JAK2 V617F Mutation Status of 232 Patients Diagnosed With Chronic Myeloproliferative Neoplasms

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Abstract

The aim of this study was to investigate the presence of Janus kinase 2 (JAK2) V617F mutation in patients with BCR-ABL negative chronic myeloproliferative neoplasms (CMPNs) in our center. JAK2 V617F mutation frequencies in our PV and ET patients were similar to those reported previously. JAK2 V617F mutation frequency in our PMF patients was greater than in previous reports.

Introduction/Background: The aim of this study was to investigate the presence of Janus kinase 2 (JAK2) V617F mutation in patients with break point cluster region-abelson negative chronic myeloproliferative neoplasms (CMPNs) in our center. **Patients and Methods:** We compared patients with and without the mutation, and also patients with the homozygous and heterozygous mutation, in terms of different clinical and laboratory features. **Results:** The JAK2 V617F mutation was detected in 77 (95%), 88 (68%), and 17 (77%) of polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF) patients, respectively. Among JAK2 V617F-positive patients, the homozygous genotype was found in 39 (50.6%) of the 77 PV, 23 (26.1%) of the 88 ET, and 11 (64.7%) of the 17 PMF patients. Bleeding was seen in 14 (6%) of all patients. Upper gastrointestinal bleeds were the most common, seen in 11 patients. Out of 232 CMPN patients, 44 (19%) had thrombosis. The most common thrombotic event was transient ischemic attack (52%). Progression to myelofibrosis was seen in 1 (1.2%) PV and 3 (2.3%) ET patients, and progression to acute leukemia was seen in 2 (2.5%) PV and 3 (2.3%) ET patients. Three patients with PV (3.7%), 3 with ET (2.7%), and 5 with PMF (2.7%) died during follow-up. **Conclusion:** JAK2 V617F mutation frequencies in our PV and ET patients were similar to those reported previously. JAK2 V617F mutation frequency in our PMF patients was greater than in previous reports. All of our PV patients with thrombosis and most of our ET patients with thrombosis (76.1%) were JAK2 V617F mutation-positive. This mutation seems to be correlated with thrombosis risk.

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Introduction

Polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF) are classified in the break point cluster region-abelson (BCR-ABL1) negative myeloproliferative neoplasm (MPN) group according to World Health Organization (WHO) 2008 classification.[1] Their disease-causing mutations remain unidentified despite many mutations described beginning in 2005. PV patients mostly harbor Janus kinase 2 (JAK2; 9p24) mutation (96% displaying mutation in exon 14, JAK2 V617F; 3% displaying mutation in exon 12; JAK2).[2,3]

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Janus kinase 2 V617F also occurs in ET (55%) and PMF (65%), but JAK2 exon 12 mutations are rare in ET and PMF.[4] Myeloproliferative leukemia virus oncogene (MPL) (MPL515W>L/K) mutations are found in approximately 4% of ET, 8% of PMF, and rarely in PV.[5] According to the 2008 WHO classification, the existence of these mutations is the major criterion in diagnosis of chronic MPNs.[1] Nonetheless, evaluation of bone marrow histopathology is still required to define the specific morphological patterns, which are essential for the diagnosis of ET and PMF. Other mutations related to the tet oncogene family member 2 (TET2), additional sex comb-like 1 (ASXL1), and isocitrate dehydrogenase (IDH1/2) genes are occasionally observed in MPNs.[6] Because the molecular pathogenesis of MPNs with nonmutated JAK2 is still obscure and diagnosis remains a challenge, the mutation status of the gene encoding calreticulin (*CALR*) was studied recently by Nangalia et al.[7] CALR mutations were found in most patients with MPNs with nonmutated JAK2.[7]

Leukocytosis, splenomegaly, thrombohemorrhagic complications, vasomotor disturbances, pruritus, and a small risk of disease progression into acute myeloid leukemia or myelofibrosis are other disease features.[4] In previous studies, the importance of mutational status of JAK2 was evaluated.

Correlations have been found between high JAK2 V617F allele burden and leukocytosis, spleen size, myelofibrosis severity, fibrotic transformation, and disease duration.[8] Many researchers have reported thrombosis risk in JAK2 V617F-positive ET patients to be greater than that of JAK2 V617F-negative ET patients.[9-11] The effect of the JAK2 V617F mutation on clinical parameters of PMF such as prognosis and the need for transfusion is unclear.[12,13] JAK2 V617F mutated status has not been shown to have an effect on survival time, but patients with low JAK2 V617F allele burden have been reported to have shorter survival times compared with those with high JAK2 V617F allele burden and wild type JAK2.[14]

In this study, we aimed to investigate the relationship between JAK2 status/quantitation and clinic and laboratory findings in our MPNs patients.

