Risk of thrombosis in patients with essential thrombocythemia and polycythemia vera according to JAK2 V617F mutation status

We compared the laboratory and clinical findings of 179 patients with essential thrombocythemia (ET) and 77 with polycythemia vera (PV) classified according to the presence of the JAK2 V617F mutation. A gradient between patients with JAK2 wild-type ET, JAK2 V617F ET and PV (all carrying the JAK2 mutation) was observed. The rate of thrombotic complications in JAK2-positive ET was significantly higher than in wild-type ET and not statistically different from that of PV patients.

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The presence of the JAK2 V617F mutation divides essential thrombocythemia (ET) into two distinct subtypes. Patients with the mutation present higher hemoglobin levels, higher white cell counts and bone marrow hypercellularity.[1,4] An increased risk of thrombosis in mutated ET patients has been also reported by some investigators,[1,2] but not by others.[3,4] These observations have generated the hypothesis of a possible biological continuum between ET and polycythemia vera (PV).[1] This interesting view would be further supported if the clinical vascular complications of JAK2 mutated ET were comparable to those of PV patients. At the best of out knowledge, a direct comparison between the thrombotic risk of patients with ET, stratified by JAK2 V617F status, and those with PV was not hitherto reported.

To tackle this issue, we evaluated the laboratory findings at presentation and the clinical complications at diagnosis and during follow-up in two parallel cohorts of 179 ET and 77 PV patients, regularly followed in our outpatient clinic, and classified according to the presence of the JAK2 V617F mutation. The following statistical analysis were carried out: (i) continuous variables were compared using the extension of the Wilcoxon rank-sum non-parametric test for trend across ordered groups; (ii) categorical variables were analyzed using the Pearson χ^2 test; (iii) the risk of thrombosis (and the corresponding 95% confidence interval) was estimated using dummy variables coding in a logistic regression model; only the first thrombotic event occurred at presentation or during the follow-up for each patient was considered. The results are shown in Table 1. A highly significant trend across patients with JAK2 wild-type ET, JAK2 V617F ET and PV (all carrying the JAK2 mutation) was observed for all laboratory values. Hemoglobin and hematocrit levels as well as white cells number and activation parameters (polycythemia rubra Vera 1 gene expression and leukocyte alkaline phosphatase mean fluorescence intensity)[5] progressively increase whereas platelet number decreases through the three disorders. In turn, a significant increase of thrombotic complications was registered in patients with JAK2 V617F ET (33%) and PV (43%) as compared with those with JAK2 wild-type ET (17%). Considering JAK2 wild-type ET as a reference group, the risk of thrombosis was 2.39 (95% CI 1.16-4.93) and 3.63 (95% CI 1.72-7.68) for JAK2 V617F and PV patients respectively. The maximum likelihood estimate of the odds ratio comparing JAK2 V617F ET and PV patients was 1.52, not statistically significant (p=0.18). The association between increased granulocyte PRV-1 and LAP expression and thrombosis is noteworthy. This finding is in line with our recent data showing that leukocytes of JAK2 mutated ET patients present a prothrombotic state indicated by a significant increased expression of surface tissue factor and fibrinogen and a tendency to form higher numbers of leukocyte-platelet mixed aggregates.[6] These results may explain why hydroxyurea, a broad myelosuppressive drug, and not anagrelide, a megacaryocyte restricted inhibitory agent, is more effective in reducing the thrombotic events, particularly in JAK2 mutated ET patients.[1,7]

Overall, the present analysis confirms that JAK2 mutation in ET identifies a distinct clinical entity with a biological phenotype intermediate between JAK2 wild-type ET and PV and for the first time presents a comparison

Table 1. Laboratory and clinical features of 256 patients with ET and PV according to their JAK2 mutation status.

	ET Jak2 wild-type	*ET Jak2 V617F*	*PV Jak2 V617F*	*p*
Patients (number)	76	103	77	
Age (years, median, range)	45 (10-78)	50 (16-92)	60 (28-88)	<0.0001
Gender, M/F (number, %)	34/42 (45/55)	37/66 (36/64)	35/42 (45/55)	n. s.
Hemoglobin (g/dL, mean±SD)	13.5±0.14	14.4±0.14	17.8±0.25	<0.0001
Hematocrit (%, mean±SD)	41±0.5	43±0.5	54±0.75	<0.0001
White cells (%, mean±SD)	8.1±0.3	9.9±0.3	11±0.4	<0.0001
Platelets (x10^9/L, mean±SD)	858±35	767±26	528 + 27	<0.0001
PRV1 expression (CtPRV/CtGUS)	1.06±0.01	0.98±0.01	0.83±0.01	<0.0001
LAP (Mean fluoresc. intens.)	66±4.5	138±9.9	249±17.2	<0.0001
High-risk* ET patients (number, %)	34 (45)	50 (49)	–	n. s.
Treated patients (number, %)				
Hydroxyurea	34 (45)	50 (49)	46 (60)	n. s.
Antiplatelet agents	48 (63)	70 (68)	67 (87)	0.02
Thrombosis° (number, %)	13 (17)	34 (33)	33 (43)	0.02
Arterial	8	22	21	
Venous	5	12	12	
Risk of thrombosis (OR, 95% CI)	1 (Ref.)	2.39 (1.16-4.93)	3.63 (1.72-7.68)	
Hematological transformation (number, %)	9 (13)	20 (20)	6 (8)	n. s.
PV	1	15		
IM	8	4	6	
AL	0	1	0	
Follow-up (years, median, range)	4.7 (0.06-20.9)	6.1 (0.06-21.6)	5.6 (0.07-22.6)	n. s.

