Real-World Assessment of Clinical Outcomes in Patients with Lower-Risk Myelofibrosis Receiving Ruxolitinib Therapy
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 up-front and salvage therapeutic options and modalities for the evaluation of treatment response in newly diagnosed and relapsed or refractory chronic myeloid leukemia (CML), myelofibrosis (MF), polycythemia vera (PV) and essential thrombocythemia (ET) 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

• Assess the recent results of the RESPONSE trial evaluating ruxolitinib for PV, and consider this information for the treatment of this disease in patients who are not responsive to or are intolerant of hydroxyurea.

• Appraise the effectiveness and tolerability of the investigational agents PRM-151 and imetelstat as single-agent therapy for patients with MF.

• Examine long-term efficacy and symptomatology results with ruxolitinib in patients with ET who are refractory to or intolerant of hydroxyurea.

• Compare and contrast the benefits and risks of discontinuing second-generation tyrosine kinase inhibitors for patients with CML in chronic phase.

• Analyze efficacy and safety results from Phase III trials evaluating dasatinib or ponatinib in comparison to imatinib for patients with CML in chronic phase.

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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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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

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

Many physicians (myself included) remember the day they first treated a patient with pulmonary edema from congestive heart failure and the exhilarating feeling of instantly relieving this profound symptomatology with the classic use of an intravenous diuretic and morphine. Medical oncology also provides many opportunities for these types of healing moments, and at the 2011 ASCO meeting the field was introduced to another powerful palliative tool for a disease desperately in need of one. Since the presentation of the aptly named COMFORT-I and II trials in Chicago, we have heard on many of our CME programs a myriad of moving patient case histories of individuals with myelofibrosis (MF) suffering from anorexia, weight loss, fatigue and massive uncomfortable spleens who experienced dramatic, life-altering changes within days or weeks of starting treatment with the JAK1/2 inhibitor ruxolitinib (rux).

Perhaps not surprisingly, the myeloproliferative neoplasm (MPN) issue of our ASH highlight series focuses in large part on this fascinating therapy, which now is showing its colors in other diseases, including, interestingly enough, pancreatic cancer. We also provide an update on papers related to the other major part of MPNs, chronic myeloid leukemia (CML), and as such I met with one of the research giants in the field, Dr Jorge Cortes, who provides his take on the most important findings.

1. Rux in patients with lower-risk MF

The Phase III COMFORT trials focused on patients with intermediate-2 or high-risk MF, but there is no intuitive reason to believe that the palliative effects of this agent would not be similar in other symptomatic patients. At ASH we saw a “real-world” retrospective analysis evaluating 108 cases of patients with low- or intermediate-1-risk MF treated by 49 US-based hematologist-oncologists mainly due to symptomatology. Perhaps not surprisingly, marked improvement in spleen size and the severity of
2. Rux in polycythemia vera (PV) and essential thrombocythemia (ET)

Perhaps the biggest MPN story at ASH was the presentation of more data from the landmark **Phase III RESPONSE trial** (originally presented last year at ASCO) demonstrating the clinical benefit of rux (10 mg BID) in patients with PV who were either intolerant of or experienced disease progression on hydroxyurea (HU). The initial data set was published in the *New England Journal* in January and revealed significant reductions in hematocrit, splenomegaly and severity of symptoms in patients randomly assigned to rux. Equally relevant, treatment was well tolerated — most patients had stable platelet counts, and secondary drops in hemoglobin were beneficial. Similar clinical improvements were observed in patients who crossed over to rux. Most importantly, as seen with the additional ASH data, patients who received rux experienced a dramatic positive impact on quality of life.

Based on the strength of these results, the FDA made rux the first drug ever approved for PV. In this regard, Dr Cortes has used the agent in patients who meet the criteria for the RESPONSE trial. However, he also believes that the definition of disease progression with PV should be expanded to include individuals with persistent symptomatology who, although not meeting the current criteria for disease progression, often experience dramatic improvements in symptoms with rux.

