

ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

Section Editor: Susan O'Brien, MD

Ruxolitinib: The First Agent Approved for Myelofibrosis

Srdan Verstovsek, MD, PhD
Associate Professor
Department of Leukemia
Division of Cancer Medicine
The University of Texas
M.D. Anderson Cancer Center
Houston, Texas

H&O What is myelofibrosis (MF), and what is the typical prognosis?

SV MF is a Philadelphia chromosome-negative myeloproliferative neoplasm (MPN) characterized by progressive bone marrow fibrosis, splenomegaly, and cytopenias. In addition, patients may experience debilitating symptoms, including fatigue, early satiety, weight loss, night sweats, fever, and pruritus that contribute to a diminished quality of life. MF is a hematologic malignancy that can occur *de novo* (primary myelofibrosis [PMF]) or after progression from the other MPNs, polycythemia vera (PV), or essential thrombocythemia (ET). On average, the survival of MF patients is 5–7 years, but it is very variable and dependent upon the presence of defined risk factors that comprise various prognostic scoring systems. For example, for MF patients with intermediate-2 and high-risk disease as categorized by the International Prognostic Scoring System (IPSS), the estimated median survival is 4 years and 2 years, respectively. Patients with low-risk disease have an average survival of 11 years.

H&O What are the treatment options for MF?

SV Previously, there were limited therapeutic options for the treatment of patients with MF. Therapies used to treat anemia include erythropoiesis-stimulation agents, steroids, and immunomodulators (such as lenalidomide [Revlimid, Celgene]). Hydroxyurea may be used to reduce splenomegaly, but responses are not durable. Splenectomy or splenic

irradiation may be considered; however, the surgical mortality peri- and post-splenectomy and the morbidity rates for either procedure are not insignificant. Allogeneic stem cell transplantation is the only curative treatment, but it is associated with significant mortality and may not be a suitable option for most patients, given the advanced patient age and multiple comorbidities associated with MF.

The Janus kinases (JAKs) play a critical role in mediating signals from extracellular cytokines and growth factors that are essential for normal hematopoiesis, inflammation, and immune response. In the recent past, the discovery of JAK2 and many other genetic mutations that lead directly or indirectly to dysregulated JAK-STAT intracellular signaling has provided significant insight into the pathophysiology of MPNs. The *JAK2V617F* mutation, initially described in about 50% of patients with MF, is the only one of many mutations now known to contribute to the pathophysiology of MPNs; it is not a causative mutation for MPN. Indeed, recent evidence strongly suggests that all patients with MPN may have a dysregulated, hyperactive, JAK-STAT pathway as the underlying pathophysiologic abnormality, regardless of the presence/absence of a known mutation. As a result, this has stimulated the development and investigation of small-molecule inhibitors of the JAK pathway (ie, JAK2 and JAK1/JAK2 inhibitors) as a novel therapeutic option for patients with MPNs. This is exemplified by the recent approval from the US Food and Drug Administration (FDA) of ruxolitinib (Jakafi, Incyte) for the treatment of patients with intermediate- and high-risk MF.

H&O What is ruxolitinib, and what is its mechanism of action?

SV Ruxolitinib is a small molecule dual JAK1/JAK2 inhibitor. By inhibiting both JAK1 and JAK2, 2 tyrosine kinases associated intracellularly with a variety of receptors for cytokines and growth factors, ruxolitinib may prevent the recruitment of signal transducers and activators of transcription (STATs) to cytokine receptors and their subsequent activation and localization to the nucleus. In the nucleus, STATs are involved in the transcriptional modulation of select gene groups that underlie the pathophysiologic manifestations of MPNs. This JAK-STAT intracellular pathway is dysregulated and hyperactive in patients with MPN. By inhibiting JAK1 and JAK2, ruxolitinib controls the activity of the JAK-STAT pathway and affects the disease processes in a positive way. Importantly, ruxolitinib is not specific for *JAK2V617F* mutation, and therefore has a potential to benefit all patients due to their underlying hyperactive JAK-STAT pathway.

H&O Can you discuss the design of your recent study presented at the 2011 American Society of Hematology (ASH) meeting?

