

● ● ● CLINICAL TRIALS & OBSERVATIONS

Comment on Passamonti et al, page 1833

Changing myelofibrosis's natural course at last

Srdan Verstovsek¹ ¹THE UNIVERSITY OF TEXAS MD ANDERSON CANCER CENTER

In this issue of *Blood*, Passamonti et al provide evidence that therapy with ruxolitinib, a Janus activated kinase (JAK) 1/JAK2 inhibitor, modifies the natural history of primary myelofibrosis (MF).¹

Typical clinical manifestations of MF, the most aggressive of the classic myeloproliferative neoplasms, are extramedullary hematopoiesis with enlargement of the spleen and liver, progressive bone marrow fibrosis with worsening blood cell count, and debilitating MF-related constitutional symptoms, including fatigue, night sweats, low-grade fever, pruritus, and bone pain, all leading to decreased performance status, cachexia, and premature death.² Whereas 20% to 30% of patients may die of transformation to acute myeloid leukemia, most succumb to MF-

related complications, commonly referred to as "disease progression."³ Median survival from diagnosis ranges from 2 to 11 years, depending on the presence of several risk factors included in the International Prognostic Scoring System (IPSS).³ Apart from allogeneic stem cell transplant, to which <10% of patients with MF submit, no treatment so far has been shown to change outcome in MF.² Passamonti and colleagues¹ report that patients with advanced MF (intermediate-2 or high risk by IPSS; expected median survivals of 4 and 2 years, respectively) treated with ruxolitinib had longer survival than those who received

conventional therapy. Ruxolitinib therapy in MF significantly reduces splenomegaly and improves MF-related constitutional symptoms and quality of life in most patients.² However, it does not eliminate the disease. How, then, would ruxolitinib prolong survival?

Hyperactive JAK-signal transducers and activators of transcription (STAT) intracellular signaling is a feature of MF, resulting in the proliferation of hematopoietic progenitor cells and a proinflammatory state.² The JAK2V617F mutation discovered in 2005, present in 50% to 60% of patients with MF, results in constitutive JAK-STAT activation, similar to the recently identified calreticulin mutation present in most of JAK2V617F mutation-negative patients with MF.^{2,4} Other rare mutations (eg, LNK, MPL, SOCS, and CBL) may explain a hyperactive JAK-STAT pathway in the remaining patients with MF.² Ruxolitinib, a JAK inhibitor, inhibits JAK-STAT pathway and may clinically benefit any patient with MF, regardless of their mutational status, due to its antiproliferative and antiinflammatory properties.² Looking for signs of anti-MF activity, we have traditionally looked at the effect of a therapy on the malignant clone or on bone marrow (BM) fibrosis as biological markers. Indeed, long-term therapy with ruxolitinib gradually reduces JAK2V617F allelic burden over the course of therapy.⁵ Recent analysis of BM biopsies in patients on long-term (5 years) ruxolitinib therapy revealed an improvement in BM fibrosis in a subgroup of patients.⁶ Yet neither a decrease in JAK2V617F mutation load nor a change in BM fibrosis grade has been correlated with clinical response or long-term outcome of patients on ruxolitinib therapy. However, the levels of inflammatory cytokines do correlate with clinical response. Levels of inflammatory cytokines are known to be extremely high in patients with MF and have been correlated with constitutional symptoms, transfusion need, leukocytosis, thrombocytopenia, splenomegaly, and overall survival.⁷ The levels of inflammatory cytokines significantly decrease in patients on ruxolitinib therapy and have been correlated with an improvement in constitutional symptoms.⁸ In a study with fedratinib, an investigational JAK inhibitor, a decrease in inflammatory cytokines was correlated with improvement in splenomegaly.⁹ Therefore, an important question is whether inflammatory cytokines are a biological marker that may partly explain



Patient with advanced MF at the start of ruxolitinib therapy (A) April 2008; and currently on ruxolitinib therapy (B) January 2014.

the life-prolonging benefit of ruxolitinib in MF. By inhibiting inflammatory cytokines and controlling the signs and symptoms of MF, the patient's body condition improves as the disease is kept under good control for a prolonged period of time, preventing "disease progression" (see figure).¹⁰

There are several prerequisites related to the optimal management of patients on ruxolitinib therapy in order to provide long-term benefit and potentially extend life expectancy.^{2,10} Guidelines for the starting dose of ruxolitinib are well established and should be followed closely: most dose adjustments happen within the first 3 months of therapy. This is a period where most benefits are also observed. Due to its short half-life, ruxolitinib should be used in a twice daily (BID) schedule; daily dosing was reported overall to be ineffective. Proactive dose adjustments are recommended to maintain patients on therapy with an effective dose and without interruptions. The higher the dose of ruxolitinib, the better is the spleen response. This appears to be important for survival benefit: 2 studies so far reported a correlation between the degree of spleen reduction and survival. However, 10 mg of ruxolitinib BID is equally as effective in controlling constitutional symptoms as higher doses (maximum dose is 25 mg BID). If starting with a low dose (eg, 5 mg BID in patients with low platelets), dose increases should be made monthly, if safe; later increases provide less benefit. Anemia has been identified as the most common side effect of ruxolitinib. The development of significant anemia on ruxolitinib therapy does not diminish its benefits: patients with or without ruxolitinib-related anemia experienced the same level of improvements in spleen and quality of life. In addition, with proper dose adjustments, there is usually a rebound in hemoglobin to near baseline levels in patients on therapy. In general, interruption of ruxolitinib therapy leads to the return of constitutional symptoms to baseline within 7 to 10 days, while regrowth of spleen usually happens at a slower rate. In a case of significant myelosuppression, 5 mg ruxolitinib BID can be used, but doses of 10 mg BID or higher have been shown to be good maintenance therapy.

