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The Analysis of the Correlation between Chronic Myeloproliferative Neoplasms and Cardiovascular Risk Factors

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Abstract

Objective: Chronic Myeloproliferative Neoplasia (CMPN) are a group of diseases characterized by uncontrolled proliferation of one or more lines of myeloerythroid cells in bone marrow and increased number of mature or immature cells in the peripheral blood and are associated with hemostasis and thrombosis anomalies as well as progression to acute leukemia. Presence of JAK2 V617F mutation has been included in the revised WHO criteria for the diagnosis of PV, ET and PMF.

Materials and Methods: This study is focused on clinical and prognostic factors such as age, thrombosis, leukocytosis, platelet count, previous history of thrombotic or hemorrhagic events, disease duration, hepatomegaly, splenomegaly and their relations with this mutation and cardiovascular risk factors in 120 patients with CMPN. The considered cardiovascular risk factors were arterial hypertension, diabetes, smoking, hypercholesterolemia, and a first degree relative with a history of thrombosis.

Results: The study included 120 patients with CMPN who were evaluated in hematology clinic. Study groups were consisted of 51 patients with PV, 44 patients with ET, 22 patients with unclassified CMPN, and 3 patients with PMF. The study population was consisted of 61 males (50, 3%) and 59 females (49, 17%). Patients' mean age at the time of diagnosis was 54 years (range 19 to 84); 65% of the patients (n=78) were under 60-year-old, and 35% of the patients (n=42) were under 60-year-old or older. JAK 2 V617F mutation was positive in 44 (46.8%) patients; JAK 2 mutation was negative in 50 (53.19%) patients. JAK2 V617F positivity rate was 38.6% in PV, 43.1% in ET and 4.55% in PMF, and 13.6% in unclassified CMPN. In our study the incidence of JAK 2 mutation were significantly lower in patients diagnosed with of PV. The incidence of the JAK2 mutation was significantly lower in patients with a diagnosis of PV. Prevalence of this mutation in ET group was correlated with literature, but prevalence of JAK2 mutation in PV and in PMF was not correlated with the literature. No statistically difference was observed in regard to distributions of JAK 2 (-) and JAK 2 (+) among disease groups.

Conclusion: We did not find any statistical difference among the groups in regard to thrombosis. CVD, JAK 2 mutation, HT was not associated with risk of thrombosis. There were no statistical differences in presence of diabetes and dyslipidemia between thrombosis (-) and thrombosis (+) groups, but the presence of smoking in thrombosis (+) group were significantly higher than thrombosis (-) group. More studies are needed in regard to define the relationship between JAK2 V617F mutation and clinical and laboratory findings of patients with CMPN.

Keywords: Chronic myeloproliferative neoplasia; JAK2 V617F mutation; Thrombosis; Cardiovascular risk factors

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Introduction

Myeloproliferative neoplasms occur after uncontrolled proliferation of myeloid-eritroid stem cells, afterwards mature and immature cells increase in peripheral blood. This group of clonal disease may progress to acute leukemia and may present with hemostatic and thrombotic complications. In

Table 1: Demografic and clinic datas compared between positive and negative JAK 2 Mutation population.

		JAK 2 (+)		JAK 2 (-)		p
Age	**<60**	27	61.36%	38	76.00%	0.125
	>60	17	38.64%	12	24.00%	
Gender	**Male**	22	50.00%	26	52.00%	0.847
	Female	22	50.00%	24	48.00%	
Disease subgroup	**P.Vera**	17	38.64%	23	46.00%	0.368
	E.Thrombocytemia	19	43.18%	18	36.00%	
	CMN, unclassified	6	13.64%	9	18.00%	
	PMF	2	4.55%	0	0.00%	
Hepatomegaly		6	13.64%	5	10.00%	0.584
Splenomegaly		4	9.09%	3	6.00%	0.569
Bleeding		0	0.00%	2	7.41%	0.183
Thrombosis		3	13.04%	3	10.34%	0.762
Smoking		3	11.54%	9	28.13%	0.121

Table 2: Laboratuary datas and physical examination findings compared for disease subgroups.

