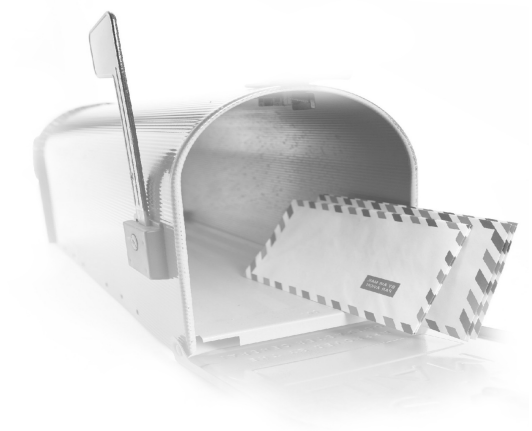

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Letter to the Editor

Many questions raised by a question on JAK1/2 inhibitors in primary myelofibrosis

TO THE EDITOR: Firstly, I congratulate Chul Won Jung for the perspectives on the role of JAK1/2 inhibitors in the management of primary myelofibrosis (PMF) [1]. I would like to share some of my thoughts on the same topic.

In comparison with conventional chemotherapeutic drugs, the expectations of targeted therapies are high. Imatinib, which targets *BCR-ABL*, and all-trans retinoic acid (ATRA) that targets *PML-RARa,* have made major impacts on medicine. It was expected that JAK1/2 inhibitors would have similar, almost magical, effects in *JAK*-positive myeloproliferative neoplasms. However, the data to date have shown that ruxolitinib, the first of the JAK1/2 inhibitors, has failed to live up to these expectations.

Ruxolitinib reduces constitutional symptoms and reduces spleen size in PMF [2]. However, the observations of reduction in constitutional symptoms and the decrease in spleen size after treatment with a JAK1/2 inhibitor in patients with wild-type *JAK2* create doubts about the targeted nature of this drug and the role of *JAK2* in the pathogenesis of PMF. In addition, it is hard to imagine how ruxolitinib reduces mortality without having a significant impact on the peripheral blood blast count, marrow fibrosis, cytogenetic remission, or reduction of *JAK2* V617F allele burden. How does a targeted drug reduce mortality without having a significant effect on the disease biology? It would have been enlightening had this question been addressed; previous articles have not touched upon this topic.

Severe splenomegaly has been associated with poor outcomes after hematopoietic stem cell transplant (HSCT). Given this, the study author predicts that ruxolitinib administered prior to HSCT may improve the outcomes of HSCT in PMF. However, as mentioned in the penultimate section of the article, it is difficult to understand how this drug would have any impact on the outcome of HSCT by decreasing the proinflammatory cytokine levels when the mechanism of action for this effect is still unknown.

The outcomes of trials of ruxolitinib in PMF have raised many questions and provided a few answers. What is the specificity of ruxolitinib as a targeted drug? Are there any other undiscovered pathways in the pathogenesis of PMF that hinder the action of ruxolitinib? These are some of the many questions that further studies need to answer. In my opinion, then and only then will the question "Will JAK1/2 inhibitors change the standard of care for myelofibrosis?" be answered appropriately.

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No potential conflicts of interest relevant to this article were reported.

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