Several other data sets were unveiled in San Francisco that further support the concept of using rux in PV, including data from the **Phase III RELIEF trial** for patients with PV considered stable on HU but with some persistent symptoms, which demonstrated an improvement in symptoms by switching to rux rather than continuing on HU.

Finally, a Phase II study of rux in 39 patients with ET refractory to or intolerant of HU demonstrated rapid decreases in and normalization of platelet and white blood cell
counts. Hemoglobin levels initially decreased and then stabilized in most patients, and a marked improvement in symptomatology was also observed. As such, Dr Cortes and other investigators believe rux is rational to use in this patient population and are hopeful that this agent will also receive approval in ET for disease palliation.

3. New agents in MF: antifibrotics, telomerase inhibitors

Although much recent MF research has focused on JAK inhibitors, a number of other novel strategies are also being explored in this disease. In this regard, at ASH we saw an early but encouraging report of 27 patients receiving PRM-151, a recombinant form of an endogenous protein that is found at sites of inflammation and prevents fibrosis by inducing macrophage differentiation. What was most noteworthy from this study was that not only was the amount of fibrosis decreased in close to half of the patients, but hemoglobin and platelet counts also often improved along with signs and symptoms of the disease. Research on this and other similar agents is proceeding rapidly, and Dr Cortes is particularly interested in trials combining PRM-151 with rux.

Telomerase is known to become more active in MF as the disease progresses, and in a report of 33 patients receiving imetelstat — a novel agent that targets the RNA template of human telomerase reverse transcriptase — 7 patients (21%) experienced a complete or partial remission. Treatment was well tolerated, although myelosuppression was observed. Dr Cortes is intrigued by these data and also the early correlation of response with specific disease mutations.

4. Second-generation tyrosine kinase inhibitors (TKIs) in CML

With the likely availability of generic imatinib in the next year as a potentially less costly alternative, the value of nilotinib and dasatinib will be increasingly discussed and debated, and several new ASH data sets will likely be referred to as part of these conversations. Specifically, in San Francisco we saw the first presentation of data from the large Phase III SPIRIT 2 trial, which, like several other prior studies, compared dasatinib to imatinib in patients with newly diagnosed CML. Although the data are not yet fully mature, this study confirms what we have known from other trials, namely that treatment with second-generation TKIs results in improved rates of complete cytogenetic response, faster rates of molecular response and fewer transformations.

It wouldn’t be ASH if we weren’t treated to an update from the landmark DASISION trial, and in addition to continuing to show excellent long-term disease outcomes, this study yielded some interesting data on toxicity over time, specifically the most common complication of dasatinib, pleural effusions, which were observed in 20% of patients, causing discontinuation of treatment in 6%. In discussing this work, Dr Cortes pointed out that multiple studies have suggested that patients experiencing a pleural effusion on dasatinib might have better disease-related outcomes, although the biologic explanation remains to be defined.

None of the second-generation TKI CML papers presented in San Francisco was able to dispel the lack of progression-free or overall survival benefit to this point, and some
investigators prefer imatinib in lower-risk scenarios. Dr Cortes, however, believes that there is an important advantage for the newer agents but that salvage treatment for imatinib failure is delaying the detection of this benefit.

5. **Current bottom line with ponatinib in CML**

As you may remember, the [Phase III EPIC study](#) comparing ponatinib to imatinib was stopped in October 2013 because of the increased risk of cardiovascular events. As a result of this toxicity, access to ponatinib is currently restricted to patients with TKI-resistant disease or those with the T315I mutation. However, the updated data from this trial tell us that the agent is associated with faster, deeper and higher rates of response than imatinib and, by way of indirect comparison, perhaps also dasatinib and nilotinib.

In this regard, there is a strong belief among investigators that there is a direct relationship between dose and cardiovascular events, and for that reason ongoing studies are attempting to define a reduced dose that will produce equal efficacy with fewer complications.

