BLEEDING AND THROMBOSIS IN PATIENTS WITH CHRONIC MYELOGENOUS LEUKEMIA

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Abstract

Backgroud: There is considerable variation in the incidence of bleeding and thrombotic complications noted among patients with myeloproliferative disorders (cMPDs).

Objective: To explore the rate of thrombotic and hemorrhagic complications in cMPD and to identify parameters that might be associated with these complications.

Methods: Fourty five patients with various entities of cMPDs were enrolled in this study, which was conducted from January, 2003 to July, 2004 and involves three medical centers in Baghdad. Additionally, 25 apparently healthy individuals were included as control group. The patients and healthy subjects were submitted for the following investigations; (plasma fibrinogen concentration, factor VIII:C, factor VII:Ag, plasma factor X:Ag and plasma D-Dimers.

Results: The total rate of haemostatic complications among cMPD patients was 20 %. These complications was significantly associated with increasing patients' ages (P=0.005) and inversely correlated with the disease duration (r =-315, P<0.05). Factor VII:Ag level was found to be significantly lower in CML patients in comparison to control (P=0.001). Concerning the plasma factor VIII: C, FX:Ag levels and plasma D-Dimer, no association was found between any of these three parameters and the occurrence of thrombohaemorrhagic complications.

Conclusion: Bleeding and thrombosis are frequent complications in patients with cMPD.

Keywords: bleeding, thrombosis, chronic myelogenous leukemia.

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Introduction

The chronic myelogenous leukemia is clonal neoplastic diseases of the bone marrow [1].Bleeding and thrombosis have been recognized as major causes of morbidity and mortality [2]. Moreover, there is considerable variation in the incidence of bleeding and thrombotic complications noted among different series[3, 4]. However, the aim of this study is to explore the rate of thrombotic and haemorrhagic complications in patients with various entities of chronic myelogenous leukemia to identify parameters that may be associated and/ or predictive for the occurrence of these haemostatic complications in those patients.

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Materials& Methods

Forty five patients with various entities of chronic myeloproliferative disorders (cMPD) were studied and collected from three medical centers in Baghdad: AL-Kadhimiya Teaching Hospital, the National Center of Hematology/AL-Mustansiriya University, and Baghdad teaching hospital. Patients who were on drugs that may affect haemostatic parameters; and those with pregnancy, chronic liver disease, chronic renal failure, and active infection were excluded from the study.

Six patients (4 with CML, 1 with PRV, and 1 with ET) were not receiving any treatment (newly diagnosed). Thirty-nine patients (32 with CML, 5 with PRV, and 2 with IMF) were on treatment.

Additionally, 25 sex-matched apparently healthy subjects of comparable age (13 men and 12 women) with a mean

age (± SD) 41.4 years (range between 24 and 66 years) were enrolled in this series as a control group. The patients and healthy subjects were submitted for the following investigations; (plasma fibrinogen concentration by clotting method of Clauss) [5], plasma factor VIII: C (FVIII:C) level by activated partial thromboplastin time (aPTT) based assay[6], plasma factor VII:Ag (FVII:Ag)[7] and plasma factor X:Ag (FX:Ag)[8] levels by enzyme linked immunosorbent assay (ELISA), and plasma D-Dimers determonation by latex agglutination test [9].

Statistical analysis:

Statistical analyses were done using SPSS version 7.5computer software (Statistical Package for Social Sciences). The statistical significance of the difference in mean of age, fibrinogen concentration, FVIII: C activity, FVII:Ag activity, and FX:Ag activity, between study groups was a tested by ANOVA and Student's *t*-test.

Results

Fourty five patients with various entities of cMPD were enrolled in the present study; thirty-six patients had CML; six patients had PV; two patients had IMF; and one patient had ET. The mean age (±SD) of cMPD patients was 41.35±10.9 years (range between 19 and 65 years). Twenty-four males and 21 females with a male: female ratio (M: F = 1.1: 1). A group of 25 apparently healthy subjects were enrolled in the current study; there were 13 men and 12 women, with male: female ratio (M: F = 1.1: 1). The mean age (±SD) of the control group was 42.2±12.0 years. Descriptions of clinical and laboratory characteristics in the different study groups are listed in Table 1.

Table 1: Description of clinical and laboratory characteristics in the different study groups

Characteristics		Study groups				P value*
		Control n=25	CML n=36	PRV n=6	(IMF and ET) n=3	
Age (Years)	Range	24-66	24-60	40-65	19-61	0.024*
	Mean±SD	42.2±12.0	39.1±7.6	53.0±8.8	45.0±22.7	
Disease duration (Years)	Range	.	0.1-3.0	0.1-5.0	0.1-1.5	0.477*
	Mean±SD	.	1.5±0.8	2.0±2.1	0.9±0.7	
Plasma fibrinogen Conc. (g/L)	Range	1.8-4.2	1.8-5.5	2.3-3.9	2.6-3.9	0.003*
	Mean±SD	2.7±0.7	3.6±1.0	3.1±0.6	3.2±0.7	
Plasma factor FVIII:C (%)	Range	63-100	60-110	70-95	80-105	0.332*
	Mean±SD	78.2±9.1	81.2±12.6	82.5±10.4	90.0±13.2	
Plasma factor FVII:Ag (%)	Range	75-105	60-97	75-92	80-90	0.011*
	Median	95	80	85	85	
	Mean±SD	90.6±8.8	82.3±10.0	85.3±5.9	85.0±5.0	
Plasma factor FX:Ag (%)	Range	75-110	85-105	70-105	95-105	0.735*
	Median	95	95	95	95	
	Mean±SD	94.8±11.0	93.9±6.5	91.7±12.5	98.3±5.8	

