JAK2 V617F Mutational Burden and Clinical Findings Relationship in Myeloproliferative Neoplasms

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Research Article

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Abstract

Background: Philadelphia-negative chronic myeloproliferative neoplasms(MPN) are associated with various genetic abnormalities. JAK2 V617F mutation is the most common one and important for diagnosis. We aimed to evaluate JAK2 mutation status and clinical parameters relationship of the MPN patients referred to our clinic.

Methods and Results: We evaluate 143 JAK-2 positive patients diagnosed with polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF). JAK2 mutational burden was higher in PV and PMF than ET. Laboratory findings were different in MPN groups and higher –lower JAK2 mutational burden groups. JAK2 mutational burden was correlated with spleen size and LDH level, particularly in PMF. There was no significant difference in age, gender, jak2 mutation burden and laboratory findings in patients with and without thrombosis and bleeding. Common treatment protocols were acetylsalicylic acid (ASA) + hydroxyurea, ASA and ASA + phlebotomy and others respectively. JAK2 mutational burden, mean age and LDH level were higher significantly in the patients treated with ASA+ hydroxyurea than the patients treated with ASA.

Conclusion: We speculate that if the spleen size in MPN is as large as the massive splenomegaly and the LDH level is high, the JAK2 mutation burden may tend to be higher. This relationship is more pronounced for PMF.

Introduction

Philadelphia-negative chronic myeloproliferative neoplasms (Ph-negative MPNs) consist of polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF) mainly[1]. Ph-negative MPNs are associated with various genetic abnormalities. Janus kinase 2 (JAK2), a protein tyrosine kinase gene, is one of these abnormalities. It is associated with cellular growth and proliferation. The most common genetic mutation found in Ph-negative MPNs is the JAK2 V617F mutation in which phenylalanine replaces valine as a result of a point mutation in Codon 617. This mutation increases tyrosine phosphorylation activity resulting in hypersensitivity of hematopoietic progenitor cells to growth factors [2, 3]. JAK2 gene is located on the short arm of chromosome 9[4].

The JAK2 V617F mutation occurs in approximately half of ET and PMF patients and in 90% of PV patients. Other common genetic abnormalities in MPNs are mutations in CALR and MPL. JAK2, CALR and MPL mutations have been among WHO's MPN diagnostic criteria[5].

Testing for JAK2 V617F mutation in MPN should be performed routinely for diagnosis as well as for prognosis. In addition, it is thought that the mutation burden may be associated with complications related to the disease[1, 6]. The clinical course of myeloproliferative diseases is known to be quite heterogeneous. It has been stated that JAK2V617 positivity is associated with clinical heterogeneity[7–9]. ASA, phlebotomy and hydroxyurea are recommended treatment choices for the patients. When hydroxyurea cannot be used due to its side effects, interferon-alpha, JAK-2 inhibitors(ruxolitinib) or

busulfan are recommended[10]. Herein,in this study we aimed to evaluate JAK2 mutation status and clinical parameters relationship of the MPN patients referred to our clinic.

Methods

The patients who were detected for JAK-2 mutation between 2019–2020 in our clinic were screened.. We identified 143 JAK-2 positive patients among 844 patients who were examined(16.94%). Patients demographics are in the Table 1. In addition, we evaluated the laboratory parameters, clinical follow-up and thrombotic complications of these JAK-2 positive patients. This study was approved by Ataturk University Clinical Research Ethic Commitee(decision number: B.30.2.ATA.0.01.00/521).Written informed consent was obtained from the participants. Our study complies with the Helsinki Declaration principles.

Table 1
JAK2 mutational burden and patient demographics

		diagnosis			**Total**	
		PV	**ET**	**PMF**		
JAK2 (1–49%)	Count	53	30	9	92	
	% within diagnosis	58.9%	88.2%	47.4%	64.3%	
JAK2(50–100%)	Count	37	4	10	51	
	% within diagnosis	41.1%	11.8%	52.6%	35.7%	
Total	Count	90	34	19	143	
	% within diagnosis	100%	100%	100%	100%	
		diagnosis			Total	**Mean age(std)**
		PV	**ET**	**PMF**		
male		56(62.2%)	14 (41.2%)	13 (68.4%)	83 (58%)	59.47 (std:14.99)
female		34(37.8%)	20 (58.8%)	6 (31.6%)	60 (42%)	60.37 (std:15.78)
Total		90(100%)	34 (100%)	19 (100%)	143 (100%)	60.29 (std:14.81)

DNA isolation from patient blood samples was performed with EZ1 DNA blood 200 µL (Qiagene)kit. DNA quality was standardized by measuring with nanodrop. Real-time PCR study was performed with 25 ng of

purified DNA. *ipsogen* JAK2Muta*Quant* Kit(Qiagene) was used for the detection and quantification of the JAK2 V617F/G1849T somatic mutation in the Rotor Gene-Q PCR system. Mutation analysis performed by the software of the PCR.