6. **In what situations, if any, is it safe to stop a TKI in CML?**

A number of prospective trials (STIM, TWISTER and EURO SKI, which was presented at ASH) suggest that imatinib may be successfully discontinued for patients with deep and sustained molecular responses, and in San Francisco we saw evidence that the same may apply to second-generation TKIs. Specifically, the [STOP 2G-TKI study](#) evaluated treatment discontinuation in 52 patients in sustained complete molecular response receiving dasatinib or nilotinib for a median of 39 months, mostly after initial imatinib therapy.

At 24 months, the probability that patients remained in major molecular response off treatment was 57%. The relapses that did occur were mainly in the first 6 months after treatment discontinuation, but those patients responded to reinstitution of second-generation therapy. Importantly, patients receiving treatment because of prior resistance to imatinib were less likely to be able to stay off treatment. Despite this mounting body of data, like most CML investigators, Dr Cortes, although interested in seeing more research on this strategy, believes that for now TKI treatment should only be stopped as part of a clinical trial and with close monitoring.

Medical oncologists are hearing a lot nowadays about “value” in cancer care, which is roughly defined as the clinical benefits (and toxicities/complications) of a therapy relative to its financial cost, and there has been a lot of discussion about the importance of incorporating the perspectives of patients themselves in the value equation.

In this regard, it would be interesting to learn more from individuals who have actually experienced the clinical outcomes of therapy for MPNs about their perceptions of the value of treatment — particularly about what it means to face a disease that was
uniformly lethal in the past and to now live a normal lifespan (CML) or to experience progressive and devastating disease-related symptoms and suddenly feel well again (MF, PV, ET).

Next on this series we review ASH papers on acute leukemias and MDS and the surprising plenary presentation on the use of sorafenib in AML.

Neil Love, MD

Research To Practice

Miami, Florida
Real-World Assessment of Clinical Outcomes in Patients with Lower-Risk Myelofibrosis Receiving Ruxolitinib Therapy

Presentation discussed in this issue


Slides from a presentation at ASH 2014 and transcribed comments from a recent interview with Jorge E Cortes, MD (1/14/15)
Background

- The Phase III COMFORT-I trial demonstrated that ruxolitinib (RUX) improves both splenomegaly- and nonsplenomegaly-related constitutional symptoms in patients with intermediate-2 and high-risk myelofibrosis (MF) (*NEJM* 2012;366:799).

- However, few trial-based assessments of RUX for patients with lower-risk MF have been conducted, and no studies to date have made such assessments in real-world populations.

- **Study objective:** To assess changes in spleen size and constitutional symptoms during RUX treatment among patients with lower-risk MF in real-world clinical settings.

Davis KL et al. *Proc ASH* 2014;Abstract 1857.

Study Methods

- A retrospective, observational review of anonymized medical record data collected in January 2014 by 49 hematologists and oncologists in the United States.

- The study was exploratory, with the use of descriptive analyses only.

- Minimum target accrual:
  - Patients with intermediate-1-risk MF (n = 50)
  - Patients with low-risk MF (n = 25)

- Predetermined maximum number of patients on study (n = 110).

- Spleen size and constitutional symptoms were retrospectively observed at MF diagnosis, at RUX initiation and at best response while on RUX.

Davis KL et al. *Proc ASH* 2014;Abstract 1857 (Abstract only).
Study Methods (continued)

- Spleen size was captured via predefined categories:
  - No splenomegaly (spleen not palpable)
  - Very mild or mild splenomegaly (<10 cm palpated)
  - Moderate splenomegaly (10-20 cm palpated)
  - Severe splenomegaly (>20 cm palpated)
- Symptoms of interest included those captured in the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF), based on medical notes recorded at each time point and categorized as:
  - Mild,
  - Moderate, or
  - Severe
- Findings on the 7 most commonly observed MPN-SAF symptoms are presented in this study.

Davis KL et al. Proc ASH 2014;Abstract 1857 (Abstract only).

