INTERVIEW

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Tracks 1-5

Case discussion

A 63-year-old man initially observed for low-risk myelofibrosis (MF) with no JAK2 or BCR-ABL mutation receives ruxolitinib after worsening of his disease

DR VERSTOVSEK: This patient was initially prescribed hydroxyurea as standard first-line therapy for his worsening symptoms. Hydroxyurea can decrease spleen size but does not affect blood count. Some improvement occurred, but eventually a referral was made to our center. I saw the patient about a year and a half ago. His spleen was enlarged and he had all the constitutional symptoms.

He was enrolled in the Phase I/II study of ruxolitinib and, like the vast majority of patients in the more recent Phase III COMFORT-I trial, he experienced benefit (Verstovsek 2012; [2.1, 2.2]). His spleen markedly decreased in size, he regained weight and he didn't have any major problems with blood cell count. He started enjoying life on a stable dose of ruxolitinib.

One noteworthy point is that this patient did not have the JAK2 mutation. Patients do

not need to be tested for the presence of the JAK2 mutation to receive JAK2 inhibitors because they inhibit JAK2 whether it's normal or not. All patients with MF have a high activity of JAK2 and should benefit.

DR LOVE: When is the optimal time to introduce a JAK2 inhibitor, and is there a rationale for treating asymptomatic patients?

DR VERSTOVSEK: The COMFORT-II study compared ruxolitinib to best available therapy, which in most cases was hydroxyurea. No benefit was reported with best available therapy (Harrison 2012; [2.1]), so one could argue that the correct way to care for patients who are symptomatic and/or have an enlarged spleen is to start with a JAK2 inhibitor. Administering a JAK2 inhibitor in patients who are at an early stage of the disease and asymptomatic seems reasonable, but we don't have data to substantiate that.

Many patients with MF are older and retired, and after treatment with ruxolitinib they improve so much that they can perform activities they have missed for years. Ruxolitinib controls the symptoms of the disease and prolongs survival, but it is not curative. The duration of the benefits of ruxolitinib is variable. The signs and symptoms will come back, at which point one can try different options. Patients feel so much better on the agent, they can consider a bone marrow transplant to attain cure.

We don't know if patients with MF can have their disease controlled indefinitely with ruxolitinib. We may be able to slowly discontinue therapy over time. The longest follow-up now is about 5 years since the initial studies were performed.

DR LOVE: Is there a role for the tools used in the COMFORT-I study for monitoring patients, or can they just be followed clinically?

DR VERSTOVSEK: In the COMFORT-1 study spleen volumes were assessed with MRI. We also used an electronic patient questionnaire called the Myelofibrosis Symptom Assessment Form (MFSAF). Patients receiving ruxolitinib showed improvement across the board, regardless of spleen shrinkage. The waterfall plot showed that all patients except 2 had some spleen shrinkage (2.2).

2.1

Phase III Trial Results with the JAK1/JAK2 Inhibitor Ruxolitinib for Patients with Myelofibrosis

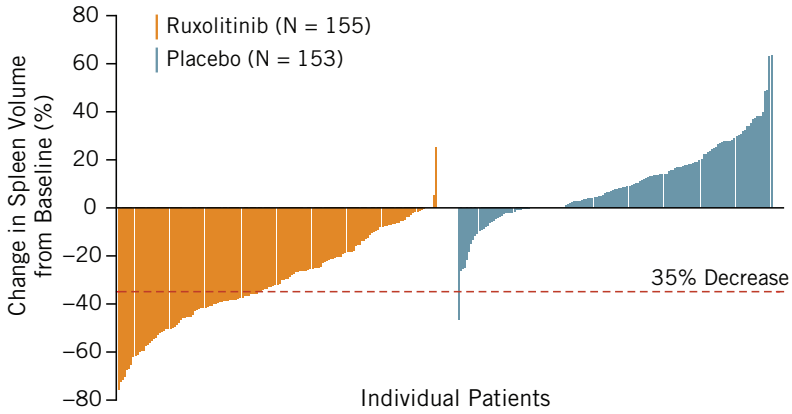
	COMFORT-I[1]		COMFORT-II[2]	
Efficacy — Primary endpoint	Ruxolitinib (n = 155)	Placebo (n = 153)	Ruxolitinib (n = 144)	Best available therapy (n = 72)
Patients with ≥35% decrease in spleen volume at 24 wk[1] and 48 wk[2]	41.9%	0.7%	28.0%	0%
	$p < 0.001$		$p < 0.001$	
Change in symptom score — Secondary endpoint	Ruxolitinib (n = 145)	Placebo (n = 145)		
Patients with ≥50% decrease in symptom score at 24 wk	45.9%	5.3%	—	—
	$p < 0.001$		—	

Symptom score = sum of scores for itching, night sweats, bone/muscle pain, abdominal discomfort, pain under the left ribs and early satiety (from the Myelofibrosis Symptom Assessment Form)

[1] Verstovsek S et al. *N Engl J Med* 2012;366(9):799-807; [2] Harrison C et al. *N Engl J Med* 2012;366(9):787-98.

2.2

COMFORT-I Study: Percent Change in Spleen Volume from Baseline in Response to Ruxolitinib versus Placebo in Patients with Myelofibrosis



Verstovsek S et al. *N Engl J Med* 2012;366(9):799-807. Copyright © 2012 Massachusetts Medical Society.

We recommend neither MRI nor the MFSAF for use in daily practice because focusing on these tools may complicate optimal delivery of therapy. Patients can be asked how they feel. This approach along with physical exam of the spleen is enough to assess utility of ruxolitinib in practice.

Track 7

DR LOVE: What is known about pomalidomide and other IMiDs in MF, and is it possible to combine them with JAK2 inhibitors?

DR VERSTOVSEK: Pomalidomide is an IMiD used in the treatment of some hematologic cancers. It is a derivative of thalidomide that has a different toxicity profile compared to the other 2 IMiDs — thalidomide and lenalidomide. It is associated with lower levels of neuropathy and myelosuppression than the levels observed with thalidomide and lenalidomide, respectively. At a low dose of 0.5 mg, it has the potential to improve the red blood cell count (Tefferi 2009). It does not have an impact on any other aspects of the disease. Its efficacy is now being tested in a randomized Phase III study for patients with MF who are red blood cell transfusion dependent (NCT01178281). If pomalidomide is found to be beneficial in this Phase III study, I would definitely like to combine it with JAK2 inhibitors. This would allow a dual effect of the JAK2 inhibitors on the spleen and symptoms and an improvement in anemia by pomalidomide. ■

SELECT PUBLICATIONS

Harrison C et al. **JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis.** *N Engl J Med* 2012;366(9):787-98.

Tefferi A et al. **Pomalidomide is active in the treatment of anemia associated with myelofibrosis.** *J Clin Oncol* 2009;27(27):4563–9.

Verstovsek S et al. **A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis.** *N Engl J Med* 2012;366(9):799-807.