Statistical analysis

The statistical analysis of laboratory results and patients' data were evaluated with SPSS version 20. Categorical data were compared with the Pearson Chi-square test. Kolmogorov-Smirnov/Shapiro-Wilk test was used to determine the distribution of continuous variables, normally distributed data were presented as mean and standard deviation (SD) and continuous data that did not show normal distribution were presented as median and interquartile range (IQR). Mann-Whitney U-test and Kruskal-Wallis tests were performed for independent samples. Statistical significance will be considered as $p < 0.05$.

Results

There were 90 (62.9%) PV, 34 (23.8%) ET and 19(13.3%) PMF patients in total of 143 patients. Male/female: 83/60(58/42%). Mean age in males was 59.47(std:14.99) and in females was 60.37(std:15.78)(Table 1)

When laboratory findings were evaluated according to diagnosis, WBC, RBC, Hgb, Htc, neu, erythropoietin and JAK2 mutational burden showed significant differences between groups. Htc, RBC, Hgb values were higher in PV group compared to ET and PMF groups ($p < 0.05$) .WBC and neu were higher in PV group than ET group ($p < 0.05$) .plt was higher in ET group than PV and PMF groups ($p < 0.05$)(Table 2). JAK2 mutational burden was different significantly in terms of diagnosis. ($p < 0.05$). (Fig. 1)

Table 2
Laboratory findings, demographics and diagnosis

	PV	ET	MF	P value
	Median(IQR)	Median(IQR)	Median(IQR)	
Hgb(g/dL)	16.10(3.67)	15(3.38)	13.90(9.30)	0.000*
Htc(%)	50.15(11.38)	44.65(10.53)	38.40(4.8)	0.000*
RBC(x 10^{12}/L)	6.26(2.19)	5.32(1.49)	4.60(0.95)	0.000*
WBC (x 10^9/L)	12.44(8.70)	10.15(3.38)	13.90(9.30)	0.018*
neu x 10^9/L	9.06(7.88)	7.08(3.08)	9.69(9.86)	0.002*
plt (x 10^9/L)	570(452.25)	641(242)	288(354)	0.000*
lymp x 10^9/L	2.01(1.23)	2.25(0.85)	1.70(0.94)	0.068
uric asid(mg/dL)	6.10(2.30)	5.60(2.08)	5.75(3.18)	0.159
LDH(U/L)	350(207)	286(153)	461(352)	0.248
erythropoietin (mU/ml)	3.03(3.65)	4.89(2.83)	20.31(36.20)	0.000*
JAK2%	33.50(35)	22.50(18)	50(45)	0.000*
spleen size(mm)	136.5(51)	140(51)	184.5(80)	0.009*
age	64(24)	61(23)	65(13)	0.473
	N(%)	N(%)	N(%)	total
patients	90(62.9%)	34(23.8%)	19(13.3%)	143(100%)
female	34(37.8%)	20(58.8%)	6(31.6%)	60(42%)
male	56(62.2%)	14(41.2%)	13(68.4%)	83(58%)

(Htc:hematocrit, Hgb:hemoglobin, RBC:red blood cell, WBC:White blood cell, neu:neutrophil, plt:platelet, lymp:lymphocyte, LDH:lactate dehydrogenase) (*significant p value)

According to JAK2 mutational burden, two groups were formed as ≥ 50% and < 50%. 92(64.3%)patients were in < 50% mutational burden group and 51(35.7%) patients were in ≥ 50% mutational burden group. When laboratory findings were evaluated according to these groups, WBC, Hgb, neu, plt, LDH values showed significant differences between groups. WBC, neu, LDH levels, spleen size (Fig. 1)and median age were higher in the high mutational burden group ($p < 0.05$). Gender was not a significant factor($p > 0.05$). (Table 3).

