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The evaluation of patients with essential thrombocythemia in terms of risk of thrombosis

Cenk Sunu[1]*, Ahmet Kursad Gunes[2], Gulten Korkmaz Akat[2], Yasin Kalpakci[1], Funda Ceran[2], Simten Dagdas[2], Gulsum Ozet[2]

SUMMARY

OBJECTIVE: The aim of this study was to compare the incidence of factors associated with an increased risk of thrombosis in patients with essential thrombocythemia.

METHODS: A total of 200 patients followed-up in our unit with a diagnosis of essential thrombocythemia in 13 years were analyzed retrospectively.

RESULTS: Of the study participants, 60.5% were females and 39.5% were males, with an overall mean (±SD) age of 54.93 (±14.21) years. In 119 patients, Janus Kinase 2 was positive with 56.3% of cases. When two patient categories were defined as those with or without history of thrombosis, no significant differences were found in terms of Janus Kinase 2 positivity, mean age, as well as white blood cells and platelet counts (p>0.05). Also, no significant differences in thrombotic event incidence were found between patient categories defined on the basis of cut-off values for white blood cells (cut-off values of $15\times10^3/mm^3$ and $8.7\times10^3/mm^3$) and platelets (cut-off values of $1500\times10^3/mm^3$) (p>0.05).

CONCLUSION: Although our results are generally in line with the published data, some divergence from previous results has been observed with respect to risk factors for thrombotic events. Absence of a correlation between leukocytosis and thrombosis may be related with the significant decline in white blood cells after treatment. Also, a significant reduction in platelet counts occurring in association with treatment is linked with a lowered incidence of thrombosis. Janus Kinase 2-positive patients had a similar thrombosis frequency with that reported in the literature.

KEYWORDS: Thrombocythemia, essential. Janus kinase 2. White blood cell count. Platelets. Thrombosis.

INTRODUCTION

Essential thrombocythemia (ET) is a clonal stem cell disorder that is characterized by isolated thrombocytosis and thromboembolic complications, and it exhibits phenotypic and pathogenetic resemblance with other myeloproliferative neoplasms (MPNs), particularly with polycythemia vera (PV) and primary myelofibrosis (PMF). Our knowledge on the pathogenesis of this disorder remained relatively limited until 2005, when acquired JAK2 mutations were reported in approximately 50% of ET patients and in great majority of PMF patients[1,2]. Nearly 55% of ET patients have JAK2V617F mutations, while JAK2 exon 12 mutations are rare[3]. MPL mutations are seen in approximately 4% of ET patients[4]. MPL mutations cluster at exon 10, most frequently at MPL W515LVK[5]. Presence of JAK2 mutations has been associated with an increased risk of arterial thrombosis and lower post-ET MF risk in ET patients[6].

Several parameters have been used to distinguish higher risk groups from lower risk groups among ET patients, and these

[1]Sakarya University Training and Research Hospital, Department of Hematology – Sakarya, Turkey.
[2]Ankara City Hospital, Department of Hematology – Ankara, Turkey.
*Corresponding author: sunucenk@gmail.com
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include age, white blood cells (WBC) count, platelet count, and history of thrombosis[7]. An increased incidence of thrombotic events has been reported in patients over 60 years of age and/or in those with leukocytosis and thrombocytosis.[8,9,10] JAK2 mutations have been associated with an increased risk of thrombosis, and JAK2 homozygous status was found to increase the risk of vascular complications[11,12].

This study was undertaken to compare the frequency of factors associated with an increased risk of thrombosis in ET patients.

METHODS

Selection of study patients

This retrospective study was undertaken with the participation of 200 patients followed-up and treated with a diagnosis of ET between 2000 and 2013 at the Hematology Unit, Ankara Research and Training Hospital, Turkey. Hemoglobin (Hb), WBC, platelet, and cytogenetic test results at baseline (pre-treatment) were recorded. At the last assessment time-point (post-treatment), Hb, WBC, and platelets were remeasured. Age, gender, and history of thrombosis and/or bleeding were also recorded in the case data form.

Statistical analysis

All the data obtained throughout this study were analyzed using "Statistical Package for the Social Science" (SPSS) version 11.5 for Windows. Descriptive statistics were expressed as frequency, percent distribution, and median values (min–max). Pre- and post-treatment complete blood count parameters were compared with Wilcoxon signed-rank test, while the comparison of WBC between those with or without the history of thrombosis was performed with Mann–Whitney U test. Categorical variables were compared with Fisher's exact test and Yates χ^2 test. The value $p<0.05$ was considered statistically significant.

