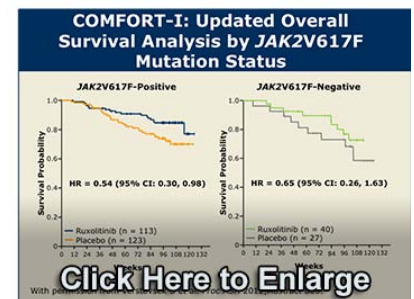
To go directly to slides and commentary for this issue, [click here](#).

Medical oncologists love to see clinical trial results that are so impressive that the effectiveness of a therapy can be immediately understood simply by viewing a single graphic. Because of this, the relatively recent innovation of waterfall plots — especially those in which the majority of the bars point down — has increasingly been used to provide poignant and memorable snapshots of antitumor efficacy.

In this regard, a unique series of waterfall plots presented at the June 2011 ASCO meeting caused an immediate stir and are still being talked about today. These startling graphics did not plot tumor size but disease-related symptoms and spleen size in the seminal Phase III COMFORT-I and II trials evaluating the JAK1/2 small molecule inhibitor ruxolitinib (Rux) in patients with myelofibrosis (MF). In addition to the rapid and profound impact in the treated group, another fascinating aspect of the waterfall plots was what was going on in the control patients, and there the bars were moving north fast, suggesting that these trials were intervening in patients who were very ill and getting worse quickly. These data paved the way for the almost immediate FDA approval of this agent for patients with intermediate-2 and high-risk MF.

In Atlanta we saw an additional year of follow-up from these studies, including my favorite graphic from the entire ASH meeting (see below), showing side by side the survival benefit seen in COMFORT-I for patients with and without JAK2 mutations.

There is considerable debate about the mechanisms that produce the often-profound symptomatic benefit with Rux, and some have postulated it's related to the suppression of release of cytokines implicated in the pathogenesis of MF clinical progression. Regardless, the clear practical message is that this is not BRAF-positive melanoma or EML4-ALK-positive non-small cell lung cancer and symptomatic patients with MF should be considered for therapy with Rux regardless of JAK2 mutation status.



In this issue of our post-ASH series we review the COMFORT updates and two related MF papers along with data sets in acute myelogenous leukemia (AML), where several intriguing agents are showing promising results.

1. COMFORT trial updates

Perhaps the MF investigators chose the COMFORT trial acronym to symbolize the profound palliative effect of Rux that had been observed even in early Phase I-II studies. **The initial published** Phase III data were derived with a median of about a year of follow-up, and now that another year has passed the results keep getting better. Perhaps the most important and “comforting” message is that most patients have maintained responses and are continuing to enjoy significant symptom palliation. In addition, an important effect on overall survival has been demonstrated in both trials in spite of the fact that crossover after progression on the control arm was allowed and occurred in more than two thirds of patients. The two ASH COMFORT updates are loaded with practical clinical information, which is summarized in the attached slide set, and it’s clear that this disease has entered a new era.

2. Use of Rux in patients with platelet counts (PC) of 50,000-100,000

MF can be associated with decreased PC through a variety of mechanisms, and Rux itself causes reversible declines in PC and hemoglobin levels, although these are rarely treatment limiting. The COMFORT trials required a minimum PC of 100,000, but the lack of an effective palliative alternative pushed investigators to determine if this agent could be safely and beneficially used in patients falling below this threshold. Two separate ASH papers evaluated a cautious stepwise approach in patients with PC between 50,000 and 100,000. In **the North American trial** led by Dr Moshe Talpaz patients started at 5 mg BID and escalated up, usually targeting a 10-mg BID dose. Interestingly, although patients in the COMFORT trials received 15 or 20 mg BID, those treated in these two new studies at reduced doses seemed to experience similar treatment benefit.

Unfortunately, there are currently no data to guide management of patients with PC under 50,000, and as such this situation probably warrants consideration of referral to a tertiary center, where many studies are being conducted with a plethora of promising agents in MF.

