Ruxolitinib for Myelofibrosis—An Update of Its Clinical Effects☆

Hagop M. Kantarjian,[1] Richard T. Silver,[2] Rami S. Komrokji,[3] Ruben A. Mesa,[4] Roland Tacke,[5] Claire N. Harrison[6]

Abstract

Myelofibrosis (MF), a Philadelphia chromosome-negative myeloproliferative neoplasm, is characterized by progressive bone marrow fibrosis and ineffective hematopoiesis. Clinical hallmarks include splenomegaly, anemia, and debilitating symptoms. In 2 randomized phase III studies, the Janus kinase (JAK) 1/JAK2 inhibitor ruxolitinib significantly improved splenomegaly and disease-related symptoms compared with placebo (Controlled Myelofibrosis Study with Oral JAK Inhibitor Treatment [COMFORT-I]) or best available therapy (COMFORT-II) in patients with intermediate-2 or high-risk MF. Although ruxolitinib therapy was associated with dose-dependent anemia and thrombocytopenia, these adverse events rarely led to treatment discontinuation. This update of the clinical effects of ruxolitinib in patients with MF was based on original articles and meeting abstracts published after the primary publication of the COMFORT trials in March 2012. Long-term follow-up data from the COMFORT trials and clinical experience with ruxolitinib in unselected patient populations suggest that improvement of splenomegaly and symptoms is durable. Patients benefit from ruxolitinib therapy across subgroups defined by age, MF type, risk category, performance status, *JAK2* V617F mutation status, extent of splenomegaly, or presence of cytopenias. In COMFORT-I, platelet counts stabilized with dose adjustments, and hemoglobin levels gradually recovered to slightly below baseline after the first 8 to 12 weeks of therapy. After initial increases, the need for red blood cell transfusions decreased to a level similar to that found in the placebo group. The 2-year follow-up data from the COMFORT trials suggest that patients with intermediate-2 or high-risk MF receiving ruxolitinib therapy may have improved survival compared with those receiving no (placebo) or traditional therapy.

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Introduction

Myelofibrosis (MF) is a pathologic entity occurring in the form of primary MF (PMF), post-polycythemia vera (PV) MF, or post-essential thrombocythemia (ET) MF. Thus, as a clinical syndrome, MF comprises a group of related disorders that constitute or develop from a Philadelphia chromosome-negative myeloproliferative neoplasm (MPN). MF is characterized by progressive bone marrow fibrosis and ineffective hematopoiesis.[1-3] Although PMF, PV, and ET have distinct disease characteristics and diagnostic criteria,[4] secondary development of MF in patients with PV or ET results in disorders with clinical and laboratory characteristics virtually indistinguishable from those of PMF.[1,3] Typical clinical manifestations of MF include anemia and splenomegaly, which are consequences of ineffective and extramedullary hematopoiesis, and debilitating symptoms (eg, fatigue, night sweats, bone pain, fever, pruritus, and weight loss) resulting from disease-related systemic inflammation and excessive catabolism.[2,3,5,6] The estimated prevalence of MF—including PMF and secondary development from PV or ET—in the United States is 3.6 to 5.7 cases per 100,000 persons.[7] For patients with PMF, the median age at the time of diagnosis is approximately 65 years.[8,9]

A hallmark of MPNs, including PMF, is aberrant myeloproliferation associated with dysregulated Janus kinase (JAK)-signal

[1]University of Texas MD Anderson Cancer Center, Houston, TX
[2]Weill Cornell Medical Center, New York, NY
[3]Moffitt Cancer Center, Tampa, FL
[4]Mayo Clinic, Scottsdale, AZ
[5]Evidence Scientific Solutions, Philadelphia, PA
[6]Guy's and St Thomas' National Health Services Foundation Trust, London, United Kingdom

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Address for correspondence: Hagop M. Kantarjian, MD, Division of Cancer Medicine, Department of Leukemia, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Box 428, Houston, TX, 77030
E-mail contact: hkantarj@mdanderson.org

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transducer and activator of transcription (STAT) signaling.[10] Patients with MPNs carry somatic mutations in hematopoietic stem cells that result in constitutive activation or overactivation of JAK-STAT pathways,[11,12] which are essential in normal hematopoiesis.[13] Although the gain-of-function mutation *JAK2* V617F is the most prevalent of these mutations—present in approximately 60% of patients with PMF and ET, and at least 95% of patients with PV[11]—an increasing number of mutations that directly or indirectly affect JAK-STAT signaling, including mutations in genetic and epigenetic regulators, have been associated with MPNs, and patients may have multiple neoplastic stem cell clones.[11,12,14] When present, the *JAK2* V617F mutation appears not to be the disease-initiating event,[15] but it may contribute to MPN disease phenotype and manifestations.[16-18] In patients with MF, dysregulated JAK-STAT signaling not only is involved in the pathogenesis of myeloproliferation but also appears to be associated with secondary pathogenic phenomena, particularly the excess production of inflammatory cytokines, which is believed to be associated with MF-related symptoms and is sensitive to JAK inhibition.[19,20]