RESULTS

The mean age of study participants (n=200) was 54.93±14.21 years. A total of 39.5% of the patients were male and 60.5% female. JAK2 analysis was available for 119 patients. JAK2 results of 56.3% of patients were positive and 43.7% negative. Pre-treatment WBC, Hb, and platelet counts were significantly higher than post-treatment counts ($p<0.001$, for all comparisons). The comparison of WBC, Hb, and platelet counts measured at different time points was shown in Table 1. A total of 13.5% of patients had a history of thrombosis, while 1% had bleeding, and 1.5% had both thrombosis and bleeding. About 3.5% of patients had myocardial infarction (MI), 6% cerebrovascular events (CVE), 1.5% portal venous thrombosis, 1.5% deep venous thrombosis (DVT), 18.5% peripheral arterial thrombus, 0.5% pulmonary embolism (PTE), 1.5% GIS bleeding, and 0.5% had abdominal aortic thrombosis. The frequency of thrombotic events in JAK2-positive patients was similar to that in JAK2 negative patients ($p=0.540$). Patients with or without history of thrombosis did not differ significantly in terms of age ($p=0.125$) as well as pre-treatment WBC ($p=0.442$) and platelet ($p=0.804$) counts. Comparison of age, WBC, and platelets between patients with or without thrombosis is shown in Table 2. Also, no statistically significant differences were found between patients with or without a history of thrombosis with respect to patient categories defined on the basis of age ($p=0.199$), pre-treatment WBC ($p=0.121$ for a cut-off value of $15\times10^3/mm^3$ and $p=0.357$ for a cut-off value of $8.7\times10^3/mm^3$), and platelet count ($p=0.508$). Distribution of patients with or without history of thrombosis with respect to patient categories defined on the basis of age, WBC, and platelet count is shown in Table 3.

DISCUSSION

The clinical course of ET is characterized by microcirculatory disorders and increased risk of arterial and venous thrombosis[13]. In this study, our aim was to evaluate the factors that increase the risk of thrombosis as well as the history of thrombosis and/or bleeding in a sample of ET patients.

Table 1. Comparison of WBC, Hb, and platelet counts measured at different time points.

	Time points										p
	Pretreatment					Posttreatment					
	Mean	SS	Median	Min	Max	Mean	SS	Median	Min	Max	
WBC ($\times10^3/mm^3$)	12.6	7.7	12	4.1	80.9	7.3	2.4	7.3	2.8	21.8	<0.001
Hb (g/dL)	13.6	2.1	13.5	7.5	18.4	12.8	1.88	12.8	7.8	17.4	<0.001
Platelet ($\times10^3/mm^3$)	1074	446	997	514	4213	431	154	431	98	1150	<0.001

WBC: white blood cells; Hb: hemoglobin.

Table 2. Comparison of age, WBC, and platelets between patients with or without thrombosis.

	History of thrombosis										p
	Yes (n=36)					No (n=134)					
	Mean	SS	Median	Min	Max	Mean	SS	Median	Min	Max	
Age (years)	58.1	13.9	58.5	20	83	54.2	14.2	55	17	80	0.125
WBC (×10³/mm³)	13.6	7.3	12.4	4.1	36.8	12.4	7.8	11.6	4.2	80.9	0.279
Platelets (×10³/mm³)	1030	330	1000	562	1985	1083	468	978	514	4213	0.804

WBC: white blood cells.

Table 3. Distribution of patients with or without history of thrombosis with respect to patient categories defined on the basis of age, WBC, and platelet count.

		History of thrombosis				p
		Yes (n=36)		No (n=134)		
		n	%	n	%	
Age (years)	≥60	17	47.2	56	34.1	0.199*
	<60	19	52.8	108	65.9	
WBC (×10³/mm³)	≥15	10	27.8	25	15.2	0.121*
	<15	26	72.2	139	84.8	
WBC (×10³/mm³)	>8.7	29	80.6	117	71.3	0.357*
	≤8.7	7	19.4	47	28.7	
Platelets (×10³/mm³)	≥150000	3	8.3	21	12.8	0.580**
	<150000	33	91.7	143	87.2	

WBC: white blood cells. *Yates χ^2 test; **Fisher's exact test.

In a study, the reported rate of JAK2 mutation positivity was 54%, while Duletic et al. reported a positivity rate of 58%[14,15]. The observed JAK2 positivity rate among our clinical sample was 56.3%.

While 26% of the ET patients in the study by Duletic et al. had vascular events, the reported rates of hemorrhage and thrombosis in the study by Chou et al. were 18.5% and 19.2%, respectively, with 2.1% of the patients having a history of hemorrhage prior to diagnosis[14,16]. In another study, 19% of the patients had thrombosis and 6% had bleeding at the time of follow-up, while 4% of the patients had MI, 4% had CVE, 1% had peripheral arterial thrombus formation, <1% had PTE, and 3% had portal venous thrombosis[5,17]. In this study, 13.5% of the subjects had a history of thrombosis, 1% had bleeding, and 1.5% had both thrombosis and bleeding. Also, history of MI, CVE, portal venous thrombosis, DVT, peripheral arterial thrombus formation, abdominal aortic thrombus formation, PTE, and GIS bleeding was present in 3.5, 6, 1.5, 1, 18.5, 0.5, 0.5, and 1.5%, respectively.