3. AML update: Homoharringtonine (HHT, otherwise known as omacetaxine)

On one of our upcoming audio programs Dr Hagop Kantarjian spins a fascinating tale of herbal drug development in China under Mao Zedong, and one of the positive outcomes (in addition to ATRA and arsenic) was this plant alkaloid that has significant activity in AML (and was recently approved in CML). In a prominent ASH report of a Phase III AML trial done in China, cytarabine (C) and an anthracycline (A) combined with HHT

resulted in more CRs and better survival but also more deaths during induction than CA alone. These findings have led to both optimism and caution as this fascinating agent is further developed.

4. More on AML: Quizartinib, a potent FLT3 receptor inhibitor

FMS-like tyrosine kinase 3 (FLT3) internal tandem duplications can be found in up to a third of patients with AML and are associated with high blast counts, increased rates of relapse and reduced survival. In an effort to potentially exploit this target, quizartinib was evaluated in a Phase II trial with 2 cohorts reported separately at ASH and revealed impressive responses in patients both without and, more commonly, with FLT3 mutations, and the drug, which was well tolerated other than prolonged QT intervals, stabilized a number of patients, enabling transplant. Enthusiasm from these findings has led to Phase III trials in FLT3-mutant AML, including efforts to combine quizartinib with the classic 3 + 7 regimen up front.

Next on this ASH highlights series we consider Hodgkin and T-cell lymphoma, where more good news on the CD30 antibody-drug conjugate brentuximab vedotin was unveiled in Atlanta.

Neil Love, MD

Research To Practice

Miami, Florida

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Phase III Trial of Homoharringtonine-Based Induction Regimens for De Novo AML

Presentation discussed in this issue

Jin J et al. **Homoharringtonine-based induction regimens for patients with de novo acute myeloid leukemia: A multicenter randomized controlled Phase 3 trial.** *Proc ASH 2012*; **Abstract 45**.

Slides from a presentation at ASH 2012 and transcribed comments from a recent interview with Moshe Talpaz, MD (2/19/13)

Homoharringtonine-Based Induction Regimens for Patients with De Novo Acute Myeloid Leukemia: A Multicenter Randomized Controlled Phase 3 Trial

Jin J et al.

Proc ASH 2012; Abstract 45.

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Background

- Homoharringtonine is a plant alkaloid that inhibits protein synthesis and has considerable activity in patients with acute myeloid leukemia (AML).
- Homoharringtonine-based induction regimens have been widely used in China for patients with AML and have been shown to improve the rate of complete remission (CR) and overall survival (*Leukemia* 2006;20:1361).
- **Study objective:** To further evaluate the efficacy and safety of homoharringtonine-based induction regimens for patients with de novo AML.

Jin J et al. *Proc ASH* 2012;Abstract 45.

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Phase III Study Methods

- This Phase III study evaluated patients between the ages of 14 and 59 with untreated AML in 17 institutions in China.
- Patients were randomly assigned to receive as induction:
 - HAA (homoharringtonine/cytarabine/aclarubicin)
 - HAD (homoharringtonine/cytarabine/daunorubicin)
 - DA (daunorubicin/cytarabine)
- Patients who achieved partial remission or had a decrease of blast >60% could receive a second induction course of the same regimen.
- All patients who achieved a complete remission (CR) were offered the same regimen as consolidation chemotherapy according to cytogenetic risk.
- **Primary endpoints:**
 - CR and event-free survival (EFS)

Jin J et al. *Proc ASH* 2012;Abstract 45.

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Complete Remission Rate with First Course of Induction Therapy (Abstract Only)

Induction regimen	Complete remission rate
HAA	67.5%
HAD	64.9%
DA	54.0%
HAA vs DA, $p = 0.005$; HAD vs DA, $p = 0.026$	

- The overall CR rate remained significantly higher in the HAA arm than in the DA arm (75.0% vs 61.9%, $p = 0.005$).

Jin J et al. *Proc ASH 2012*;Abstract 45.

