

## **Editorial-I**

# Myeloproliferative Neoplasms: The Era of JAK2 Mutations and More...

Recent years have seen renewed interest in the molecular characterization, classification and targeted therapy of myeloproliferative disorders (MPDs), now known as 'myeloproliferative neoplasms (MPNs).<sup>1</sup> This development, initiated by the discovery of Imatinib mesylate against BCR-ABL tyrosine kinase domain in CML was subsequently continued by the detection of JAK2 (Janus Kinase 2) mutations in BCR-ABL negative MPDs. Currently we appear to be heading towards the age of JAK2 inhibitors, which are indeed already in clinical trials.

JAK2 mutations (JAK2 *V617F*, a G → T somatic mutation at nucleotide 1849 in exon 14, resulting in the substitution of valine to phenylalanine at codon 617) were first reported in 2005, almost simultaneously by four groups<sup>2,3</sup> in BCR-ABL-negative MPDs. However, the significance and the exact role of JAK2 mutations still remain to be completely elucidated. It is not clear from the available data whether it is the first event in some of the MPNs, and if so, does it play a role in hematopoietic stem cell (HSC) renewal? Are secondary events a must for clonal disease to develop in HSCs harboring the JAK2 *V617F* mutation as a first event? Or, in contrast, is JAK2 *V617F* a mutation appearing subsequent to an initial, yet to be discovered, genetic or epigenetic event?

The JAK2V617F mutational frequencies are estimated at approximately 95% in polycythemia vera (PV), 50% in essential thrombocythemia (ET), primary myelofibrosis (PMF) or refractory anemia with ringed sideroblasts & thrombocytosis, 20% in

nonclassical MPDs and 3% in de novo AML or myelodysplastic syndrome.<sup>4</sup> The mutation however has not been seen in non-myeloid neoplasms or reactive myeloid proliferation. Clinically, the JAK2 *V617F* mutation status has been variably linked with a higher risk of thrombosis, fibrosis, splenomegaly and transformation to leukemia.

In 2006, a few new mutations were described in BCR-ABL negative MPDs e.g. *MPLW515L*, *MPLW515K* and exon 12 JAK2 mutations. *MPL W515L* is a somatic gain of function mutation (a G → T transition at nucleotide 1544 resulting in a tryptophan to leucine substitution at codon 515) in JAK2 *V617F*-negative PMF.<sup>5</sup> Subsequently, an additional MPL mutation involving the same 515 codon (*MPL W515K*) was incidentally discovered. The prevalence of both mutations has been estimated at approximately 5% in PMF and 1% in ET but they have not been documented in patients with PV or other myeloid disorders.<sup>6</sup> Interestingly, some patients with MPL mutations also display a minor JAK2V617F clone. Although it is unclear whether the MPL and JAK2 mutations arise in independent clones or whether the JAK2V617F cell emerges as a subclone of the MPL mutation-carrying progenitor cell.

In 2007, four exon 12 JAK2 mutant alleles were described including F537-K539delinsL, H538QK539L, K539L and N542-E543del in JAK2V617F-negative patients with PV.<sup>7</sup> At present, the estimated frequency of JAK2 exon

12 mutations is 3% in PV. Nevertheless, current reports suggest substantial overlap in both bone marrow histology and clinical presentation between JAK2 exon 12 and exon 14 mutations.<sup>6</sup>

Another change in the proposed 2008 classification of MPNs is that they now include mast cell disease as a separate category. Also, the previous CMPD subcategory of chronic eosinophilic leukemia / hypereosinophilic syndrome (CEL/HES) is now reorganized into HES, 'CEL, not otherwise categorized (CEL, NOC)' and 'myeloid neoplasms associated with eosinophilia and abnormalities of PDGFRA, PDGFRB and FGFR1', the latter group being assigned a new category of its own.

In conclusion, the evolution of nomenclature, classification and molecular pathogenesis of the MPDs (now MPNs) has come a long way since their first description by William Dameshek in 1951. These insights into basic disease biology and behaviour will ultimately present hematologists with robust tools in the form of targeted therapy for these difficult to manage disorders in the near future.

#### References:

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