*** Test of significance for difference in mean by ANOVA, ** Test of significance for difference in median by Kruskal wallis test.**

Hemorrhagic complications were observed in 5 out of 45 patients (11.1%), while thrombotic complications occurred in 4 out of 45 patients (8.9%). The total rate of occurrence of thrombohaemorrhagic complications was (20%). In addition, there were fewer complications in CML group (5.6 %) than in other cMPD groups (77.8 %), with statistical significance (χ^2-test, P<0.001)(Table 2).

Table 2: Occurrence rate of thrombohaemorrhagic complications in the different cMPD groups

Classification of cMPD patients by clinical evidence of coagulation derrangement	cMPD groups						P value χ^2-test
	CML n=36		(PRV, IMF, ET) n=9		Total n=45		
	No.	%	No.	%	No.	%	
Bleeding	2	5.6	3	33.3	5	11.1	0.04
Thrombosis	0	0	4	44.4	4	8.9	0.001
Asymptomatic	34	94.4	2	22.2	36	80	0.001
Symptomatic patients*	2	5.6	7	77.8	9	20	0.001

***Symptomatic patients; total number of patients with haemostatic complications.**

The rate of these complications was 83.3 % in PV group and 66.7% in (IMF and ET) group without significant difference between these two groups (P=1), However, it was significantly higher in these two groups as compared to CML group (P<0.001, and P=0.02), respectively.

The occurrence rates of thrombo-haemorrhagic complications were significantly associated with increasing age trend (P=0.005)(Table-3) and these complications were directly correlated with age (r =0.469, P<0.01) and were inversely correlated with the disease duration (r=-315, p<0.05).

Table 3: The rate of having disturbed haemostasis (bleeding/ thrombosis) in cMPD patients by certain clinical parameters

Parameters	Disturbed hemostasis (bleeding/thrombosis)						P value χ^2-test
	Negative Asymptomatic		Positive Symptomatic		Total		
	No.	%	No.	%	No.	%	
Age group (years)							0.005
<30	4	80	1	20	5	100	
30-39	14	100	0	0	14	100	
40-49	15	88.2	2	11.8	17	100	
50+	3	33.3	6	66.7	9	100	
Gender							
Female	17	81	4	19	21	100	ns
Male	19	79.2	5	20.8	24	100	

ns= non significant

The mean plasma fibrinogen concentration in CML group was significantly higher than control group (P<0.001) (Table 1). But the differences between other cMPD groups and control were insignificant (P>0.05). However the mean plasma fibrinogen concentration (±SD) in patients with disturbed haemostasis was insignificantly different in comparison with the asymptomatic group of patients (P=0.732). The difference in mean FVIII: C level among these four groups was insignificant (P=0.332).

The mean plasma FVII:Ag levels (±SD) in patients with disturbed haemostasis (81.9±9.9%) was insignificantly different from asymptomatic patients (83.1±9.2%), (P=0.728). The mean plasma FX:Ag (±SD) levels in patients with disturbed haemostasis (95.6±11.6%) was insignificantly different from asymptomatic patients (93.5±6.1%), (P=0.463). The difference in rate of positive plasma D-Dimers between patients with disturbed haemostasis and those who are asymptomatic was statistically insignificant (P=0.5).

Discussion

Bleeding and thrombosis in cMPD occur in varied patterns and incidence. Schafer *et al*[2] found that thrombohaemorrhagic complications occur in about 60% of patients with cMPD. The bleeding syndrome is more frequent than thrombosis, accordingly, the former is most frequent in IMF, while thrombotic complications are most common in PV patients [2,10]. In CML, disordered haemostasis is rare [3]. Besides, disorders of the microcirculation are the most common complaint in patients with ET [10].

Data presented in this series revealed that the total rate of occurrence of haemostatic complications in cMPD patients was 20% (11.1% bleeding episodes, and 8.9% was thrombotic episodes). The previous studies reported a wide range of occurrence rate for the thrombohaemorrhagic events in cMPD patients. For examples, the total incidence of haemostatic complications was 21% as reported by Barbui *et al*[11] while Schafer [2] mentioned a total incidence of 60%. Bleeding events were observed in 33.3% of patients with (IMF and ET) group, 33.3% with PV, and only 5.6% in CML patients, while, thrombotic events were most common in PV patients (50%), followed by (IMF and ET) group (33.3%), whereas, CML patients did not experience thrombotic complications. Accordingly, the occurrence of haemostatic complications was most frequent in PV (83.3%), and least frequent in CML (5.6%), (P<0.001).

