



## The Revised Classification and Diagnosis of Chronic Myeloproliferative Diseases: Impact on Laboratory Management

The 2001 World Health Organization (WHO) classification and diagnosis of chronic myeloproliferative diseases (CMPD) has been recently updated to reflect new developments in molecular research. The major changes were triggered by the dramatic discovery of activating tyrosine kinase mutations (i.e. JAK2, KIT) that were found to be key players in the pathogenesis of chronic myeloproliferative diseases.

ABL. BCR-ABL gene has a potent and constitutive tyrosine kinase activity that causes autonomous phosphorylation and neoplastic proliferation of myeloid cell lineage specific for CML. Philadelphia chromosome is detected by cytogenetic analysis of cultured cells from peripheral blood and bone marrow. This is present in more than 95% of CML patients. BCR-ABL gene, on the other hand, is detected by fluorescent in-situ

of molecular pathways, and neoplastic myeloid proliferation.<sup>4</sup> JAK2 V617F mutation is found in 65-97% of PV, 23-57% of ET and 35-57% of PMF.<sup>5</sup> The fact that PV, ET, and PMF share similar mutation raises speculation that perhaps they represent a spectrum of the same disease and are not really distinct from each other. This is a topic of debate among researchers these days.<sup>2,6</sup>

In the revised 2008 classification, the neoplastic nature of CMPD was recognized, thus the category “Chronic myeloproliferative diseases (CMPD)” has been replaced by “Myeloproliferative neoplasms (MPN)”. In the new classification, systemic mastocytosis has been included in MPN category because the investigators found that it is almost always associated with mutation in the gene encoding receptor tyrosine kinase KIT. The neoplasms associated with eosinophilia and PDGFRA, PDGFRB, or FGFR1 abnormalities have been given a separate category. The bulk of revisions was in the diagnostic criteria for PV, ET, and PMF, and included the presence of JAK2 V617F or similar mutation as one of the major criteria for all three diseases. In addition, the threshold of platelet count for the diagnosis of ET has been lowered from  $\geq 600 \times 10^9/L$  to  $\geq 450 \times 10^9/L$ .<sup>1</sup> The changes are further detailed in “The 2008 WHO classification of haematopoietic and lymphoid tissue” which was just recently made available in print. Diagnostic algorithms have been suggested by several authors to simplify the approach to the diagnosis of MPN.<sup>1,7</sup>

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Chronic myeloproliferative disease (CMPD) is the neoplastic proliferation of myeloid stem cells within the bone marrow that leads to increased counts of granulocytes, red cells, or platelets in the peripheral blood. CMPD are classified according to the predominant lineage affected. In the 2001 WHO classification, the four main diseases were chronic myelogenous leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF), and the rare entities were chronic neutrophilic leukemia (CNL), chronic eosinophilic leukemia (CEL)/hypereosinophilic syndrome (HES), and CMPD unclassifiable.<sup>1</sup> CML is the prototype disease mainly because it was the first disease to be described clinically and morphologically and the first to be explained by specific cytogenetic and molecular abnormalities. It was also the first disease in which a therapeutic agent was developed to target the molecular defect specific to it.

For many years, the diagnosis of CMPD was solely based on morphology and clinical observations. This was changed in 1960 when the first cytogenetic marker for CML was discovered. Philadelphia chromosome is a small chromosome, a product of reciprocal translocation between chromosome 9 and 22 that was subsequently found to contain a fusion gene product called BCR-

hybridization (FISH) or polymerase chain reaction (PCR), and is present in 100% of CML patients. The detection of Philadelphia chromosome and/or BCR-ABL gene, given the right clinical setting, is considered pathognomonic of CML.<sup>2</sup> The understanding of tyrosine kinase and its role in the pathogenesis of CML paved the way towards the development of a tyrosine kinase inhibitor, STI-571 (imatinib mesylate; Gleevec®), an oral medication that targets the BCR-ABL protein and induces complete hematologic, cytogenetic, and molecular remissions in many CML patients.<sup>3</sup>

It was the promise of success in molecular-targeted therapy for CML patients that inspired researchers to look for similar markers that can be used for the diagnosis and therapy of other chronic myeloproliferative diseases (BCR-ABL negative CMPD). It was not until 2005 that a unique marker for BCR-ABL negative CMPD, JAK2 V617F, was reported by six groups of investigators. JAK2, also called “just another kinase” or “Janus kinase” after the Roman God of Gates, is a cytoplasmic tyrosine kinase. In JAK2 V617F mutation, valine is replaced by phenylalanine in codon 617 of the JH2 domain. This removes the inhibition of JH2 to kinase domain JH1, which results in JAK2 autophosphorylation, activation

### Conclusion

The discovery of JAK2 V617F and similar mutations has opened opportunities for further research, foremost of which is the possibility for a molecular-targeted therapy against JAK2 V617F similar to the success of Gleevec® in the therapy of CML. Although this has yet to be developed, the trend in the field of myeloproliferative neoplasms these days is toward a classification system that is based on genetic and molecular markers specific and relevant to the diagnosis, therapy, and monitoring of the neoplasms. The

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## New Board Members



Linda Elvin, MLT District 2 Director

After obtaining certification in 1987, I began my career working in a private laboratory in Toronto. I soon decided to get back to my roots in Northern Ontario and covered maternity leaves at various hospitals until a full time position became available at St. Joseph's General Hospital in Elliot Lake, where I have been employed for 19 years.

There have been many changes to healthcare over the intervening years, not the least of which was the creation of a College for Medical Laboratory Technologists of Ontario. The OSMT has always tried to be involved with these changes, informing

the members and making sure our voice is heard by all concerned parties. I have been a member of OSMT since graduation as I have felt it was one of the best ways to keep abreast of the changes affecting our profession. When the opportunity arose at the conference this year to represent District 2, I thought it was a great opportunity to get involved with an organization that has given so much to this profession, and to ensure that this area has representation on the Board.

I look forward to working with, and learning from, the many experienced Board members in the upcoming months.



Kerry Condirston, ART District 8 Director

I am very pleased to be back on the OSMT Board as Director of District 8. My previous stint was 2000 – 2004 during which time I held the position of Vice-President, President, and 2003 Conference Chair for the 40<sup>th</sup>

anniversary of the OSMT, which was held in London, ON. I believe that my previous experience on the Board of Directors will enable me to better serve the membership, and I look forward to the opportunity to do so.

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possibilities in myeloproliferative neoplasms are vast and far reaching that additional information can effect changes very fast. It is incumbent upon medical technology to keep up with the pace of development in research. The challenge to medical technology today is in the development of laboratory techniques that will increase the sensitivity and specificity of tests for these markers, standardization of procedures that will improve the reproducibility of the tests, and adequate training of laboratory personnel; thus, contributing to improvement of overall patient care. ❖

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