	PolistemiaVera	Essential Thrombocytemia	CMN.unclassified	PMF	p
WBC(10^3/ul)	10.75 ± 4.81	10.62 ± 4.93	13.42 ± 5.4	13.05 ± 12.32	0.16
HGB (g/dl)	17.87 ± 2.01	13.77 ± 2.05	13.62 ± 2.36	9.5 ± 4.36	0.0001
HCT(%)	53.26 ± 6.07	41.8 ± 5.89	41.32 ± 7.23	29.87 ± 12.24	0.0001
MCV(fl)	85.52 ± 7.93	84.33 ± 7.31	84.57 ± 10.27	84 ± 5.29	0.904
RDW(%)	14.37 ± 3.18	15.09 ± 3.47	16.14 ± 3.9	22.73 ± 4.6	0.001
Platelet (10^3/Ul)	351.1 ± 201.21	932.57 ± 401.35	594.52 ± 292.48	353.33 ± 288.23	0.0001
MPV(fl)	7.63 ± 1.29	7.18 ± 1.21	7.28 ± 1.3	6.57 ± 1.37	0.239
Neutrophil (%)	65.62 ± 11.21	66.22 ± 8.49	64.51 ± 18.71	75.93 ± 7.84	0.491
Lymphocyte (%)	24.71 ± 9.76	24.04 ± 7.66	21.37 ± 8.15	14.27 ± 3.7	0.129
Monocyte (%)	6.45 ± 2.59	5.78 ± 2.35	6.53 ± 2.61	6.03 ± 4.35	0.575
ESR (mm/h)	7.54 ± 10.64	14 ± 17.68	30.09 ± 36.83	21 ± 10.44	0.021
CRP (mg/dl)	0.45 ± 0.35	1.32 ± 4.66	1.44 ± 2.63	1.49 ± 1.51	0.685
INR	1 ± 0.11	1.12 ± 0.32	1.03 ± 0.11	1.24 ± 0.15	0.112
Hepatomegaly	14.00%	16.28%	0.00%	66.67%	0.01
Splenomegaly	4.00%	9.30%	4.17%	66.67%	0.001

WHO classification of myeloid neoplasms; PV, PMF, ET and MPN, unclassified are placed under the Myeloproliferative Neoplasms (MPN) group [1-3].

Polistemia Vera (PV), Essential Thrombocythemia (ET) and Primary Myelofibrosis (PMF) are clonal stem cell diseases originating from multi-potential hematopoietic cell. There is not a clear correlation between JAK2 V617F mutation and either survival advantage or leukemic transformation [4]. However the mutation was shown to be related to pruritus and bone marrow fibrosis [5]. JAK2 V617F mutation is associated with age >60 years, higher hemoglobin level, leukocytosis and low platelet count [6]. Currently age >60 years, history of thrombosis, cardiovasculary risk factors (hypertension, hypercholesterolemia, diabetes and smoking) are risk factors and treatment indications for PV patients. Higher white blood cell count and higher JAK2V617F allele levels are potential risk factors for thrombosis.

In this trial we have aimed to analyze the risk factors for thrombosis and bleeding diathesis complications in BCR/ABL negative CMN patients.

Material and Methods

We enrolled 120 patients who were referred to put patient hematology clinic and diagnosed BCR/ABL negative CMN (PV, ET, PMF and CMN unclassified). Patients with bleeding or coagulation disease history, hormone disorders, liver and renal failure were excluded. JAK2 V617F mutation analysis was performed from peripheral blood via real time PCR method. Statistical analysis was performed with NCSS (Number Cruncher Statistical System) 2007 statistical software (Utah, USA) program. Datas were evaluated with definitive statistical methods (mean, standard derivation) and also one way analysis of variance, Tukey multiple comparison analysis, independent t test was performed for group analysis; qualitative datas were analyzed with Chi-square test. Significance was defined as $p<0.05$.

Results

Total number of patients with CMN were 120; Polistemia Vera

Table 3: Tukey multipl comparison analysis.