Eligibility Criteria

- Patients diagnosed with lower-risk MF
- International Prognostic Scoring System score of 0-1
- First treatment with RUX ≥3 months before the medical record abstraction date
- Age ≥18 years at RUX initiation
- Patients with a complete medical history from MF diagnosis until the medical record abstraction date
- Patients who never enrolled in an MF-related interventional trial

Davis KL et al. Proc ASH 2014;Abstract 1857 (Abstract only).
Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Low risk (n = 25)</th>
<th>Intermediate-1 risk (n = 83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤65 years of age</td>
<td>100%</td>
<td>~80%</td>
</tr>
<tr>
<td>Male</td>
<td>60%</td>
<td>69%</td>
</tr>
<tr>
<td>JAK2 V617F-mutant MF</td>
<td>56%</td>
<td>72%</td>
</tr>
<tr>
<td>Patients still receiving RUX at MRAD</td>
<td>92%</td>
<td>77%</td>
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</table>

MRAD = medical record abstraction date

- RUX start dates spanned from January 2012 to November 2013.
- The median observed RUX exposure time was approximately 8 months in both risk groups.


Spleen Size Measurements

- Patients with low-risk MF
  - The combined proportion of patients with moderate or severe splenomegaly (≥10-cm palpated spleen) decreased from 64% at MF diagnosis to 16% at best response during RUX treatment.
- Patients with intermediate-1-risk MF
  - Similar findings were observed: The proportion of patients with moderate or severe splenomegaly decreased from 53% at MF diagnosis to 10% at best response.

Constitutional Symptoms of Interest During RUX Treatment

- General fatigue was the most commonly observed constitutional symptom in both groups of patients (low-risk and intermediate-1-risk MF).
- Shifts in symptom severity from more severe to less severe were observed in both groups of patients.
- Among patients with low-risk MF, the proportion with moderate or severe fatigue decreased from 90% at MF diagnosis to 37% at best RUX response.
- Among patients with intermediate-1-risk MF, the decrease was from 76% at MF diagnosis to 42% at best response.
- For most other symptoms, similar improvements in severity distribution were observed.

Davis KL et al. *Proc ASH 2014;Abstract 1857 (Abstract only).*

Author Conclusions

- Patients with low-risk and those with intermediate-1-risk MF experienced a substantial decrease in spleen size from MF diagnosis through RUX treatment in real-world clinical settings.
- Furthermore, for most symptoms examined, there was a distinct improvement in the distribution of symptom severity at the time of best response during RUX treatment.
- These findings suggest that patients with lower-risk MF may benefit clinically from RUX treatment.
- Further studies are needed to assess adverse effects and evaluate the benefit-risk tradeoff of RUX therapy.

Davis KL et al. *Proc ASH 2014;Abstract 1857 (Abstract only).*
Investigator Commentary: Evaluation of Clinical Outcomes in Low-Risk and Intermediate-1-Risk MF Treated with RUX

This is an interesting study because it addresses 2 important questions. First, whether a clinical trial really reflects what you would expect in general practice because many features change when you take them to a broader audience, such as the selection of patients and expertise in managing the therapeutic agent. Second, it focuses on patients with low-risk and intermediate-1-risk MF, whereas much experience has been generated in the higher-risk patient population. All patients had received RUX because they had symptoms of MF such as splenomegaly. The study essentially demonstrated that RUX can produce a significant reduction in spleen size.

The percentage of patients in the moderate to severe splenomegaly category was reduced significantly from 64% at diagnosis to 16% with RUX. Similar findings were observed in the low-risk and intermediate-1-risk groups. Evaluation showed benefit with RUX for many general symptoms. Fatigue decreased from 90% to 37% of patients with low-risk MF. Clearly patients with indications for treatment benefit from RUX in general and community practice, even those with low-risk MF. My clinical experience aligns with the benefits shown in this study, even though RUX is indicated only for patients with intermediate- and high-risk disease.

*Interview with Jorge E Cortes, MD, January 14, 2015*