# The importance of cytogenetics in polycythemia vera, primary myelofibrosis and essential thrombocythemia

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In this issue of the *Revista Brasileira de Hematologia e Hemoterapia*, Santos et al. write about cytogenetics, in particular, the *JAK2* and *MPL* mutations in polycythemia vera, primary myelofibrosis and essential thrombocythemia.[1]

Myeloproliferative neoplasms (MPNs) are a heterogeneous group of clonal disorders derived from multipotent hematopoietic myeloid progenitors. The 2008 World Health Organization (WHO) classification splits them into two large groups: those that bear the BCR-ABL1 fusion protein (e.g. chronic myeloid leukemia – CML) and those that are BCR-ABL1-negative. A number of diseases are included in this latter group including mastocytosis, chronic neutrophilic leukemia, chronic eosinophilic leukemia not otherwise specified, essential thrombocythemia (ET), polycythemia vera (PV) and myelofibrosis (MF). These MPNs are not derived from a single molecular event, in contrast with CML, which is solely characterized by the BCR-ABL fusion. Instead, BCR-ABL-negative MPNs are derived from a variety of molecular abnormalities that lead to aberrant cell proliferation.[2]

Chromosomal abnormalities occur in approximately 30-40% of patients with PV or MF, while chromosomal aberrations are found infrequently (5-6%) in ET. The most common chromosomal abnormalities in MPNs are 20q-, 13q-, +8, +9 and partial duplication of 1q. Balanced translocations are rare.

Several studies have shown that an abnormal karyotype at the diagnosis of PV is associated with a poor prognosis, while the proportion of patients with an abnormal karyotype increases during the course of the disease. PV may progress to a terminal phase, which can involve transformation to myelofibrosis or acute leukemia. Almost all PV patients who develop acute leukemia in late disease stages have chromosomal abnormalities. Trisomies 8 or 9 may persist in PV without further clonal evolution or leukemia development for up to 15 years, while other chromosomal abnormalities, such as -7 or 5q- or complex changes, may signal the terminal phase of the disease.

In MF, conventional cytogenetic studies are limited due to the difficulty in obtaining adequate bone marrow aspirates and the low proliferative capacity of the clonal cells. The application of fluorescence *in situ* hybridization (FISH) techniques can partly overcome these limitations. A retrospective multivariate analysis of a series of 165 patients with MF showed that the presence of an abnormal karyotype did not carry an adverse prognosis. However, a significant difference in survival among patients with either 13q- or 20q- lesions

and those with either +8 or 12p- abnormalities was observed. A prospective FISH study of 107 MF patients correlated cytogenetic findings with clinical outcome and survival. Interestingly, FISH was superior to karyotyping in eight karyotype-normal patients, who presented various chromosomal abnormalities. The main recurrent chromosomal aberrations did not correlate with clinical features or prognosis. In contrast, patients with the 7q- or -7 chromosomal abnormalities had worse outcomes.

The number of cytogenetically studied untreated ET patients is limited. Cytogenetic abnormalities occur in less than 55% of patients at diagnosis and are non-specific and are therefore of limited value.[3]

At the molecular level, there are no specific biologic markers for MPNs, however, there are some that provide additional tools in establishing diagnosis, especially for PV.

*JAK2 V617F* is the most prevalent mutation in BCR-ABL1-negative MPN with mutation frequencies of 96% in PV, 55% in ET and 65% in MF. The presence of the *JAK2 V617F* mutation in MPN has been associated with older age, higher hemoglobin count, leukocytosis and lower platelet count. In PV, a higher mutant allele burden has been associated with pruritus and fibrotic transformation, but does appear to affect the risk of thrombosis, survival or leukemic transformation in PV and ET. The *JAK2 V617F* mutation is sufficiently prevalent in MPNs to be useful as a clonal marker, with screening of this mutation being indicated for the evaluation of erythrocytosis, thrombocytosis, splanchnic vein thrombosis and otherwise unexplained BCR-ABL1-negative granulocytosis. However, the mutation does not provide additional value in the presence of unequivocal morphologic diagnosis and its presence does not necessarily distinguish one MPN from another or provide useful prognostic information. *JAK2* exon 12 mutations are relatively specific to *JAK2 V617F*-negative PV and are diagnostically useful. Screening of these mutations is indicated only in the presence of *JAK2 V617F*-negative erythrocytosis which is associated with a subnormal serum erythropoietin level.[4]

Reduced expression of the thrombopoietin-receptor, c-Mpl, was the first molecular marker described in PV. Moliterno et al. reported a reduced expression of the c-Mpl in PV, as well as in MF, but not in patients with ET. However, subsequently, several other studies have shown conflicting results. Thus, reduced c-Mpl expression has been reported in ET patients, but at different rates. *MPL* mutations are neither frequent nor specific enough to warrant their routine use for MPN diagnosis, but they may be useful in resolving specific diagnostic problems. To date it is unclear whether this molecular change could contribute to the molecular pathology of MPNs.[5]

*MPL* and *JAK2 V617F* mutation analysis was performed in 603 patients with primary myelofibrosis (PMF) seen at the Mayo Clinic, USA (n = 329) or the University of Florence, Italy (n = 274). *MPL* mutations were detected in 49 (8.1%) patients and *JAK2 V617F* in 350 (58%); four patients showed both mutations. Patients without these mutations were significantly younger in both patient cohorts (p-value < 0.01). In the Florence cohort, the presence of the *MPL* mutation was associated with older age (p-value < 0.01) and constitutional symptoms (p-value = 0.04) and *JAK2 V617F* with higher hemoglobin (p-value < 0.01) and leukocyte counts (p-value = 0.03). Neither patient cohort showed significant associations with platelet count, hemoglobin < 10g/dL, abnormal/unfavorable karyotype, spleen size or prognostic score distribution. At the time of this publication, 240 deaths and 79 leukemic transformations were documented among all 603 study patients. Multivariable analysis showed no significant difference in overall or leukemia-free survival between the three molecular subgroups. The study concluded that the presence of the *MPL* mutation has a narrow, inconsistent phenotypic effect in PMF and does not influence overall or leukemia-free survival.

In conclusion, in MPNs, the chromosomal gains and deletions are the prominent cytogenetic findings. Cytogenetic analysis has an important role in establishing the diagnosis and disease outcome. Although the discovery of alterations of certain genes such as *JAK2* has not translated into changes in the treatment of the PV, ET and MF, it represents the most important advance in understanding the pathogenesis, contributing to a more accurate classification and management of patients.[6]

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