How to further optimize therapy with ruxolitinib is a goal of many ongoing clinical studies, where new investigational agents are being combined with ruxolitinib to further increase its benefits, decrease its side effects

(eg, improve platelets or red blood cell count), or bring additional benefits (eg, antifibrotic agents). These efforts may make MF even more indolent and prolong life further.

Conflict-of-interest disclosure: S.V. receives research funding for the conduct of clinical trials from Incyte Corporation, AstraZeneca, Lilly Oncology, Geron, NS Pharma, Bristol Myers Squibb, Novartis, Celgene, YM Biosciences, Gilead, Seattle Genetics, Promedior, and Cell Therapeutics, Inc. ■

REFERENCES

1. Passamonti F, Maffioli M, Cervantes F, et al. Impact of ruxolitinib on the natural history of primary myelofibrosis: a comparison of the DIPSS and the COMFORT-2 cohorts. *Blood*. 2014;123(12):1833-1835.
2. Mascarenhas J, Mughal TI, Verstovsek S. Biology and clinical management of myeloproliferative neoplasms and development of the JAK inhibitor ruxolitinib. *Curr Med Chem*. 2012;19(26):4399-4413.
3. Cervantes F, Dupriez B, Pereira A, et al. New prognostic scoring system for primary myelofibrosis based on a study of the International Working Group for Myelofibrosis Research and Treatment. *Blood*. 2009; 113(13):2895-2901.
4. Nangalia J, Massie CE, Baxter EJ, et al. Somatic CALR mutations in myeloproliferative neoplasms with

nonmutated JAK2. *N Engl J Med*. 2013;369(25): 2391-2405.

5. Cervantes F, Vannucchi AM, Kiladjan JJ, et al; COMFORT-II investigators. Three-year efficacy, safety, and survival findings from COMFORT-II, a phase 3 study comparing ruxolitinib with best available therapy for myelofibrosis. *Blood*. 2013;122(25):4047-4053.
6. Thiele J, Bueso-Ramos CE, Sun W, et al. Effects of five-years of ruxolitinib therapy on bone marrow morphology in patients with myelofibrosis and comparison with best available therapy [abstract]. *Blood*. 2013;122(21): Abstract 4055.
7. Tefferi A, Vaidya R, Caramazza D, Finke C, Lasho T, Pardanani A. Circulating interleukin (IL)-8, IL-2R, IL-12, and IL-15 levels are independently prognostic in primary myelofibrosis: a comprehensive cytokine profiling study. *J Clin Oncol*. 2011;29(10):1356-1363.
8. Verstovsek S, Kantarjian H, Mesa RA, et al. Safety and efficacy of INCB018424, a JAK1 and JAK2 inhibitor, in myelofibrosis. *N Engl J Med*. 2010;363(12):1117-1127.
9. Pardanani AD, Jamieson CHM, Gabrail NY, et al. Updated results from a randomized phase II dose-ranging study of the JAK2-selective inhibitor SAR302503 in patients with myelofibrosis (MF). *J Clin Oncol*. 2013; 31(Suppl):7109.
10. Mascarenhas J, Hoffman R. A comprehensive review and analysis of the effect of ruxolitinib therapy on the survival of patients with myelofibrosis. *Blood*. 2013; 121(24):4832-4837.

© 2014 by The American Society of Hematology

● ● ● PHAGOCYTES, GRANULOCYTES, & MYELOPOIESIS

Comment on Weckbach et al, page 1887

Midkine, a middle manager of β_2 integrins

Jan M. Herter¹ and Tanya N. Mayadas¹ ¹HARVARD MEDICAL SCHOOL

In this issue of *Blood*, Weckbach et al demonstrate that midkine (MK), a described regulator of inflammation, supports neutrophil recruitment by promoting the high-affinity conformation of the β_2 integrin lymphocyte function-associated antigen 1 (LFA-1), a step required for neutrophil arrest on the activated endothelium.¹

The authors report that the heparin-binding growth factor MK (also referred to as neurite growth-promoting factor 2) is essential for neutrophil arrest at the site of inflammation.¹ Mice deficient for MK had markedly reduced numbers of adherent neutrophils in response to tumor necrosis factor (TNF), as assessed by intravital microscopy. This correlated with an impressive decrease in extravasated neutrophils and amelioration of tissue damage in a model of limb ischemia.¹ These findings are in line with previous studies showing that MK-deficient mice are protected from organ

damage in a variety of sterile inflammatory models, including rheumatoid arthritis, renal ischemia/reperfusion injury, and inflammatory bowel disease.² Furthermore, others have used anti-sense oligoDNA and an RNA aptamer to inhibit MK functions and have shown a reduction in leukocyte infiltration in models of nephritis and autoimmune encephalitis (for an overview, see Muramatsu³). Thus, several lines of evidence suggest that MK plays a critical role in leukocyte recruitment.

Weckbach et al now identify a molecular mechanism that can explain the observed