Risk grading systems have been proposed for ET patients to assist in predicting the risk of thrombotic complications[18]. Risk factors that utilized to define risk categories in ET patients (low, 0 risk factor; high, 1 or 2 risk factors) include age, WBC count, platelet count, and history of thrombosis[7].

In the multicenter retrospective analysis of Turkish patients, 708 patients who were diagnosed between 1987 and 2014, 55.1% of all patients had ET. JAK2 mutation was found positive in 51.5% of patients with ET. At diagnosis, thrombosis was observed in 15.12% and bleeding occurred in 9% of ET patients. The incidence of JAK2 mutation, the history of thrombosis, and the median age at diagnosis were lower than in the literature[19]. JAK2 mutation, observed in 50–60% of patients with ET, has been an independent risk factor for thrombosis, but less is known about the underlying mechanism of this relation[20]. However, in this study, patients with JAK2 positivity did not exhibit a significant increase in thrombotic events as compared with patients who were JAK2 negative. The main limitation of this study is the retrospective and observational data collection techniques, which restricts making causal assumptions.

Advanced age is an important risk factor for thrombosis, with patients over 60 years of age having an increased occurrence of thrombotic events[8]. Although ET patients

with thrombotic events were slightly older than those without such events, the difference did not reach statistical significance in our study.

Previous research has provided evidence for an increased risk of thrombosis in ET patients with leukocytosis[8,9]. WBC count higher than $8.7\times10^3/mm^3$ or higher than $15\times10^3/mm^3$ was proposed to represent an independent risk factor for thrombotic events[17]. Although ET patients with a history of thrombosis had higher WBC counts than those without such a history, the difference was insignificant. Therefore, our results suggest that no associations may be present between thrombotic event frequency and the two separate cut-off values for WBC. The absence of a correlation between leukocytosis and thrombosis may be related to the significant reduction in WBC counts with treatment in our patients. In the last decade, several studies have investigated the association between leukocytosis and risk of thrombosis in patients with MPN, but the conclusions were not univocal. Furthermore, even in studies concluding that leukocytosis was associated with thrombosis, no consensus was found on the numerical cut-off that should be used to define leukocytosis[21].

Another important consideration in reducing the risk of thrombosis involves the prevention of thrombocytosis[22]. Platelet count of $<1000\times10^3/mm^3$ in a patient over 60 years of age or a platelet count $\geq1500\times10^3/mm^3$ in those less than 60 years of age may be considered an indication for the use of agents that reduce the number of platelets[10].

The hypercoagulability state is a condition that may induce the thrombosis phenomenon. The markers of this state were identified in patients who received estrogen associated with progestagens. Furthermore, patients who received oral estrogen plus medroxyprogesterone showed a decrease in antithrombin III, which is a risk factor for thrombosis. Therefore, this association may lead to a procoagulant state in ET patients who received estrogen plus medroxyprogesterone[23]. Also, the inflammatory changes are part of coronavirus disease 2019 (COVID-19) pathophysiology and this might generate a higher thromboembolic risk in patients using combined hormonal contraception and menopausal hormone therapy. The thrombosis risk of ET patients affected by COVID-19 using combined hormonal therapy should also be evaluated in this respect[24].

Our results are in disagreement with the previous reports in terms of the incidence of thrombotic events in patients with leukocytosis, increased platelet count, or JAK2 positivity. The absence of a correlation between leukocytosis and thrombosis may be related to the significant reduction in WBC counts with treatment in our patients. Similarly, significant reductions in platelet counts that achieved by treatment have been associated with reduced frequency of thrombosis. JAK2 mutations could be evaluated in only 119 of our patients due to technical constraints between the years 2000 and 2006. In this regard, the inconsistency between the previous reports and this study in terms of the thrombotic events in JAK2-positive patients may be related with the small sample size.

CONCLUSION

The thrombo-hemorrhagic events occur in patients with ET. JAK2 mutation, leukocytosis, and thrombocytosis are associated with a high risk of thrombosis. We concluded that the effective control of WBC and platelet counts can reduce the risk of thrombosis.

AUTHORS' CONTRIBUTIONS

CS: Writing – Review & Editing. **AG:** Investigation. **GA:** Data Curation. **YK:** Resources. **FC:** Methodology. **SD:** Validation. **GO:** Supervision.

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