	Hemoglobin	Hematocrite	RDW	Platelet	ESR
P.Vera/E.Trombositemia	0.0001	0.0001	0.754	0.0001	0.63
P.Vera/CMN	0.0001	0.0001	0.223	0.013	0.012
P.Vera/PMF	0.0001	0.0001	0.001	0.998	0.681
E.Trombositemia/CMN	0.993	0.992	0.68	0.0001	0.112
E.Trombositemia/PMF	0.007	0.012	0.002	0.011	0.937
CMN/PMF	0.013	0.023	0.014	0.578	0.895

(PV), Essential Thrombocythemia (ET), Primary Myelofibrosis (PMF), CMN unclassified patient numbers were 50(41.67%), 43(35.83%), 3(2.5%) and 24(20%); respectively. JAK2 mutation results were positive in 46.81% (n:44), negative in 53.19% (n:50). Mean age of these patients was 54, 3 years (range: 19 to 84). Male and female rates were 50.3% (n:61) male, 49.17% (n:59) female. 65% of the patients (n:78) were <60 years and 35% of them were (n:42) >60 years. Risk factor ratios were as following; 34 patients (28.3%) HT, 21 patients (17.5%) DM, 2 patients (3.3%) bleeding history, 8 patients (12.9%) thrombosis, 3 patients (3.95%) ischemic cardiac disease (Table 1).

JAK2 mutation ratio for 120 CMN patients was 46.8%. JAK2 mutation positivity was 38.6% in PV, 43.1% in ET and 4.55% in PMF, 13.6% in CMN unclassified.

There was statistically significant difference between the disease sub groups and HGB (Hemoglobin), HCT (Hematocrit), RDW (Red cell Distribution Width), platelet count, ESR ($p<0.05$) (Table 2 and 3).

In patient with positive JAK2 mutation; RDW ($p=0.0001$), platelet count ($p=0.033$), neutrophil (%) ($p=0.004$) mean values were statistically higher than in patients with negative JAK2 mutation; however, MCV ($p=0.002$), lymphocyte (%) ($p=0.0001$), monocyte (%) ($p=0.036$) mean values were statistically lower (Table 4).

Forty three of the patient (44.17%) were on hydroxyurea, 26(21.67%) had performed phlebotomy, 77(64.17%) were on acetylsalicylic acid, 33(27.5%) were on allopurinol and 4(3.33%) were on anti-aggregating agent.

Thrombosis rates were 4, 1 and 2 respectively in ET, PV and CMN unclassified patients. These 7 cases were cerebral arterial thrombosis (n:3); cerebral and retinal arterial thrombosis (n:1); splenic and portal vein thrombosis (n:1); retinal arterial and retinal vein thrombosis (n:1); lower extremity vein thrombosis (n:1). Two patients showed up with aorta anevrism rupture and gastric hemorrhage. Smoking rate for patients with thrombosis was statistically significantly higher when compared with patients without thrombosis ($p=0.043$).

Table 4: Laboratuary results compared between JAK2 mutations positive and negative patient groups.

	JAK 2 (+)	JAK 2 (-)	p
WBC(10^3/uL)	11.95 ± 5.06	10.52 ± 5.11	0.184
HGB g/dl	15.41 ± 3.56	15.46 ± 3.02	0.941
HCT(%)	47.1 ± 10.44	45.69 ± 8.25	0.474
MCV(fl)	82.01 ± 8.99	86.91 ± 5.53	0.002
RDW(%)	16.12 ± 3.8	13.54 ± 2.75	0.0001
Platelet(10e3/ul)	707.79 ± 377.5	524.53 ± 423.63	0.033
MPV (fl)	7.47 ± 1.13	7.11 ± 1.22	0.155
Neutrophil (%)	69.13 ± 11.06	61.76 ± 12.46	0.004
Lymphocyte(%)	20.47 ± 8.21	27.32 ± 7.6	0.0001
Monocyte(%)	5.65 ± 2.84	6.75 ± 2.05	0.036

Discussion

There has been articles presenting the elderly age as an independent risk factor for thrombosis, such as Stein et al. [7], they have published the higher ratio of positive JAK2 V617F mutation in the elderly group of 270 CMN patients. In our study population, however, there was no statistically significant difference between JAK 2 (+) and JAK 2 (-) groups for age and thrombosis ($p=0.125$).

JAK2 V617F mutation frequency in PV is approximately 95%. JAK2 exon 12 mutation may be positive in JAK2 V617F negative PV patients. JAK2 mutation is a diagnostic criterion for PV. This mutation may be positive in both ET and PMF patients (40% to 50%) but not as a diagnostic criteria [8,9]. In our patient group JAK2 positive ET patient frequency was similar to the literature. Our results for PV patients have been slightly lower than the literature because of the technical and material reasons leading to failure to reach some of the genetic results of patients. We did not evaluate the frequency in PMF group because our patient number was not enough for significant statistical analysis.

