

Janus kinase 2 mutations in cases with BCR-ABL-negative chronic myeloproliferative disorders from Turkey

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ABSTRACT

Objective: We aimed to investigate the frequency of Janus kinase 2 (JAK2) mutations in cases with chronic myeloproliferative disorders (CMDs), and the relationship between the presence of JAK2 mutation and leukocytosis and splenomegaly, retrospectively. **Materials and Methods:** Patients, who were diagnosed with BCR-ABL-negative CMDs according to diagnosis criteria of the World Health Organization and followed up at the hematology clinic between 2013 and 2015, were investigated in terms of the frequency of JAK2 mutation in cases with CMDs, and the relationship between the presence of JAK2 mutation and leukocytosis and splenomegaly, retrospectively. **Results:** In total, 100 patients, who were diagnosed with BCR-ABL-negative CMDs, were evaluated retrospectively. The mean age of the patients with JAK2 positivity was significantly higher compared to patients with negative. JAK2-positivity rates in the age groups were significantly different. Gender, diagnosis, splenomegaly, and leukocytosis were not statistically different for JAK2 positivity between the groups. **Conclusion:** JAK2 V617F mutation is more commonly seen in older age as a risk for complications related to CDMS. Splenomegaly and leukocytosis are not associated with JAK2 V617F mutation.

Key words: Chronic myeloproliferative disorders, Janus kinase 2 V617F mutation, leukocytosis, splenomegaly

INTRODUCTION

Chronic myeloproliferative disorders (CMDs) are associated with proliferation in one or more hematopoietic cell groups, and clonal hematopoietic disorders. CMDs are divided into four different groups in traditional classifications of Dameshek: Chronic myeloid leukemia (CML), polycythemia vera (PV), essential thrombocytosis (ET), and primary myelofibrosis (PMF).^[1] CML is characterized by t (9;22) mutual replacements between chromosomes 9 and 22. The other diseases in this group, PV, ET, and PMF, are known as BCR-ABL-negative myeloproliferative disorders.^[2,3] Diagnostic criteria (major) of classical CMDs

have been updated with the discovery of the Janus kinase 2 (JAK2) mutation that was detected in almost all cases of PV, in approximately 50%–70% of ET and 40%–50% of PMF patients as JAK2 mutation has taken place in the criteria.^[3] JAK2 is constitutively active tyrosine kinase, which activates the JAK-STAT signal transduction. JAK-STAT pathway is especially important for hematopoiesis. It allows cell proliferation, differentiation, and the regulation of apoptosis

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in the cell. After defining JAK2 V617F mutation in patients with CMDs in 2005, JAK2 exon 12 mutations in JAK2 V617F-negative PVR patients and thrombopoietin receptor mutation (MPLW515 L) in a minority of 5% of cases with ET and PMF were discovered.^[3]

Information about the pathogenesis of BCR-ABL-negative CMDs has increased, diagnosis algorithms information has developed, and new options have emerged for advanced treatment after discovery of JAK2 V617F mutations in cases with CMDs. The frequency of the mutation was reported to be 90%–95% in PV patients, 50%–70% in ET, and 40%–50% in PMF patients. Recent studies are about the relationship between the presence of JAK2 mutation and risk factors, such as thrombosis, including age at diagnosis, presence of leukocytosis, and signs and symptoms, such as organomegaly and itching.^[4,5] The presence of the JAK2 mutation in ET is related to advanced age, increased hemoglobin, increased leukocyte counts, and decreased platelet counts.^[6] JAK2 has been found to be positive in almost all of the cases with PV, hemoglobin, and leukocyte levels were higher, and platelet count was lower in the heterozygous genotype group compared to homozygous genotype group.^[4] It was reported that JAK2 V617F-positive PMF cases have higher leukocyte count and larger spleen size, a history of thrombosis or pruritus, greater need for cytoreductive therapies, and require less transfusion during follow-up.^[4,7,8] In this study, we aimed to investigate the frequency of JAK2 mutation in cases with CMDs, and the relationship between the presence of JAK2 mutation and leukocytosis and splenomegaly, retrospectively.

MATERIALS AND METHODS

Patients, who were diagnosed with BCR-ABL-negative CMDs according to diagnosis criteria of the World Health Organization and followed up at the hematology clinic of Ministry of Health Istanbul Training and Research Hospital between 2013 and 2015, were investigated in terms of the frequency of JAK2 mutation in cases with CMDs, and the relationship between the presence of JAK2 mutation and leukocytosis and splenomegaly, retrospectively.^[3] Splenomegaly was defined by >12 cm diameter.^[9] Polymerase chain reaction-based DNA sequencing method has been performed for detection JAK2 V617F mutation in whole blood samples of the patients.

