INTERVIEW

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Tracks 1-14

Track 1	Recent advances and remaining challenges in understanding the pathogenesis and pathophysiology of myeloproliferative neoplasms
Track 2	Use of cytogenetics in risk stratification of patients with myelofibrosis (MF)
Track 3	Lack of correlation between JAK2 mutation status and response to ruxolitinib in MF
Track 4	Update on selective JAK1 and JAK2 inhibitors currently under investigation in MF
Track 5	Correlation between specific cytokine expression and disease phenotype
Track 6	Indications for use of ruxolitinib in patients with low-risk MF
Track 7	Use of ruxolitinib in asymptomatic intermediate- and high-risk MF
Track 8	Comprehensive review of the effect of ruxolitinib on survival in patients with MF
Track 9	Symptom control and improvements in quality of life with ruxolitinib
Track 10	Ruxolitinib dosing in patients with MF and low platelet counts and/or anemia
Track 11	Clinical experience with ruxolitinib-induced thrombocytopenia and anemia
Track 12	Therapeutic approach for patients with MF who initially respond to ruxolitinib but who then experience stable disease or disease progression
Track 13	Use of immunomodulatory drugs in MF
Track 14	A Phase II trial of ruxolitinib prior to allogeneic transplant for patients with MF

Select Excerpts from the Interview

Tracks 3, 6-7, 10, 12

DR LOVE: Would you discuss the efficacy of JAK inhibitors, especially ruxolitinib, in patients with myelofibrosis (MF) with and without JAK mutations?

DR MASCARENHAS: It was initially thought that only patients with JAK mutations would benefit from JAK inhibitors. That turned out not to be the case. All patients with MF have heightened expression of the JAK-STAT signaling pathway within their hematopoietic system. The JAK2 V617F mutation is only one factor that can lead to upregulation of this pathway. It's because of the heightened activity of this pathway that the JAK1/2 inhibitor ruxolitinib in particular has been successful in the treatment of MF, irrespective of V617F mutational status.

DR LOVE: How do you decide whether to administer ruxolitinib?

DR MASCARENHAS: The commercial availability of ruxolitinib has changed the treatment landscape. Ruxolitinib is effective in palliating symptoms and reducing splenomegaly, and some evidence indicates that prolonged therapy for 24 to 48 months may

lead to the retardation of fibrosis in the marrow. That's an interesting finding with compelling implications. Despite the fact that the COMFORT-I and II trials were for intermediate- and high-risk MF (Verstovsek 2012; Cervantes 2012), I believe that patients with symptomatic low-risk MF can benefit from ruxolitinib. For patients with platelet counts lower than 50 x 10^9/L or those with transfusion-dependent anemia, ruxolitinib is not an option.

DR LOVE: Do you base your treatment decision-making about ruxolitinib mainly on disease symptomatology?

DR MASCARENHAS: I consider the bigger picture. It is not known whether a patient with low-risk MF who has a large spleen but otherwise feels well will benefit in the long term from ruxolitinib. I don't administer ruxolitinib to such patients, but I'm not necessarily opposed to it.

DR LOVE: What are your treatment considerations for patients with intermediate- or high-risk MF?

DR MASCARENHAS: Patients with intermediate- or high-risk MF do not necessarily need to have symptoms to be eligible for ruxolitinib. Although longer-term follow-up and more studies are needed, the evidence thus far from the COMFORT-I and II studies of a modest but statistically significant improvement in overall survival suggests that symptoms alone should not be the trigger for ruxolitinib therapy for these patients.

DR LOVE: How do you dose ruxolitinib in patients with thrombocytopenia?

DR MASCARENHAS: It's well established from the COMFORT-I and II studies that patients with platelet counts greater than 100 x 10^9/L can receive ruxolitinib. Based on data presented from Study 258, it is also possible to treat patients with platelet counts of 50 to 100 x 10^9/L (Talpaz 2012; [3.1]). My recommendation is to start low and titrate upward. I wouldn't recommend ruxolitinib at a platelet count lower than 50 x 10^9/L.

With a platelet count of 50 to 100 x 10^9/L, I start at 5 mg BID and slowly increase that on a monthly basis. At times, I titrate up so that the patient receives 5 mg in the morning and 10 mg in the evening. I adopt a stepwise and careful approach. With platelet counts of 100 to 150 x 10^9/L, I tend to use 10 mg BID. I follow these patients weekly for the first 1 to 2 months to avoid abrupt cessation of the agent.

