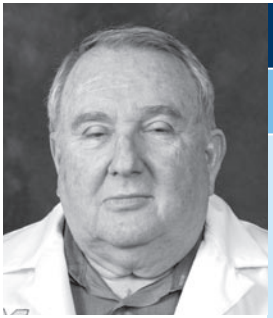

INTERVIEW

Moshe Talpaz, MD

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Tracks 1-14

Track 1 Choice of initial tyrosine kinase inhibitor (TKI) for chronic myeloid leukemia (CML)

Track 2 Selection of second-generation TKIs nilotinib or dasatinib for initial treatment of CML

Track 3 Potential influence of once-daily (dasatinib) versus twice-daily (nilotinib) dosing on patient adherence

Track 4 Complexities in comparing toxicities among imatinib, nilotinib and dasatinib

Track 5 Pathophysiology and treatment of dasatinib-associated pleural effusion

Track 6 Monitoring patients with CML who are receiving TKI therapy

Track 7 Defining the major goal of TKI treatment in CML: Complete cytogenetic remission with major molecular response

Track 8 Influence of side effects and patient age on adherence to TKI therapy in CML

Track 9 Relationship between compliance and inadequate response to TKI therapy in younger patients with CML

Track 10 Historical perspective on the treatments for MF

Track 11 JAK STAT signaling and the modes of action of JAK2 inhibitors

Track 12 JAK2 inhibitor-associated anticytokine and antiproliferative responses

Track 13 Durability and rates of response to ruxolitinib in patients with MF

Track 14 Side effects and quality of life with long-term ruxolitinib treatment for patients with MF

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: What is your approach to selection of first-line therapy for a patient with chronic myeloid leukemia (CML)?

DR TALPAZ: We start every patient with CML on a second-generation tyrosine kinase inhibitor (TKI), specifically nilotinib or dasatinib. As long as the cost differential between imatinib and these new agents is not large — and it isn't at this point — I see no reason to start a patient today on imatinib. That may change eventually when imatinib becomes generic, so we can reevaluate this discussion then based on financial grounds.

The outcome milestones that have been defined are driven primarily by results with imatinib, and they may have to be modified because the new agents are more efficient and attain results more quickly. Nevertheless, our expectations are that patients will at least have complete hematologic remission by 3 months, with normal counts and some minor cytogenetic response. This is what we call the European Leukemia Network criteria, and it is a good set of criteria likely to be adopted by the NCCN also.

DR LOVE: How might you choose — or how should an oncologist in practice choose — between nilotinib and dasatinib?

DR TALPAZ: These agents were studied in large Phase III studies, and they were not identical studies. To compare the results and say one agent is better than the other is unfair.

The results of the ENESTnd trial are somewhat superior, primarily in one aspect — rate of progression to accelerated or blast phase at 1 and 2 years on nilotinib compared to imatinib. The rate of progression was about 6% on imatinib. If we include clonal evolution, the rate of progression on 300 mg twice daily of nilotinib was only 0.7% (Kantarjian 2011a). In the DASISION study, by 2 years one started to see a bifurcation, and the rate of progression on imatinib was higher than on dasatinib (Kantarjian 2011b).

The rate of complete cytogenetic remission is similar between the studies. The rate of molecular responses is not dramatically different. Overall, it may well be that choice of agent should be based on toxicity rather than activity, and it will depend to a large degree on the patients.

Given a patient with lung disease, I would choose nilotinib. For a patient with pancreatic or liver disease, I would choose dasatinib. For a patient with significant fluid retention, I would opt for nilotinib. Given a patient with a history of migraines, I would not choose dasatinib because it can activate migraines. Basically, I would make the decision based not on activity of the agents but on how the patient will live with the drug.

Tracks 13-14

DR LOVE: What are your thoughts on the durability and rates of response with the novel JAK1/2 selective inhibitor ruxolitinib in MF?

DR TALPAZ: I worked not only with the COMFORT study but also with other JAK inhibitors. Most patients will respond to these agents. As far as symptoms, within a week patients feel better, and that's dramatic. The night sweats go away quickly, appetite improves and patients start to put on muscle. The reduction in spleen size is relatively quick (1.2, page 5).

Perhaps the more important issue is durability of response. Initially we thought these agents would only produce a trivial effect with rapid resistance. But I now have patients who are going for 4 years or more who are completely asymptomatic.

DR LOVE: What side effects have been reported with ruxolitinib?

DR TALPAZ: We deal with myelosuppression, which requires dose reduction/dose interruption. That's not a big factor in quality of life. Quality-of-life issues are diarrhea, fatigue, lack of energy, infections and so forth (Harrison 2011; [4.1]). Those are uncommon.

The quality of life, overall, is equal to or better than what we have seen with imatinib in CML. Granted, we may see other unique, rare toxicities with time, but the initial impression is that this is not chemotherapy. This is targeted therapy. ■

4.1

COMFORT-II Study: Common Nonhematologic Side Effects of the JAK1/2 Inhibitor Ruxolitinib in Patients with Myelofibrosis (MF), Postpolycythemia Vera MF or Postessential Thrombocythemia MF

	Ruxolitinib (n = 146)		Best available therapy (n = 73)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Diarrhea	23%	1%	11%	0%
Peripheral edema	22%	0%	26%	0%
Asthenia	16%	1%	10%	1%
Dyspnea	16%	1%	18%	4%
Pyrexia	14%	2%	10%	0%
Nausea	13%	1%	7%	0%
Arthralgia	12%	1%	7%	0%
Fatigue	12%	1%	8%	0%

Harrison CN et al. *Proc ASCO* 2011;**Abstract LBA6501**.

SELECT PUBLICATIONS

Harrison CN et al. **Results of a randomized study of the JAK inhibitor ruxolitinib (INC424) versus best available therapy (BAT) in primary myelofibrosis (PMF), post-polycythemia vera-myelofibrosis (PPV-MF) or post-essential thrombocythemia-myelofibrosis (PET-MF).** *Proc ASCO* 2011;**Abstract LBA6501**.

Kantarjian HM et al. **Nilotinib versus imatinib for the treatment of patients with newly diagnosed chronic phase, Philadelphia chromosome-positive, chronic myeloid leukaemia: 24-month minimum follow-up of the phase 3 randomised ENESTnd trial.** *Lancet Oncol* 2011a;12(9):841-51.

Kantarjian H et al. **Dasatinib or imatinib (IM) in newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP): Two-year follow-up from DASISION.** *Proc ASCO* 2011b;**Abstract 6510**.

Verstovsek S 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).** *Proc ASCO* 2011;**Abstract 6500**.