Statistical analysis

SPSS 15.0 (SPSS Inc, Chicago, IL) for Windows was used for statistical analysis. Numbers and percentages for categorical variables and minimum, maximum, mean, and standard deviation for numeric variables were given for

descriptive statistics. Quantitative comparison of two groups of independent variables was performed by Mann–Whitney U-test. Rates of categorical variables between the groups were analyzed by Chi-square test. If conditions were not provided, Monte Carlo simulation was performed. Statistical significance was considered as alpha level of $P < 0.05$.

RESULTS

In total, 100 patients, who were diagnosed with BCR-ABL-negative CMDs, were evaluated retrospectively. The mean age was 56.8 ± 15.1 years, and 53 patients were female. Distribution of disorders was 68 with ET, 23 with PMF, and 9 with PV [Table 1]. Splenomegaly was examined in 46 patients, and 44 patients had leukocytosis. Rates of JAK2 gene positivity were 64% ($n: 64$). The mean age of the patients with JAK2 positivity was significantly higher compared to patients with negative ($P: 0.014$). JAK2-positivity rates in the age groups were significantly different ($P: 0.002$, Table 2). Gender ($P: 0.089$), diagnosis ($P: 0.495$), splenomegaly ($P: 0.253$), and leukocytosis ($P = 0.233$) were not statistically different for JAK2 positivity in the groups [Table 3].

DISCUSSION

JAK2, which is the somatic mutation of V617F and detected in different percentages in different subgroups of CMDs, is usually determined in DNA obtained from peripheral

Table 1: Characteristics of the patients with chronic myeloproliferative disorders

	n
Age group (years)	
20-29	6
30-39	5
40-49	23
50-59	19
60-69	25
70-79	14
80-89	8
Gender	
Female	53
Male	47
Diagnosis	
Essential thrombocytosis	68
Polisitemia vera	23
Primary myelofibrosis	9
Splenomegaly	
Positive	46
Negative	54
Leukocytosis	
Positive	44
Negative	56
JAK2	
Positive	64
Negative	36
JAK 2: Janus kinase 2	

Table 2: Janus kinase 2 positivity by age groups

Age group (years)	JAK 2, n (%)		P
	Positive	Negative	
Essential thrombocytosis			
20-29	6 (100)	0	0.019
30-39	2 (66.7)	1 (33.3)	
40-49	5 (31.3)	11 (68.8)	
50-59	6 (50.0)	6 (50.0)	
60-69	11 (64.7)	6 (35.3)	
70-79	9 (81.8)	2 (18.2)	
80-89	3 (100)	0	
Primary myelofibrosis			
40-49	0	2 (100.0)	0.015
50-59	1 (100)	0	
60-69	4 (100)	0	
70-79	0	2 (100.0)	
Polisitemia Vera			
30-39	1 (50.0)	1 (50.0)	0.065
40-49	2 (40.0)	3 (60.0)	
50-59	6 (100)	0	
60-69	2 (50.0)	2 (50.0)	
70-79	1 (100)	0	
80-89	5 (100)	0	

JAK 2: Janus kinase 2

Table 3: Rates of leukocytosis and splenomegaly by Janus kinase 2 positivity

	JAK 2, n (%)		P
	Positive	Negative	
Essential thrombocytosis			
Leukocytosis			
Positive	9 (27.3)	24 (72.7)	0.071
Negative	17 (48.6)	18 (51.4)	
Splenomegaly			
Positive	9 (33.3)	18 (66.7)	0.450
Negative	17 (42.5)	23 (57.5)	
Primary myelofibrosis			
Leukocytosis			
Positive	2 (66.7)	1 (33.3)	0.524
Negative	2 (33.3)	4 (66.7)	
Splenomegaly			
Positive	4 (44.4)	5 (55.6)	-
Negative	0	0	
Polisitemia vera			
Leukocytosis			
Positive	2 (25.0)	6 (75.0)	1.000
Negative	4 (26.7)	11 (73.3)	
Splenomegaly			
Positive	17 (42.5)	23 (57.5)	0.179
Negative	5 (38.5)	8 (61.5)	