The prognoses of patients with PMF vary widely depending on age, presence of symptoms and anemia, leukocyte and platelet counts, percentage of circulating blasts, and karyotype.[8,21,22] Based on the number of prognostic factors, a patient's risk status is classified as low (no risk factors), intermediate-1, intermediate-2, or high. Although risk classification and prognostic estimates vary with the prognostic scoring system used, the median survival time is < 2 years for high-risk patients and 3 to 7 years for intermediate-risk patients with PMF.[8,21,22]

Before the recognition of the critical role of aberrant JAK-STAT signaling in the pathophysiology of MF, available treatment options in general were palliative and associated with limited and transient responses.[23] Treatment with the oral JAK1/JAK2 inhibitor ruxolitinib has been evaluated in patients with intermediate-2 or high-risk MF, including PMF, post-PV MF, and post-ET MF in 2 large randomized phase III studies, the double-blind placebo-controlled COMFORT (Controlled Myelofibrosis Study with Oral JAK Inhibitor Treatment)-I study[24] and the COMFORT-II study, which compare the effects of ruxolitinib therapy and best available therapy (BAT).[25] In both, ruxolitinib therapy was associated with significant improvements in splenomegaly and MF-associated symptoms compared with the controls. Mean reductions from baseline in spleen volume with ruxolitinib therapy were approximately 30% in both studies, whereas spleen volumes increased in the placebo group in COMFORT-I and in the BAT group in COMFORT-II.[24,25] In COMFORT-I, ruxolitinib therapy also was associated with a mean decrease of 46% in MF-related symptoms, based on total symptom score (TSS) assessed using the modified MF Symptom Assessment Form version 2.0—compared with a 42% increase in TSS in the placebo group.[24] Furthermore, compared with placebo, ruxolitinib therapy was associated with significant improvements in measures of the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 (EORTC QLQ-C30), including global health status/quality of life (QoL) and physical, role, emotional, and social functioning.[24] Patients treated with ruxolitinib in COMFORT-II experienced clinically meaningful improvements in symptoms and QoL measures including fatigue, dyspnea, insomnia, appetite loss, and physical- and role-functioning scales, as evaluated using the EORTC QLQ-C30, whereas BAT was generally associated with no change or symptom worsening.[25,26] Symptom improvements with ruxolitinib therapy were accompanied by decreases in the plasma levels of proinflammatory biomarkers.[24,25] No major changes in bone marrow histomorphology were observed.[25] Although ruxolitinib was generally well tolerated in both trials, patients in the ruxolitinib groups experienced increased rates of dose-dependent anemia and thrombocytopenia compared with that of the control groups; however, these events rarely led to treatment discontinuations.[24,25]

The purpose of this review is to provide an update of the clinical effects of ruxolitinib in patients with myelofibrosis. The updated information was obtained from original articles and abstracts from professional society presentations published in the 12 months following the primary publication of the clinical data from the COMFORT trials in March 2012.

Discussion

Effect on Survival

In the publications of the primary results of the COMFORT studies, the 1-year follow-up data from COMFORT-I suggested that ruxolitinib therapy was associated with improved survival in patients with intermediate-2 or high-risk MF relative to that of the placebo group.[24] However, this was not seen with ruxolitinib therapy versus BAT in COMFORT-II (Table 1).[25] The 2-year follow-up data from both COMFORT studies were presented at the annual meeting of the American Society of Hematology in December 2012.[27,28] Kaplan-Meier analyses of overall survival were based on the intended treatment at randomization and did not take into account crossover of patients from the control to the ruxolitinib groups, which was permitted in both trials according to protocol-specified criteria of disease progression. In both trials, the 2-year analyses showed a reduction in the risk of death for patients randomized to ruxolitinib compared with those randomized to the control groups (Table 1). The 2-year survival data from COMFORT-I confirmed those reported after 1 year of follow-up, suggesting that ruxolitinib therapy, relative to placebo, may be associated with prolonged survival in patients with intermediate-2 or high-risk MF.[24] Improved survival was seen, although all patients originally randomized to the placebo group had discontinued or crossed over to ruxolitinib therapy at the time of the 2-year analysis. The 2-year survival data from COMFORT-II[28,29] are the first indication of improved survival of patients who received ruxolitinib therapy rather than BAT (Table 1). Possible reasons that improved survival with ruxolitinib therapy relative to BAT was not observed at earlier follow-up times[25] include the 2:1 randomization scheme in favor of ruxolitinib therapy and potentially biased survival estimates caused by the relatively high proportion of patients in the BAT arm who were censored (27.4% vs. 14.4% in the ruxolitinib arm) because of a lack of relevant follow-up information.[29]

Cachexia-related persistent weight loss and decreases in total cholesterol are common in patients with MF and are associated with shortened survival.[8,30,31] In both COMFORT studies, ruxolitinib therapy was associated with substantial median weight gains, whereas placebo treatment and BAT were associated with