Table 3
Laboratory findings in terms of JAK2 mutational burden

	JAK2%(1–49)	JAK2%(50–100)	p value
	Median(IQR)	Median(IQR)	
Hgb(g/dL)	15.65(3.20)	13.50(4.60)	0.005*
Htc(%)	49.30(9.60)	47.10(16.10)	0.141
RBC(x 10^{12}/L)	5.82(1.63)	5.15(3.11)	0.677
WBC(x 10^9/L)	10.325(4.98)	16.130(10.52)	0.000*
Neu (x 10^9/L)	7.26(4.28)	12.54(8.87)	0.000*
plt(x 10^9/L)	644(397.5)	439.(364)	0.001*
lymp (x 10^9/L)	2.11(1.03)	2.14(1.25)	0.066
uric asid (mg/dL)	5.72(1.84)	6.76(2.50)	0.3
LDH(U/L)	287(159)	436.5(241))	0.003*
eritropoetin(mU/ml)	4.31(4.54)	3.34(4.37)	0.5
age	61(22)	65(16)	0.003*
spleen size(mm)	133(48)	162(76)	0.002*
	N(%)	N(%)	
patients	92(64.3%)	51(35.7%)	
female	38(63.3%)	22(36.7%)	0.8
male	54(65.1%)	29(34.9%)	

(Htc:hematocrit, Hgb:hemoglobin, RBC:red blood cell, WBC:White blood cell, neu:neutrophil, plt:platelet, lymp:lymphocyte, LDH:lactate dehydrogenase)(*significant p value)

Thrombosis was occured in 26(%18.2) patients of 143 and in three(2.1%) patients gastrointestinal bleeding was occured. Of the patients with thrombosis, four had cerebrovascular event, two had pulmonary thromboembolism, 10 had myocardial infarction, four had pulmonary vein thrombosis, two had splenic vein thrombosis, one had deep vein thrombosis and one had digital arterial thrombosis. When the groups with and without thrombosis were compared, there was no statistical difference in age, JAK2 mutational burden, spleen size and laboratory findings. Only lymphocyte count was lower ($p < 0.05$). Gender was not a significant factor($p > 0.05$). 18 PV, seven ET and one PMF patients were in the thrombosis group.

Those with a spleen size ≥ 160mm in the USG were considered massive splenomegaly and those 130-160mm were considered mild splenomegaly. Laboratory findings were evaluated according to mild and massive SM groups and Htc, Hgb, plt, LDH, lymp, JAK2 mutational burden values showed significant differences between groups(p < 005). RBC, Htc, Hgb, plt, lymp were higher in the mild splenomegaly group and LDH, JAK2(%) were higher in the massive splenomegaly group. Gender, age and thrombosis were not a significant factors (p > 0.05) (Table 4) Massive splenomegaly rate was 57.1% in the group of JAK2 ≥ 50% mutation burden. Splenomegaly was found to be associated with JAK2 mutation burden (p: 0.002). (Table 2) Massive splenomegaly rate was 48.7% in PV, 35.3% in ET and 83.3% in PMF patients. PMF group was significantly different from other groups(p:0.009)

Table 4
Laboratory findings in terms of splenomegaly groups

	Spleen size(130-159mm)	**Spleen size(≥ 160mm)**	**p value**
	Median(IQR)	Median(IQR)	
Hgb(g/dL)	15.30(4.05)	12.60(4.30)	0.003*
Htc(%)	48.40(11.90)	40.20(13.20)	0.006*
RBC(x 10^{12}/L)	5.91(2.20)	4.80(2.22)	0.008*
WBC(x 10^{9}/L)	11.02(8.14)	11.46(12.43)	0.830
neu (x 10^{9}/L)	7.67(7.39)	8.80(8.38)	0.480
Plt(x 10^{9}/L)	623(304.5)	391(336)	0.005*
lymp(x 10^{9}/L)	2.19(1.18)	1.41(1.00)	0.018*
uric asid (mg/dL)	5.90(2.60)	6.60(2.85)	0.299
LDH(U/L)	315(216)	504(224.75)	0.007*
eritropoetin(mU/ml)	3.65(3.55)	4.04(4.31)	0.716
JAK2%	30(29)	52(40)	0.004*
age	64(17)	64(25)	0.917
spleen size(mm)	138.30(14)	180(54)	0.000*
	N(%)	N(%)	
patients	33(48.53%)	35(51.47%)	
*significant p value, independent samples mann -whitney u test			

We also evaluate the treatment protocols of the patients. Most of the patients were treated with acetylsalicylic acid(ASA) + hydroxyurea (59.4%) and 64.7% of the patients using this treatment were PV

patients, 22.4% were ET, 12.9% were PMF patients. The second most common treatment option were ASA (14.7%) and ASA + phlebotomy (14.7%). 71.4% of the patients with treated with ASA were ET, 23.8% were PV, 4.8% were PMF patients. 100% of the patients with treated with ASA + phlebotomy were PV patients. The other treatment protocols were ASA + ruxolitinib in 4.2%, ASA + Interferon-α(IFN-α) in 3.5%, ruxolitinib in 1.4%, clopidogrel + hydroxyurea in 0.7%, hydroxyurea in 0.7% and allogenic bone marrow transplantation in 0.7%. Htc and lymp level were higher and age was lower significantly in the patients treated with ASA + phlebotomy than the patients treated with ASA + hydroxyurea. JAK2 mutational burden, mean age and LDH level were higher significantly in the patients treated with ASA + hydroxyurea than the patients treated with ASA.