JAK 2: Janus kinase 2

blood leukocyte by genomic polymerase chain reaction and restriction enzyme-based assay.^[5] Since 2005, when screening of JAK2 mutation has begun, it was reported that the rates of correct ET diagnosis have increased by 31% and the rates of correct PV diagnosis have decreased by 21%.^[10] In our study, the frequency of the JAK2 V617F mutation has been found 73% in PV patients, and 61% in ET, as those rates were found to be lower in PV patients compared to reported rates.^[11] JAK2 mutation has been found in five

of nine cases (55%) with PMF. Although the number of patients in this group is few and not sufficient for statistical interpretation, the presence of the mutation in the PMF group could be shown. In previous studies, the frequency of the JAK2 V617F mutation in PMF patients was reported by 50% that is consistent with our rates with 55%. In addition, the frequency of the JAK2 mutation was not significantly different in both sexes.^[12] In a study of 140 cases with CMDs, the presence of JAK2 mutation found 82% (23/28) in PV cases, 53.1% (17/32) in ET patients, 40% (4/10) in PMF cases, and 60% (6/10) in other indistinguishable CMD cases.^[13] In another study conducted in Taiwan, Lieu *et al.* screened JAK2 mutation in the 108 CMDs cases, and it was found positive in 85% (28/33) PV cases, 59% of patients (29/49) in ET patients, 33% (2/6) in PMF cases, 0/11 in MDS patients, and 0/10 in the other cases with 10 different hematological diseases.^[14]

JAK2 V617F mutation is known to stimulate the proliferation causing growth factor hypersensitivity on the progenitor hematopoietic cells. A significant relationship was found between the presence of JAK2 positivity, splenomegaly, high leukocyte count, and higher hemoglobin levels; however, there was no correlation between JAK2 positivity thrombosis and hemorrhage risk.^[14] A significant increase in spleen size has been observed in PMF cases that JAK2 V617F mutation is homozygote.^[11] A significant increase in spleen size has been reported to be in patients with PV JAK2 V617F allele burden more than 75%.^[15] A higher frequency of JAK2 mutation has been reported to be in ET patients with organomegaly.^[16] There was no relation between the presence of mutations and the presence of splenomegaly in the time of diagnosis in our PV and ET patient groups. The study that Carobbio *et al.* evaluated the relationship between the presence of leukocytosis in ET patients and risks observed in CMDs revealed that leukocytosis is a risk factor for thrombosis.^[12] It has not found a relationship between the JAK2 V617F allele burden and leukocytosis. In our study, there was no significant relationship between JAK2 mutation and the presence of leukocytes at diagnosis.

Higher leukocytes and platelet counts have been reported to be in PV patients with JAK2 mutation compared to those without JAK2 mutation, and elevated hemoglobin values were found in patients with JAK2 negative. Higher leukocyte counts, elevated hemoglobin values and thromboembolic events, have been reported to in ET cases with JAK2 mutation.^[17] Ha JS *et al.* revealed that there was no relationship between the presence of leukocytosis and JAK2 positivity.^[16] Likewise, in our study, there was no significant relationship between cases with leukocytosis

and those without leukocytosis in terms of frequency of JAK2 in three groups. In a study evaluating the relationship between the presence of JAK2 mutation and thrombosis, hemorrhage, and some clinical signs and symptoms in 157 cases with CMDs between 2003 and 2013, both arterial and venous thrombosis risks were the most common in PV group (29%), followed by in the ET group (14%), and 0% in PMF group; however, bleeding was mostly observed in PMF group (17%), followed by 11% in ET, and 7% in PV, respectively.^[18] In addition, it was reported that JAK2 V617F mutation is more frequently higher in older age, and those patients have a higher risk of thrombosis.^[19] In another study that evaluated 135 cases with CMDs, JAK2 was found positive in 95 cases (95/135) and levels of JAK2 V617F mRNA were found higher in patients above 60 years of age compared to patients younger than 60 years of age.^[20] JAK2 positivity was found to be higher in older ages, but there was no significant relation between JAK2 positivity and leukocytosis in our study. A study that contains a larger patient group is needed for an accurate conclusion.

Limitations of our study are the small sample size that was evaluated from a single center, retrospectively. The JAK2 mutation rates can vary in different provinces depending on the number of cases. A prospective, multicenter study with a big sample size may present the exact mutation rates. The relationship between thrombosis/hemorrhage complications and JAK2 positive/negativity could not be evaluated; as another limitation of our study is that relevant data of patients could not obtain.

CONCLUSION

JAK2 V617F mutation is more common in ET and PMF cases and the elderly cases. It poses a risk factor for developing complication in cases with CDMs. The presence of JAK2 mutation is not related to gender, splenomegaly, and higher leukocyte count.

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Conflicts of interest

There are no conflicts of interest.

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