At the time of diagnostic evaluation, JAK2 V617F positive CMN patients experienced three times higher leukocytosis and two times higher thrombosis [10]. In our analysis we could not demonstrate the positive correlation between leukocytosis, thrombosis and JAK2 V617F positivity.

Thrombosis complication is more frequent in PV patients. Patients untreated are at higher risk for thrombosis and hemorrhagic events. In a serial of 1,213 patients thrombosis as the reason of mortality in 30% to 40% patients [11]. Two third of the thrombotic events were arterial. The most frequent events are ischemic stroke, myocardial infarction and transient ischemic attack. Deep vein thrombosis, pulmonary emboli, peripheral vascular occlusion may be seen, too. In ET patients; both thrombosis and minor bleeding complications are seen. Arterial thrombosis is slightly more often seen than venous. Hemorrhagic events have been seen in 13% to 37%, thromboembolic events in 22% to 84% patients [12]. Most common arteries are serebral, coronary and peripheral arteries. Microvasculary thrombosis complication is more common in ET patients; platelets cause the transient occlusion inside the arterial circulation causing this event [13].

Barbui and Finazzi [9] has studied 1,638 PV patients and found the major thrombosis incidence as 11.5%. 70.4% of these thrombosis were arterial, 29.6% were venous thrombosis. Fenaux et al. has shown 13.6% major thrombosis in 147 ET patients, 86% of them occurring

in arterial system, 14% venous system. Generally in the literature frequency incidence is 11% to 25% in ET, 11% to 39% in PV [14]. In 2008 Ziakas published a meta-analysis of 2,905 ET patients and revealed 778 thrombosis events, either arterial or venous. Patient with positive JAK2 V617F mutation had higher thrombosis incidents [15]. Lussana et al. worked on 3,150 ET and PV patients in 2009 and showed the higher ratio for thrombosis in homozigot JAK2 V617F mutation positive patient group [15]. In a retrospective analysis, 124 PV, 93 ET and 23 PMF patients were evaluated; patients with positive JAK2 mutation had higher thrombotic risk [13]. ET patient's homozigot for JAK2 V617F mutation and PV patients with heterozigot and wild type has been compared in a multicenter trial. Statistical analysis revealed that ET patients had 3.9 fold higher cardiovascular events [13]. Thrombosis and bleeding leads to higher morbidity in PV and ET patients. Barbui et al. presented the hemorrhage rate 3.9% to 63% and thrombosis rate 9% to 84% in their cohort analysis of 21 retrospective trials [16]. In our trial 4 ET, 1 PV, 2 CMN unclassified patients had thrombotic events. Three of them had serebral arterial thrombosis, one serebral and retinal arterial thrombosis, one splenic and portal vein thrombosis, one retinal arterial and retinal vein thrombosis, one femoral vein thrombosis. In our patient groups thrombosis complication were not statistically different between JAK 2 (+) and JAK 2 (-) patients (p=0.762). However JAK2 (-) patients did not experience bleeding complication, but 2 JAK 2 (+) patients had hemorrhage.

European Collaboration of Low Dose Aspirin in Polycythemia Vera (ECLAP) trial showed the higher arterial thrombotic risk in the smoker patient group [17]. Similar risk has been shown in ET patients [18]. Our patient groups of thrombosis (-) and (+) were similar for standard cardiovasculary risk factors (p=0.762). JAK 2 (+) and JAK 2 (-) patient groups were also similar for smoking habit (p=0.847). Smoking rate was statistically higher in thrombosis (+) group (p=0.043).

White blood cell count has been shown to be a risk factor for vasculary disease in PV and ET [17,19]. We analysed PV and ET patients with JAK2 mutation and leukocytosis at the time of diagnosis ($>15x10^3/\mu L$) but there was no significant difference. Similarly between thrombosis (+) and (-) groups leukocyte count did not show a significant difference (p=0.984).

Consequently, BCR/ABL negative CMN patients should be followed up closely for thrombotic and hemorrhagic complications. We have found that smoking has been directly involved in thrombotic events, and we should advise our patients to cease smoking.

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