Discussion

We evalute JAK2-V617F positive MPN patients with laboratory findings, trombosis status and treatments. There were studies evaluating MPN patients with and without JAK2-V617F mutation in only PV [9], only in ET [7, 11–14] ,both in PV and ET[15–17] or in ET and PMF[1] or in PV, ET, PMF [18]. In these studies; in JAK2 positive group, Hgb[15, 19], Htc [1, 11, 12, 16],RBC[17] levels were higher and plt [1, 11, 12, 15, 17] levels were lower significantly. In other various studies WBC[1, 15–17, 19]and neu[7] were also higher significantly. In our study we evaluated PV, ET and PMF patients who had already JAK2 mutation.

There were studies evaluating JAK2 mutational burden in MPN patients similar to our study. In the study of Tefferi et al., JAK2 heterozygous and homozygous PV patients were compared and no statistical difference was found in age, gender, leukocyte or platelet count or thrombosis or bleeding cases at the time of diagnosis. However, in homozygous patients, a significantly higher hemoglobin level at the time of diagnosis, increased pruritus, higher rate of fibrotic transformation were found[9]. In the study of Zhou et al., JAK2V617F mutational burden was found to be significantly higher in PV compared to ET and PMF. It was reported that the JAK2 mutational burden was positively correlated with WBC and plt counts in ET patients and in PV patients with WBC and RBC counts [17]. In the study of Liu et al., high to low JAK2 mutation burden was determined in patients with PV, PMF and ET, respectively. Patient age and WBC in PV, WBC in ET and Hgb, WBC, plt count in PMF were significantly correlated with higher mutation burden[18]. In our study, Htc, Hgb, RBC were higher significantly in PV group comparing to ET and PMF groups, consistent with previous studies[15, 17] and WBC, neu were higher significantly in PV group comparing to ET group. JAK2 mutational burden was higher significantly in PV and PMF group comparing to ET group. The levels of lymp, LDH, uric acid were not different in the different diagnosis groups. Eritropoetin was higher significantly in PMF group. In addition WBC, neu, LDH and age were higher significantly in JAK2(≥ 50%) mutational burden group and plt, Hgb were higher in JAK2 (< 50%) mutational burden group. Contrast to our study. Vanucchi et al indicated that age, Htc, WBC levels were not different in terms of diagnosis of PV or ET. In various studies, LDH levels were not different in JAK2 mutant patients[1, 7, 14, 20] while in another studies, LDH was different consistent with our study[21] .

In the study of Kittur et al., it was stated that JAK2 mutational burden was associated with splenomegaly and male gender in ET patients[11].There were various studies that stated splenomegaly rate was

correlated with JAK2 mutation in ET patients[1, 12, 15, 16] In our study, massive splenomegaly and JAK2 mutational burden were associated but gender was not associated similiar to other various studies[13, 22]. In our massive splenomegaly group JAK2 mutational burden, LDH level were higher and plt, neu, lymp, Hgb, Htc and RBC counts were lower significantly than mild splenomegaly group. We speculate that patients with massive splenomegaly may have a higher JAK2 mutational burden.

There is conflicting information in the literature about the relationship between the JAK2 mutation and thrombosis. Various studies stated that JAK2 mutation was associated with thrombosis in ET patients[4, 7, 11, 13, 16]. According to another study, MPN patients with an allele burden of ≥ 50% JAK2, had increased the risk of vascular complications and these patients account for most of PV and a small proportion of ET[4]. In the contrary, thrombosis or bleeding risk was not found as associated with the JAK2 mutation in myeloproliferative diseases in various studies[1, 9, 14, 19].In our study, there was no significant difference between the groups with and without thrombosis in terms of age, gender, JAK2 mutational burden and laboratory parameters except lymp count. lymp count was higher significantly in the group without thrombosis.