**High-risk ET patients = age >60 years or previous thrombosis or major bleeding or platelet count >1,500×10^9/L; °at presentation or during follow-up; IM: idiopathic myelofibrosis; AL: acute myelogenous leukemia; n.s.: not significant (p>0.05).*

between the thrombotic risk of ET and PV patients defined on the basis of their JAK2 mutational status.

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ERRATA CORRIGE

In two articles published during 2006, an author name was erroneously written (Van de Broek I, instead of Vande Broek I); correct citations becomes:

Menu E, Asosingh K, Indraccolo S, De Raeve H, Van Riet I, Van Valckenborgh E, Vande Broek I, Fujii N, Tamamura H, Van Camp B, Vanderkerken K. The involvement of stromal derived factor 1alpha in homing and progression of multiple myeloma in the 5TMM model. Haematologica 2006;91:605-12.

Vande Broek I, Leleu X, Schots R, Facon T, Vanderkerken K, Van Camp B, Van Riet I. Clinical significance of chemokine receptor (CCR1, CCR2 and CXCR4) expression in human myeloma cells: the association with disease activity and survival. Haematologica 2006;91:200-6.

In the article by *Were T, Ouma C, Otieno RO, Orago AS, Ong'echa JM, Vulule JM, Keller CC, Perkins DJ. Suppression of RANTES in children with Plasmodium falciparum malaria* published on *Haematologica 2006;91:1396-9* the name of dr. Hittner JB was omitted from the list of authors.
Correct citation should read *Were T, Hittner JB, Ouma C, Otieno RO, Orago AS, Ong'echa JM, Vulule JM, Keller CC, Perkins DJ. Suppression of RANTES in children with Plasmodium falciparum malaria. Haematologica 2006;91:1396-9.*

In the article by *Zijlstra JM, Lindauer-van der Werf G, Hoekstra OS, Hooft L, Riphagen II, Huijgens PC. ^{18}F-fluoro-deoxyglucose positron emission tomography for post-treatment evaluation of malignant lymphoma: a systematic review. Haematologica 2006;91:522-9*, a wrong version of Table 6 have been published. Correct version is published in right column of this page.

Table 6. Parameters of diagnostic accuracy of PET for post-treatment evaluation of lymphoma.

Study	*Patients*	*HD*	*NHL*	*Prev of relapse*	*PPV*	*95%CI*	*NPV*	*95%CI*
Bangerter[19]	N=58	N=45	N=43	14%	0.75	0.41-0.93	0.98	0.90-0.99
Bangerter[20]	N=36	N=14	N=22	19%	0.56	0.27-0.81	0.93	0.77-0.98
Cremerius[21]	N=41	N=22	N=34	46%	0.84	0.62-0.94	0.86	0.67-0.95
De Wit[22]	N=33	N=37	–	30%	0.67	0.42-0.85	1.0	0.82-1.00
Dittmann[23]	N=26	N=26	–	31%	0.87-	0.53-0.98	0.94	0.74-0.99
Hueltenschmidt[24]	N=47	N=51	–	40%	0.86	0.65-0.95	0.96	0.81-0.95
Jerusalem[25]	N=54	N=19	N=35	26%	1.0	0.61-1.00	0.83	0.70-0.91
Mikhaeel[26]	N=32	N=15	N=17	32%	0.89	0.56-0.98	0.91	0.73-0.98
Mikhaeel[27]	N=45	–	N=45	33%	1.0	0.70-1.00	0.83	0.68-0.92
Naumann[28]	N=58	N=43	N=15	12%	0.50	0.25-0.75	0.98	0.89-0.99
Spaepen[29]	N=93	–	N=93	40%	1.0	0.87-1.00	0.84	0.73-0.91
Spaepen[30]	N=60	N=60	–	17%	1.0	0.57-1.00	0.91	0.80-0.96
Stumpe[31]	N=50	N=35	N=15	42%	0.95	0.77-0.99	0.91	0.76-0.97
Weihrauch[32]	N=28	N=28	–	31%	0.60	0.31-0.83	0.84	0.62-0.94
Zinzani[33]	N=44	N=13	N=31	32%	1.0	0.77-1.00	0.97	0.84-0.99

Prev: prevalence; PPV: positive predictive value; NPV: negative predictive value.