Patients and Methods

Demographic and clinical features of 233 patients diagnosed with MPNs at our hematology department between November 2000 and November 2012 were evaluated retrospectively. The median age was 63 years (range, 18 to 89 years) with a male to female ratio of 0.9 to 1 (110 men, 123 women). BCR-ABL molecular analysis and fluorescence in situ hybridization analysis for t(9;22) were made in all MPN patients and found as not amplified. During retrospective evaluation, 1 male patient was excluded from the study because of diagnosis of chronic myelomonocytic leukemia. Eighty-one patients were rediagnosed with PV (34.9%), 129 with ET (55.6%), and 22 with PMF (9.5%) according to polycythemia vera study group or WHO 2008 criteria. White blood cell (WBC), hemoglobin (Hb), and hematocrit (htc) levels, and platelet (plt) count, and serum lactic dehydrogenase (LDH) level were recorded. Spleen size was measured in centimeters below the midpoint of the left costal margin, and spleen size > 5 cm was accepted as gross splenomegaly. JAK2 V617F analysis was performed at the time or after the time of diagnosis depending on the availability of this test. Thrombotic and hemorrhagic events before or after diagnosis were recorded. Clinical thrombotic events included ischemic stroke, cerebral transient ischemic attack (TIA), acute myocardial infarction (AMI), peripheral arterial thrombosis (PAT), pulmonary thromboembolism (PE), and venous thromboembolism (VTE). Most patients received 1 or more of the following: acetyl salicylic acid (ASA), some form of myelosuppressive therapy as hydroxyurea (HU), anagrelide, interferon (IF), phosphorus-32 (P-32). Patients with PV were phlebotomized to maintain an htc level $\leq 45\%$. This study was approved by the local ethics committee.

Quantification of JAK2 V617F mutation was detected using an allele-specific real-time quantitative polymerase chain reaction (RQ-PCR) assay (JAK2 MutaQuant Kit, Ipsogen). RQ-PCR was performed using a Rotor-Gene (Corbett Research). Patients with $\geq 50\%$ mutational load and those with $< 50\%$ mutational load were considered 'homozygotes' and 'heterozygotes,' respectively, as has been previously designated.[15,16]

Table 1 Characteristics of 232 Patients With MPNs

	MPN	PV (81 Pts)	ET (129 Pts)	PMF (22 Pts)
M/F	109/123	30/51	65/64	14/8
Mean Age (Minimum-Maximum), Years	59.9 (18-89)	62 (35-86)	58 (18-89)	62.8 (32-85)
Splenomegaly, n (%)	125 (59.8)	46 (67.6)	57 (47.5)	22 (100)
Thrombosis, n (%)	44 (19)	23 (28.3)	21 (16.3)	NR
Bleeding, n (%)	14 (6)	4 (4.9)	10 (7.6)	NR
Diabetes Mellitus, n (%)	29 (12.5)	12 (14.8)	16 (12.4)	1 (4.5)
Hypertension, n (%)	42 (18.1)	15 (18.5)	25 (19.4)	2 (9)
Mean Hemoglobin Level ± SD, g/dL	14.6 ± 3.0	17.6 ± 1.8	13.26 ± 2.0	11.3 ± 1.9
Mean Hematocrit Level ± SD, %	13.6 ± 10.3	53.6 ± 5.9	39.8 ± 8.3	33.6 ± 5.5
Mean Leukocyte Count ± SD, × 10^9/L	15.2 ± 8.0	15.2 ± 5.6	13.7 ± 5.9	23.9 ± 16.6
Mean Thrombocyte Count ± SD, × 10^9/L	344.7 ± 22.9	646.9 ± 268.4	971.0 ± 319.9	344.6 ± 73.5
Mean Serum LDH ± SD, U/L	313.7 ± 219	297 ± 115	271.9 ± 110.5	648.1 ± 556.2

Abbreviations: ET = essential thrombocythemia; F = female; LDH = lactic dehydrogenase; M = male; MPN = myeloproliferative neoplasm; PMF = primary myelofibrosis; pts = patients; PV = polycythemia vera.