Low and high risk patient groups are defined for PV and ET patients[23]. Acetylsalicylic acid is recommended in low risk patients to prevent venous and arterial thrombosis. Phlebotomy is performed in both high and low risk groups to keep the hematocrit values below 45%. Patients over 60 years old and /or the presence of arterial or venous vascular complications are considered high-risk group[23]. Low-dose ASA, phlebotomy and hydroxyurea are recommended for patients in the high risk category. Hydroxyurea regulates the plt count and reduces the risk of vascular complications. When hydroxyurea cannot be used due to its side effects, Interferon-α(IFN-α), JAK-2 inhibitor or Busulfan are used[10].In our study, consistent with literature, ASA + hydroxyurea, ASA + phlebotomy and ASA were the common treatment options. The patients treated with ASA + hydroxyurea were older than the patients treated with ASA and ASA + phlebotomy.

21 of the patients with thrombosis were treated with acetylsalicylic acid + hydroxyurea, three with ASA + IFN-α, one with ASA + ruxolitinib and one with clopidogrel + hydroxyurea.

In conclusion, the patients with a higher JAK2 mutational burden were older and had higher WBC, neu, LDH levels and massive splenomegaly probability.

The most commonly used treatment in MPN patients were ASA + hydroxyurea in our patients (59.4%). JAK2 relationship with vascular complications such as thrombosis and bleeding were not significant. There were significant differences in laboratory parameters and JAK2 mutational burden according to diagnoses of PV, ET and PMF. PMF patients had the highest JAK2 mutational burden, LDH levels and massive splenomegaly rates. We speculate that if the spleen size in MPN is as large as the massive splenomegaly and the LDH level is high, the JAK2 mutation burden may tend to be higher. This relationship is more pronounced for PMF.

Declarations

The authors declare no conflict of interest. None funding.

Authors' contributions

Concept – C.Y.K. ; Design – C.Y.K., G.S. ; Supervision – A.T.; Data Collection and/or Processing – C.Y.K.,G.S., A.T.; Analysis and/or Interpretation – C.Y.K.,G.S.; Literature Search – C.Y.K., G.S.; Writing Manuscript – C.Y.K,G.S. ; Critical Review – C.Y.K., G.S.,A.T.

Ethics Committee Approval: This study was approved by Ataturk University Clinical Research Ethic Commitee (decision number: B.30.2.ATA.0.01.00/521).

Informed Consent: Written informed consent was obtained from the participants for participation and publication.

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Figures

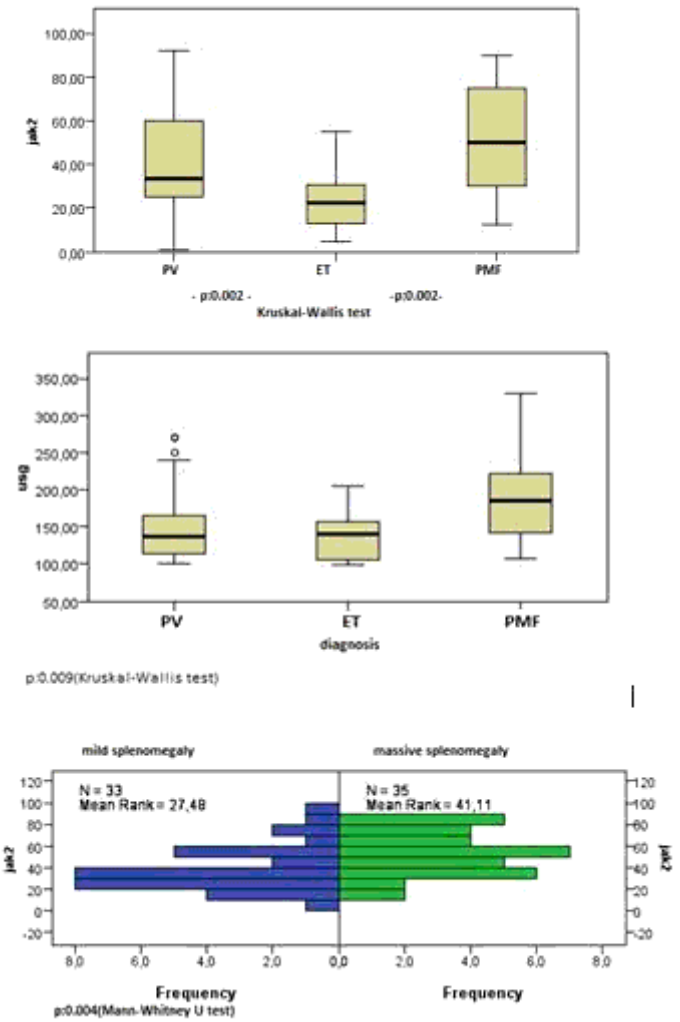

Figure 1

JAK2 mutational burden was different significantly in terms of diagnosis. ($p < 0.05$).