The different faces of Janus kinase inhibition

Peter Vandenberghe

Center for Human Genetics, KU Leuven, Leuven, Belgium

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As of March 1st 2012, two phase III multicenter studies have been published reporting significant clinical efficacy of ruxolitinib in intermediate-2 or high-risk myelofibrosis. One study (COMFORT-I) assessed ruxolitinib (15-20 mg bid) against placebo.[1] The other study (COMFORT-II) compared ruxolitinib with best available therapy in a 2:1 randomization.[2] The primary end point in both studies was reduction in splenic volume of at least 35%. This was achieved by 42% of patients at 24 weeks in COMFORT-I and by 28% of patients at 48 weeks in COMFORT-II. In both studies, patients under ruxolitinib experienced substantial symptomatic improvement. Anemia or thrombocytopenia constituted the most common toxicities but were manageable while non-hematologic toxicities were rare and mild. In the control arms, no significant reductions in splenic volume were observed while symptoms remained stable or worsened. Finally, COMFORT-I showed a significant overall survival advantage for ruxolitinib at a median follow up of 51 weeks, while no influence on overall survival could be documented in COMFORT-II.[1,2]

The *JAK2* V617F mutation was discovered in 2005 by four independent teams.[3-6] Its transforming character was proven in cell-based as well as in animal models, providing a clear case for the clinical development of JAK2 inhibitors. The results obtained with the JAK inhibitor ruxolitinib are unprecedented in intermediate-2 and high-risk myelofibrosis and constitute yet another landmark in the history of targeted therapy. Yet, despite the spectacular improvement in splenic volume and patient symptom scores, ruxolitinib did not lead to an equally substantial reduction in leukemic burden.

So why are splenic volume and the patient's subjective status disproportionately responsive to ruxolitinib compared with the leukemic burden? Importantly, ruxolitinib is not specific for V617F mutant JAK2 but attenuates cytokine signaling via the inhibition of JAK2 (wild-type or mutant forms) and of JAK1.[7] By virtue of its anti-JAK1 activity, it exerts a significant and unanticipated beneficial inhibition on several receptors controlling immune cell activation and, hence, secondary systemic inflammation. On the other hand, its activity against wild-type JAK2 inhibits signaling of the receptors for erythropoietin and thrombopoietin in myeloid cells. This determines the drug's major toxicities and precludes maximal targeting of V617F mutant JAK2 in neoplastic cells. The starting dosage in the Comfort studies was 15-20 mg bid, allowing escalation to 25 mg bid to increase efficacy. In fact, 25 mg bid had been previously established as the maximum tolerated dose.[8]

Myelofibrosis is a chronic myeloproliferative neoplasm often associated with constitutional symptoms and a profound impact on the quality of life. Certainly, part of the effects of ruxolitinib are mediated by collateral inhibition of immune activation. However, a modest reduction in the *JAK2* V617F allele burden was also observed in JAK2 V617F positive disease.[1] Therefore, it remains plausible that a significant part of the action of ruxolitinib is through a direct effect on the neoplastic clone and its proinflammatory properties. For the moment, it is not possible to determine exactly what contribution each of these pathways makes, nor whether they interact additively or synergistically. Finally, the median follow up in both studies is relatively short, and the long-term effects of ruxolitinib on the *JAK2* V617F allelic burden, on thrombotic events, and on progression-free, leukemia-free and overall survival have still to be seen.

Peter Vandenberghe is a senior clinical investigator of the FWO-Vlaanderen.

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