SV The COMFORT-I (Controlled Myelofibrosis Study With Oral JAK Inhibitor Treatment-I) study was a randomized, double-blind, placebo-controlled phase III trial that evaluated the efficacy and safety of ruxolitinib in patients with PMF, post-PV MF, or post-ET MF. IPSS intermediate-2 and high-risk patients were enrolled from 89 centers in the United States, Canada, and Australia. Patients were randomized to receive ruxolitinib (15 or 20 mg orally twice daily) or placebo for 24 weeks. The starting dose of ruxolitinib depended on baseline platelet counts (15 mg: 100–200 × 10⁹/μL; 20 mg: >200 × 10⁹/μL). The study protocol mandated interruption of study treatment if platelet counts fell below 50,000/μL or if the absolute neutrophil count fell below 500/μL. The primary endpoint was the proportion of patients who achieved at least a 35% reduction in spleen volume, as measured by magnetic resonance imaging (MRI) or computed tomography (CT). Key secondary endpoints were the proportion of patients who achieved at least a 50% reduction in the total symptom score [TSS], which was calculated from the patients' daily assessment of MF-related symptoms (abdominal discomfort, pain under left ribs, early satiety, itching, night sweats, and bone/muscle pain) and overall survival.

At ASH 2011, results from an analysis of ruxolitinib efficacy across patient subgroups from COMFORT-I were presented. The analyses were conducted by MF disease subtype (PMF, post-PV MF, or post-ET

MF), age (≤65 years or >65 years), IPSS risk group (intermediate-2 or high-risk), presence or absence of the *JAK2V617F* mutation, baseline hemoglobin level (≥10 g/dL or <10 g/dL), baseline palpable spleen length (≤10 cm or >10 cm), and baseline TSS quartile. Results from an analysis on adverse events and MF-related symptoms after interruption of study treatment and an overall survival analysis conducted at the time of a preplanned safety update were also presented.

A total of 309 patients were enrolled in the study, with 155 patients randomized to ruxolitinib and 154 to placebo. Overall, baseline characteristics were similar between treatment groups. The median age was 66 years in patients receiving ruxolitinib and 70 years in patients receiving placebo. Both IPSS risk categories were well represented within each treatment arm, and the median spleen length was 16 cm in both treatment groups. More than two thirds of patients had the *JAK2V617F* mutation (73%, ruxolitinib; 80%, placebo).

H&O What were the main findings and implications of this study?

SV The main findings of the COMFORT-I study were presented at the 2011 American Society of Clinical Oncology (ASCO) meeting and showed that at 24 weeks, 41.9% of patients in the ruxolitinib group achieved at least a 35% reduction in spleen volume as measured by MRI or CT compared with 0.7% in the placebo group ($P<.001$). Overall, patients treated with ruxolitinib experienced a mean reduction from baseline in spleen volume of 31.6% compared with a mean increase of 8.1% in the placebo group. A significantly greater proportion of ruxolitinib-treated patients achieved at least a 50% improvement in TSS at 24 weeks compared with placebo (45.9% vs 5.3%; $P<.001$). Overall, patients receiving ruxolitinib had a mean improvement of 46.1% in TSS, whereas patients receiving placebo experienced a mean worsening of 41.8%.

In the ASH 2011 presentation, we showed that the benefits of ruxolitinib therapy were evident across all subgroups evaluated. Treatment with ruxolitinib led to reductions in spleen volume and improvements in MF-related symptoms across the COMFORT-I subgroups. In contrast, patients receiving placebo experienced increases in spleen volume and worsening of symptoms in all evaluated subgroups. Mean percent changes from baseline in spleen volume and TSS for each treatment arm within a subgroup were consistent with those seen for the overall treatment group.

We also showed that, after interruption of ruxolitinib treatment, MF-related symptoms gradually returned to baseline levels within approximately 1 week

after discontinuation. Analysis of serious adverse events after treatment interruption showed a similar incidence for ruxolitinib and placebo treatment groups, and there was no clear pattern of a withdrawal effect. In addition, the percentage of patients who stopped therapy due to side effects related to ruxolitinib was the same as the percentage of patients who stopped therapy due to side effects related to the placebo, at 11%. Most importantly, the overall survival analysis showed a benefit with ruxolitinib therapy over placebo. After a median follow-up of 51 weeks, there were 13 deaths in the ruxolitinib group and 24 deaths in the placebo group (hazard ratio [HR], 0.50; 95% confidence interval [CI], 0.25–0.98; $P=.04$). Therapy with ruxolitinib had positive effects on the life expectancy of patients.

H&O What are some aspects of ruxolitinib that need further examination?

