Comment on Takahashi et al, page 3784

Clearing the path for MPN therapy monitoring

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In this issue of *Blood*, Takahashi and colleagues have helped clarify the validity of using peripheral blood for monitoring the JAK2-V617F allele burden among the myeloproliferative neoplasms.[1] The understanding of the BCR-ABL–negative MPNs of essential thrombocythemia (ET), polycythemia vera (PV), and primary myelofibrosis (PMF) encountered a true watershed in 2005 with the discovery of the JAK2 V617F mutation.[2] This latter discovery had an incredible impact on many levels, inspiring the hematology research community to investigate the pathophysiology of these MPNs as well as begin development of new MPN-directed therapies. Subsequently, multiple additional mutations in the molecular pathways that can be involved with the pathophysiology of MPNs include the JAK2 Exon 12; mutations in *MPL, ASXL1, IDH1/2, EZH2*; and deletions in *TET2*.[3] Although many of these additional molecular and genetic discoveries may have important implications in terms of the behavior of subsets of myeloproliferative neoplasia of MPNs, they may have prognostic implications particular to the area of leukemic transformation, but most of these remain relatively low-prevalence mutations; now almost 9 years after the discovery of the JAK2 V617F, this mutation remains by far the most prevalent, widely tested, and impactful of the MPN mutations.

Chronic myeloid leukemia has historically been considered a parallel disease process to the BCR-ABL–negative MPNs, and after the discovery of the JAK2 V617F, it was the initial hope that inhibition of JAK2 could lead to significant and profound molecular responses, as had been observed with the use of tyrosine kinase inhibitor therapy for CML. These past 8.5 years have led to the development of several very important inhibitors of JAK2, one of which is ruxolitinib, which is approved in the US and Europe for patients with myelofibrosis; SAR302503 (fedratinib) has completed a phase 3 trial and is being considered for registration; CYT387 (momelotinib) and SB1518 (pacritinib) are currently undergoing phase 3 clinical trials; and other JAK2 inhibitors remain in testing, including NS018 and LY27A4544.[4] All of the JAK inhibitors have demonstrated activity in improving splenomegaly and the symptoms of MPNs—and even survival (thus far with only ruxolitinib use in myelofibrosis[5]); however, this class still has a modest benefit in terms of reduction of the molecular allele burden of JAK2 V617F. Two therapies have been effective in the reduction of the JAK2 V617F allele burden; the first with prognostic significance has been in the setting of successful allogeneic stem cell transplantation, in which European clinical trials of transplantation have demonstrated that the rate of clearance of this molecular marker does have prognostic relevance.[6] In addition, anticlonal therapy with interferon has been demonstrated, in particular in patients with PV, to lead to not only hematologic response but also in some individuals to a molecular response associated with therapy.[7] In aggregate, demonstrating that although JAK inhibitors have not shown direct significant evidence of molecular response, this potentially does remain a valuable goal for patients with MPNs and is clearly part of the end points of future clinical trials.

The year 2013 has ushered in 2 new sets of revised response criteria for the spectrum of patients with MPNs—both the European Leukemia Net (ELN) guidelines for patients with PV or those with PV and ET,[8] as well as the International Working Group for Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) for patients with myelofibrosis.[9] Both groups revised response criteria (see Table) for ET, PV, and MF, and both groups broke down the potential depth of response to therapy into the categories of complete remission and partial remission, and in myelofibrosis, added a lower tier of response including clinical improvements for anemia, splenomegaly, or symptoms. Both groups identified that achieving these top levels of response were based on marrow histology, blood counts, and symptoms but did not mandate a molecular response. Thus both groups continue to (1) identify that molecular remission or response may be an important end point as our understanding of these diseases evolves and (2) put this into guidance regarding molecular response. Both response guidelines define molecular response as recording analysis in peripheral blood granulocytes, identifying complete response as eradication of a preexisting abnormality, and a partial response with at least 20% mutant allele burden at baseline and at least a 50% decrease in that allele burden.

