Impact of Bone Marrow Pathology on the Clinical Management of Philadelphia Chromosome–Negative Myeloproliferative Neoplasms☆

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Abstract

Philadelphia chromosome-negative myeloproliferative neoplasms include primary myelofibrosis (PMF), polycythemia vera (PV), and essential thrombocythemia (ET). Although these 3 entities share many pathogenic characteristics, such as dysregulated Janus kinase (JAK)/signal transducer and activator of transcription signaling, they differ substantially regarding prognosis, progression to myelofibrosis (MF), risk of leukemic transformation, and specific medical needs. Accurate diagnosis and classification of myeloproliferative neoplasms are prerequisites for appropriate risk-based therapy and should be based on an integrated approach following the World Health Organization guidelines that, in addition to clinical, molecular, and cytogenetic evaluation, includes the examination of bone marrow morphology. Reticulin fibrosis at presentation in ET and PV is associated with increased risk of myelofibrotic transformation, and higher fibrosis grade in patients with MF is associated with worse prognosis. Additional assessment of collagen deposition and osteosclerosis may further increase diagnostic and prognostic precision. Moreover, the evaluation of bone marrow pathology has become very important in the new era of disease-modifying agents. In randomized controlled phase 3 studies, the JAK1/JAK2 inhibitor ruxolitinib provided rapid and lasting improvement in MF-related splenomegaly and symptom burden as well as a survival advantage compared with placebo or best available therapy. Follow-up for up to 5 years of patients who participated in a phase 1/2 study of ruxolitinib, revealed stabilization or reversal of bone marrow fibrosis in a proportion of patients with MF. Combinations of JAK inhibitors with other therapies, including agents with antifibrotic and/or anti-inflammatory properties, may possibly decrease bone marrow fibrosis further and favorably influence clinical outcomes.

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Introduction

Classic *BCR-ABL1*–negative myeloproliferative neoplasms (MPNs) include 3 clinically distinct hematologic diseases—primary myelofibrosis (PMF), polycythemia vera (PV), and essential thrombocythemia (ET)[1,2]—that share specific somatic stem cell mutations[3] and are characterized by general dysregulation of the Janus kinase/signal transducer and activator of transcription (JAK-STAT) signaling pathway,[4] abnormal hematopoiesis, myeloproliferation, and cytokine overproduction. The most prevalent mutation in all MPNs is the *JAK2*V617F mutation, which is present in more than 95% of patients with PV and more than half of those with PMF or ET.[3] *JAK2*V617F is a gain-of-function mutation that obviates the need for binding of hematopoietic cytokines such as erythropoietin and thrombopoietin to their cognate receptors to mediate JAK-STAT activation. Most patients with MPNs who lack the *JAK2*V617F mutation have one of several other somatic mutations that lead to JAK-STAT activation, including *JAK2* exon 12 mutations, thrombopoietin receptor (*MPL*) mutations, and mutations in the calreticulin (*CALR*) gene.[3,5,6] In addition to these "driver" mutations, which are mutually exclusive, many other mutations have been described in patients with MPNs. Associations of mutations and cytogenetic aberrations with disease progression are summarized in Table 1.[5-19]

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Despite common features in their molecular pathogenesis, MPNs display key morphologic differences as well as variation in disease progression, prognosis, and medical management. A number of prognostic factors have been reported to affect the survival of patients with PMF.[19-21] The International Prognostic Scoring System (IPSS) uses a number of clinical parameters at diagnosis to assess the risk of early death in patients with PMF.[20] Median overall survival times range from 2 years for high-risk patients to 11 years for low-risk patients.[20] Subsequent modifications of the IPSS include the Dynamic IPSS (DIPSS), which allows risk stratification at any time during the clinical course,[21] and the DIPSS Plus, which also considers additional clinical parameters and karyotype features.[19] Prognostic factors associated with the risk of transformation to acute leukemia include adverse karyotype, circulating blasts $\geq$ 2%, and platelet count $\leq 50 \times 10^9$/L; the 3-year risk of leukemic transformation varies between 3% and 35%.[22]

Table 1 Effects of Mutations and Cytogenetic Aberrations in MPNs on Disease Progression