3.1

Efficacy of Titrated Low-Dose Ruxolitinib (Rux) in Patients with Low Platelet Counts (Study 258) versus Efficacy at Full Dose (COMFORT-I Study)

	Study 258	COMFORT-I study	
Efficacy parameter	Titrated low-dose rux (n = 22)	Rux (n = 155)	Placebo (n = 154)
≥50% reduction in total symptom score	36.4%	45.9%	5.3%
≥35% reduction in spleen volume	33.3%	41.9%	0.7%

For patients with baseline platelet counts of 50 to 100 × 10^9/L, starting rux at a dose of 5 mg BID and titrating to 10 mg BID or greater resulted in spleen volume reductions and improvements in symptoms and quality of life that were consistent with those seen in the COMFORT-I study.

Talpaz M et al. *Proc ASH* 2012;**Abstract 176**.

DR LOVE: What about the issue of cytopenias and ruxolitinib, particularly anemia? Does the presence or absence of anemia influence your starting dose?

DR MASCARENHAS: It is important for patients who are transfusion independent at baseline and their family members to understand that, although ruxolitinib effectively addresses symptoms and reduces spleen size, it can cause anemia. This is usually predictable and occurs within 3 months. One needs to weigh the quality-of-life aspect of blood transfusions versus symptom improvement. For most patients, the odds are in favor of remaining on the drug, especially after they start ruxolitinib and are feeling better.

DR LOVE: Would you discuss the withdrawal symptoms that can be associated with sudden discontinuation of ruxolitinib and how you approach stopping therapy?

DR MASCARENHAS: This has been an area of controversy. In the COMFORT-I and II studies, symptoms returned to baseline within 7 to 10 days of stopping. This was predictable. A single-institution study reported that patients who stopped treatment abruptly developed withdrawal syndrome, which in one case was a sepsis-like state (Tefferi 2011; [3.2]). In my experience, symptoms rebound. My practice is to try to taper treatment when I can. If I have to stop abruptly, I almost always use a prednisone taper to blunt the return of symptoms. ■

3.2

Serious Adverse Events During Ruxolitinib Therapy Discontinuation in Patients with Myelofibrosis (MF)

- This report discussed the occurrence of sometimes severe withdrawal symptoms during ruxolitinib discontinuation and described the details of these events in 5 severely affected cases among 47 Mayo Clinic patients with MF in whom ruxolitinib therapy had been discontinued.
- This "ruxolitinib withdrawal syndrome" was characterized by acute relapse of disease symptoms, accelerated splenomegaly, worsening of cytopenias and occasional hemodynamic decompensation, including a septic shock-like syndrome.
- It is speculated that the underlying mechanism for "ruxolitinib withdrawal syndrome" involves rapid changes in inflammatory cytokine activity, but such challenges do not necessarily undermine the benefit of ruxolitinib in a select patient group with advanced MF, including those with severe constitutional symptoms, profound cachexia and symptomatic splenomegaly.

"Our experience calls for full disclosure of the ruxolitinib withdrawal syndrome to patients with MF before initiating ruxolitinib therapy, and treatment discontinuation must be done under close physician supervision and preferably in a tapering schedule."

Tefferi A et al. *Mayo Clin Proc* 2011;86(12):1188-91.

SELECT PUBLICATIONS

Cervantes F et al. **Long-term safety, efficacy, and survival findings from COMFORT-II, a Phase 3 study comparing ruxolitinib with best available therapy (BAT) for the treatment of myelofibrosis (MF).** *Proc ASH* 2012;**Abstract 801**.

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):4832-7.

Talpaz M et al. **Efficacy, hematologic effects, and dose of ruxolitinib in myelofibrosis patients with low starting platelet counts (50-100 x 10^9/L): A comparison to patients with normal or high starting platelet counts.** *Proc ASH* 2012;**Abstract 176**.

Tefferi A, Pardanani A. **Serious adverse events during ruxolitinib treatment discontinuation in patients with myelofibrosis.** *Mayo Clin Proc* 2011;86(12):1188-91.

Verstovsek S et al. **Long-term outcome of ruxolitinib treatment in patients with myelofibrosis: Durable reductions in spleen volume, improvements in quality of life, and overall survival advantage in COMFORT-I.** *Proc ASH* 2012;**Abstract 800**.