2013 revised response criteria for myeloproliferative neoplasms[8,9]

	Essential thrombocythemia	Polycythemia vera	Myelofibrosis
Complete response	X	X	X
Partial response	X	X	X
Clinical improvement			X
Stable disease			X
No response	X	X	
Relapse			X
Other responses*	Molecular	Molecular	Cytogenetic and molecular

See Table 1 in the article by Takahashi et al that begins on page 3784.

Complete response = eradication of a preexisting abnormality; partial response = >50% decrease in allele burden (with at least 20% mutant allele burden at baseline).

*Other responses were measured in peripheral blood granulocytes.

The article by Takahashi and colleagues is impactful because it helps validate the decision of both sets of response criteria that focus on peripheral blood analysis for the assessment of the JAK2 V617F allele burden. The quality demonstration in a high number of samples across MPNs demonstrating the interchangeable nature of measuring allele burden in blood and bone marrow will be very helpful in clinical trials moving forward, as well as potentially clinical practice as we further validate the impact that reduction in allele burden is helpful. In addition, it helps validate the practice even today of monitoring the JAK2 V617F allele burden in patients post stem cell transplantation in terms of monitoring for both response and relapse. As the current clinical trials of MPNs are evolving from single agent to combination strategies, the ability to dynamically follow allele burden in the course of these trials through the peripheral blood is an important advancement. Whether in the future monitoring the lower prevalence MPN molecular mutations will be helpful in assessment of therapeutic response remains a question to be answered.

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● ● ● PLATELETS & THROMBOPOIESIS

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Causal role for JAK2 V617F in thrombosis

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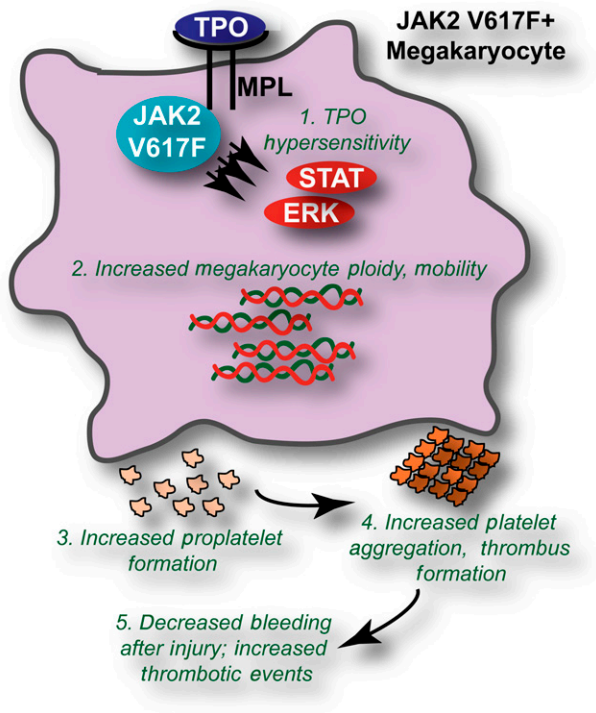
In this issue of *Blood*, Hobbs et al use a JAK2 V617F knock-in mouse model to interrogate the impact of JAK2 V617F on thrombosis and demonstrate altered function of megakaryocytes and platelets in the context of JAK2 V617F expression.[1]

Thrombosis is a major cause of disease-related morbidity and mortality in myeloproliferative neoplasm (MPN) (reviewed in Barbui et al[2]). Accordingly, reduction of thrombotic risk is a central therapeutic goal for this disease. The increased risk of thrombosis observed in MPN patients is a consequence of not only



JAK2 V617F induces biological changes to megakaryocytes and platelets leading to increased thrombotic events. The presence of JAK2 V617F leads to (1) hypersensitive signaling through the thrombopoietin (TPO)/MPL pathway in megakaryocytes, leading to increased activation of downstream molecules such as signal transducer and activator of transcription 3 and extracellular signal-regulated kinase. Phenotypically, this manifests in (2) increased ploidy and mobility of JAK2 V617F megakaryocytes; (3) increased formation of proplatelets; and (4) increased aggregation, spreading, and thrombus formation of platelets. The ultimate consequence of these biological changes is (5) decreased bleeding volumes in response to injury and increased thrombotic events.