Mutations/Cytogenetic Aberration	Associated Effect
Driver mutations (mutually exclusive)	
*JAK2*V617F or *JAK2* exon 12 in PV only	High allele burden is associated with PV phenotype and increased risk of transformation to MF[8,9]
MPL exon 10 (eg, *MPL*W515)	High allele burden in ET is associated with increased risk of transformation to post-ET MF[10]
CALR exon 9	Early pathogenic event in MPNs[5-7] Favorable prognosis[6,11] Reduced risk of thrombosis in ET (vs. *JAK2*V617F)[9,12] Increased risk of MF transformation (vs. *JAK2*V617F)[5,12]
"Triple-negative" (wild-type *JAK2, MPL, CALR*)	Increased risk of LT, unfavorable prognosis in PMF[13]
Mutations in epigenetic modifiers	
ASXL1	Increased risk of LT, unfavorable prognosis in PMF[11,14]
EZH2	Unfavorable prognosis in PMF[14]
IDH1/IDH2	Increased risk of LT, unfavorable prognosis in PMF[14,15]
SRSF2	Increased risk of LT in PMF[14]
TET2	Early pathogenic event in MPNs[7] Increased risk of LT, unfavorable prognosis in MPNs[7]
TP53	Increased risk of LT, unfavorable prognosis in MPNs[7]
Cytogenetic aberrations	
Chromosome 1	Common in post-PV MF[16]
Chromosome 5, 7, or 17p	Increased risk of LT (in combination with *JAK2*V617F or *MPL* mutation)[17]
9pUPD or 9p gain	MF progression in PV[17]
Del(20q)	Common in PMF[16] Favorable prognosis, if sole abnormality[18]
Del(13q) or +9	Favorable prognosis, if sole abnormality[18]
Complex karyotype or sole or 2 abnormalities that include +8, 7/7q−, i(17q), 5/5q−, 12p−, inv(3), or 11q23 rearrangement	Unfavorable prognosis in PMF[18,19]

Abbreviations: ET = essential thrombocythemia; LT = leukemic transformation; MF = myelofibrosis; MPN = myeloproliferative neoplasms; PMF = primary myelofibrosis; PV = polycythemia vera; UPD = uniparental disomy.

Patients with PV or ET have a much longer median life expectancy and a much lower risk of leukemic transformation than those with PMF.[23,24] The primary medical concern in patients with PV is the increased risk of thrombosis, which remains a leading cause of death among these patients.[23] However, a considerable proportion of patients with PV (15%-25%) may acquire significant bone marrow fibrosis over time. When accompanied by increasing splenomegaly, anemia, systemic symptoms, leukoerythroblastosis, and other factors, this marks the transformation to post–polycythemia vera myelofibrosis (post-PV MF), an entity recognized by the World Health Organization (WHO) that is associated with outcomes similar to those of PMF. The risk of acute leukemic transformation in patients with PV increases gradually from the time of diagnosis: it is less than 3% at 10 years and 5% to 8% at 15 years and later.[23] The risk of thrombotic or hemorrhagic events is the leading concern in patients with ET, whereas disease progression to post–essential thrombocythemia myelofibrosis (post-ET MF) and leukemic transformation are relatively rare events in this MPN subtype.[25] Because patients with PMF, post-PV MF, and post-ET MF often have indistinguishable clinical features, the term "myelofibrosis" (MF) is commonly used by clinicians to collectively describe all 3 distinct entities.[26] However, notwithstanding clinical similarities, patients with different subtypes of MF may have distinct cytogenetic and morphologic characteristics related to the underlying clonal neoplasm.[16]

Diagnosis of Myeloproliferative Neoplasms: Importance of Bone Marrow Histomorphologic Assessment

Revised diagnostic criteria for PMF, PV, and ET were proposed in 2007 by an international panel of experts in hematology and hematopathology,[1] and these were adopted by the WHO in 2008 (Table 2).[2] In the same year, the International Working Group for Myelofibrosis Research and Treatment proposed criteria for the diagnosis of post-PV and post-ET MF (Table 3).[27]

Reliable diagnosis of MPNs according to WHO criteria requires an integrated approach based on morphology, genetic, and clinical criteria. Genetic mutation analysis is essential to exclude reactive polycythemias, reactive thrombocytosis, and some other myeloid neoplasms (such as *BCR-ABL1*+ chronic myelogenous leukemia) and to help establish an MPN diagnosis. However, because the somatic mutations seen in MPNs (such as *JAK2*V617F) and patient symptoms are not disease specific, even a combination of molecular and clinical criteria is often insufficient to unequivocally confirm and correctly classify MPNs, particularly at early disease stages. For example, the historically large discrepancies in the estimated rates of bone marrow fibrosis in patients with ET were likely the result of misdiagnosis of prefibrotic PMF with thrombocytosis