Data from various reports indicated that in PV, thromboembolic and haemorrhagic complications occur at rates of 26-63 % and 16-35 %, respectively [12]. Therefore, these figures are comparable with the rates of 50 % and 33.3 % observed in the present study.

Increasing patients' ages were regarded as an important risk factor for cardiovascular events in cMPD patients [2,13,14] For example, in ECLAP study, the incidence of cardiovascular complications was much higher in patients aged more than 60 years or with a history of thrombosis than in younger subjects with no history of thrombosis [15] In agreement with these reports, the occurrence of thrombohaemorrhagic complication was significantly associated with increasing patient age, so 66.7% of patients aged more than 50 years had haemostatic complications, while only 20% of those less than 30 years age had haemostatic complications (p=0.005). Moreover there was significant correlation between age and occurrence of these complications (r =0.469, P<0.01).

Although, the clinical observations revealed insignificant association between the occurrence of haemostatic complication and disease duration (P =0.454), there were out of nine patients with thrombohaemorrhagic complications, six

(66,6%) were newly diagnosed (less than 3 months). As well, correlation study revealed significant inverse correlation between disease duration and the occurrence of these complications (r=-315, P<0.05). These observations be consistent with that of Wehmeier *et al* [16] who reported that the rate of bleeding and thrombosis was highest just before and during the first months after diagnosis and decline there after.

In this study the mean plasma fibrinogen concentration in CML patients were significantly higher as compared to control subjects (2.7±0.7 g/L), (P<0.001). While, the mean plasma fibrinogen concentration in patients with thrombohaemorrhagic complications was insignificantly different from asymptomatic patients (P=0.732). These findings were in agreement with Günay and Öztürk[17] who reported a significantly elevated plasma fibrinogen level in PV (3.83 g/L), and CML (3.73 g/L) patients, though, these elevations were not related with the increased risk of thrombotic episodes in cMPD patients.

Our data revealed that FVIII: C level in cMPD patients were only slightly but not significantly higher than the control subjects (p>0.05). Also, there was insignificant difference between patients with disturbed haemostasis and those with out complications (p=0.786). So the alteration in FVIII: C level does not relate with the occurrence of these complications in cMPD patients. These results are similar to previous reports by Günay and Öztürk[17]. FVII:Ag level were significantly lower in cMPD patients than the respective values in the plasma of healthy subjects (p<0.001), but there was no association with the occurrence of thrombo-haemorrhagic complications in cMPD patients (P=728).

Falanga *et al* found that FVIIt and FVIIz parameters were higher in (30 %) of ET patients than the respective values in the plasma of healthy control subjects, although the elevation in mean concentrations of these two FVII parameters in ET was not significant, but it indicates an increased in vivo proteolysis of FVII in ET that is consistent with hypercoagulation state in ET, and this may be a contributory factor for the increased rates of thrombosis associated with ET [18]. Therefore, further studies are required to elucidate the role of this parameter in haemostatic complications in cMPD patients.

Results in the current study revealed that the FX:Ag level were within the normal range. The mean FX:Ag level in cMPD patients did not significantly differ from that in healthy subjects (p>0.05). As well, there was no association with the occurrence of bleeding or thrombotic complications in cMPD patients. Although, there were no previous reports available about the alteration of FX in the cMPD disorders, results which obtained in the present study might suggest that FX had neither play an important role in the pathogenesis of thrombohaemorrhagic complications nor has a predictive value for these complications in cMPD.

So, it is obvious that both FVII and FX:Ag assay were of little help in the exploration of part of the problem of haemostasis in MPD. It may be suggested that antigenic assay does not reflect a qualitative alteration of these factors and another factor parameters may be more helpful (e.g., procoagulant activity).

Plasma D-Dimers are by products of the coagulation reactions, liberated during clotting activation, that provide a biochemical tool for the definition of the hypercoagulable state and are modulated by therapy. In the current study only 3 (8.3 %) patients (all within CML group) had elevated plasma D-Dimer level (>0.05µg/ml). Moreover, there were insignificant difference in the rate of positive plasma for D-Dimer between patients with disturbed haemostasis and those who are asymptomatic (p=0.5). Falanga *et al*, found a significantly elevated D-Dimer level in PV compared with controls [19], a finding that support a previous observation of a hypercoagulable state in a group of patients with ET [20]**.** This difference in results between the current study and

these previous reports might result from a different way of analysis used in these studies (ELISA method) for measuring plasma D-Dimer level.

Conclusion

1. Bleeding and thrombosis are frequent complications in patients with cMPD. These complications occur
in varied patterns, most commonly in PV, but rarely in CML.
2. Plasma FVIII and plasma FX:Ag activity may have no role in the pathogenesis of haemostatic complications in cMPD. While Plasma fibrinogen and plasma FVII:Ag may play a limited role in the pathogenesis of these complications in cMPD.

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