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Median EFS for All Patients (Abstract Only)

Induction regimen	n	Events	Censored	Median EFS
HAA	206	127	79	11.7 mo
HAD	198	130	68	8.6 mo
DA	205	154	51	6.9 mo

- Three-year EFS was greatly improved in the HAA arm versus the DA arm ($35.4 \pm 3.5\%$ vs $23.1 \pm 3.1\%$, $p = 0.002$).
- Three-year EFS was not significantly improved in the HAD arm versus the DA arm ($32.7 \pm 3.5\%$ vs $23.1 \pm 3.1\%$, $p = 0.078$).
- Patients in the HAD arm with NPM1 but not FLT3 ITD mutations had an improved EFS versus those in the DA arm ($p = 0.038$).

Jin J et al. *Proc ASH 2012*;Abstract 45.

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Median Overall Survival (OS) for Patients with Favorable or Intermediate Cytogenetic Profiles (Abstract Only)

Induction regimen	n	Deaths	Censored	Median OS
HAA	149	66	83	Not reached
HAD	139	73	66	20.6 mo
DA	147	88	59	18.4 mo

HAA vs DA, $p = 0.014$; HAD vs DA, $p =$ not significant

- In patients with favorable or intermediate cytogenetic profiles, an OS advantage of the HAA arm over the DA arm was observed.
- In the overall patient population, OS did not differ significantly in the HAA or HAD arms versus the DA arm.

Jin J et al. *Proc ASH 2012*;Abstract 45.

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Median Relapse-Free Survival (RFS) for Patients with Favorable or Intermediate Cytogenetic Profiles (Abstract Only)

Induction regimen	n	Relapse/ deaths	Censored	Median RFS
HAA	119	50	69	Not reached
HAD	94	48	46	17.8 mo
DA	93	55	38	15.9 mo

HAA vs DA, $p = 0.022$; HAD vs DA, $p =$ not significant

- In patients with favorable or intermediate cytogenetic profiles, an RFS advantage of the HAA arm over the DA arm was observed.
- Patients with intermediate cytogenetic profile and mutant CEBPA had prolonged RFS in the HAA arm versus the DA arm ($p = 0.045$).
- In the overall population, RFS did not differ significantly in the HAA or HAD arms versus the DA arm.

Jin J et al. *Proc ASH 2012*;Abstract 45.

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Adverse Events (Abstract Only)

- The HAA and HAD regimens had similar rates of adverse events as compared to the DA regimen.
- **Significant increase in risk of induction death:**
 - HAA vs DA (5.8% vs 1.0%, $p = 0.007$)
 - HAD vs DA (6.6% vs 1.0%, $p = 0.003$)

Jin J et al. *Proc ASH 2012*;Abstract 45.

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Author Conclusions

- Homoharringtonine-based induction regimens are associated with higher rates of complete remission and improved survival compared to the DA regimen for patients with de novo AML and favorable or intermediate cytogenetic profiles.
- Toxicities were mild with the exception of a higher rate of induction death:
 - HAA versus DA (5.8% vs 1.0%, $p = 0.007$)
 - HAD versus DA (6.6% vs 1.0%, $p = 0.003$)

Jin J et al. *Proc ASH 2012*;Abstract 45.

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Investigator Commentary: A Phase III Trial of Homoharringtonine-Based Induction Regimens for Patients with De Novo Acute Myeloid Leukemia

Homoharringtonine (HHT) is an old drug, also known as omacetaxine. It was recently approved as a treatment for chronic myeloid leukemia. This intriguing study included a large number of patients treated in 3 different arms. The induction included an anthracycline/cytarabine with or without HHT. The 2 arms including HHT demonstrated about a 10% better response rate with an improved survival advantage compared to the arm without HHT. However, there was a higher risk of death among the patients who received HHT. Further analysis of prognostic features showed that patients with AML harboring NPM1 mutations or CEBPA mutations, who are considered to be at low risk, tend to respond better to combination therapy including HHT. The difference was more pronounced in this particular group.

Although I am unable to attest to how carefully this study was conducted, these data need to be verified and should not be ignored. HHT is a protein synthesis inhibitor, and perhaps because its mechanism of action is different from anthracyclines and nucleoside analogs, it is synergistic with those drugs.

Interview with Moshe Talpaz, MD, February 19, 2013

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