SV Based on the results from the COMFORT-I subgroup analysis, mean reductions in spleen volume or improvements in TSS across the subgroups studied were consistent with the results in the overall ruxolitinib group. Further, our findings were consistent with a subgroup analysis also presented at ASH 2011 from the COMFORT-II trial, a randomized, open-label, phase III study in Europe that evaluated the efficacy and safety of ruxolitinib compared with investigator-determined best available therapy in adult patients with PMF, post-PV MF, or post-ET MF.

Although we did not observe evidence of an acute withdrawal effect after treatment interruption in COMFORT-I, select patients who may be at risk from a rapid return of their MF symptoms and splenomegaly may benefit from a tapered discontinuation of ruxolitinib (vs an abrupt drug cessation). The decision to use such a taper should be based on clinical judgment and individualized. Continued patient follow-up is necessary in all MF patients after ruxolitinib initiation to continually evaluate the long-term efficacy and safety of ruxolitinib, as is the case for any novel drug that enters clinical practice.

Anemia was the most common hematologic adverse event reported in COMFORT-I. The incidence of grade 3/4 anemia was 45.2% with ruxolitinib and 19.2% with placebo. However, anemia was manageable with dose modifications, and only 1 ruxolitinib-treated patient discontinued due to anemia. In addition, mean hemoglobin levels in ruxolitinib-treated patients reached a nadir of approximately 9.5 g/dL (1.5–2 g/dL below baseline) after 8–12 weeks of treatment, and then gradually recovered to a new steady state of 10.1 g/dL (approximately 1 g/dL below baseline) after 24 weeks of treatment. Importantly, ruxolitinib-treated patients who developed grade 3/4 anemia while on treatment experienced spleen volume

reductions and TSS improvements similar to ruxolitinib-treated patients without anemia.

H&O What does the future hold for MF treatment?

SV The FDA approval of ruxolitinib in the United States is a watershed event for the clinical management of this disease. I predict that it will increase the knowledge basis of the plurality of community specialists who care for MF patients, and put MF on the map in the minds of physicians and patients. MF and MPNs in general have been considered rare and rather neglected diseases, and until recently there has been a dearth of focused interest in the disease process and the burden of patient chronic suffering, both from scientific research and clinical care perspectives. This is now changing rapidly. Indeed, the pace of clinical research and development in MF has picked up significantly in that several JAK inhibitors are currently in various stages of development for MF and other MPNs. These include SAR302503 (TG101348), CYT387, pacritinib (SB1518), LY2784544, NS-018, and BMS-911543. In addition, several other agents are being investigated alone or in combination with JAK inhibitors, including immunomodulators (ie, pomalidomide [Actimid, Celgene]) and histone deacetylase inhibitors (ie, panobinostat [LBH589], vorinostat [MK0683], and givinostat [ITF2357]). Further, the intercalation of ruxolitinib in pretransplant conditioning regimens aiming to improve overall tolerability and outcomes for MF patients undergoing allogeneic stem-cell transplant is being studied. It remains to be seen how novel clinical trial data will affect the treatment paradigm for MF. I am personally excited about the future, and anticipate close collaboration of large academic centers and patient advocacy groups (like the MPN Foundation) in pursuing greater understanding of MPN pathophysiology and the development of additional new therapies.

Suggested Readings

Verstovsek S, Mesa RA, Gotlib JR, et al. Results of COMFORT-I, a randomized double-blind phase III trial of JAK 1/2 inhibitor INCB18424 (424) versus placebo (PB) for patients with myelofibrosis (MF). *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2011;29: Abstract 6500.

Verstovsek S, Gotlib JR, Gupta V, et al. Consistent benefit of ruxolitinib over placebo in spleen volume reduction and symptom improvement across subgroups and overall survival advantage: results from COMFORT-I. *Blood* (ASH Annual Meeting Abstracts). 2011;118: Abstract 278.

Ostojic A, Vrhovac R, Verstovsek S. Ruxolitinib for the treatment of myelofibrosis. *Drugs Today (Barc)*. 2011;47:817-827.

Ostojic A, Vrhovac R, Verstovsek S. Ruxolitinib: a new JAK1/2 inhibitor that offers promising options for treatment of myelofibrosis. *Future Oncol*. 2011;7:1035-1043.

Harrison CN, Kiladjan J-J, Al-Ali HK, et al. Health-related quality of life and symptoms in myelofibrosis patients treated with ruxolitinib versus best available therapy. *Blood* (ASH Annual Meeting Abstracts). 2011;118: Abstract 795.