Thrombotic and hemorrhagic complications in idiopathic erythrocytosis

THROMBOTIC AND HEMORRHAGIC COMPLICATIONS IN IDIOPATHIC ERYTHROCYTOSIS

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To the Editor

The diagnosis of Idiopathic erythrocytosis (IE) is ruled out when all the known causes of erythrocytosis are excluded after a complete and accurate diagnostic process.
The estimated prevalence of IE is 1.1 cases per 1,000 persons, for secondary acquired erythrocytosis (SAE), mediated by altere\d production of erythropoietin, is 2.2 per 1,000 persons [1] and for polycythemia vera (PV), a myeloproliferative neoplasm characterized by a consistent risk of hemorrhagic and thrombotic complications, is 0.3 per 1,000 persons. Therefore, the prevalence of IE is four times higher than PV and half than SAE in general population [2].
In spite of its relative frequency, few papers have focused on IE and information about thrombotic and haemorrhagic risk in this setting are lacking.
We report clinical features of a large cohort of patients with IE compared to a cohort of patients with PV, focusing on the thrombotic and hemorrhagic risk.
Between 1980 and 2015, we studied and followed 145 patients with IE in two Centers of Veneto Region,Italy, expert in the field of erythrocytosis. In these patients, all known causes of familial and SAE were excluded and JAK2V617F or JAK2 exon 12 mutations were not found. As controls, we used 145 patients with PV, strictly diagnosed in agreement with WHO criteria, studied in the same period and matched for Ht values.

We collected in all IE and PV patients disease-relevant parameters, including blood count at diagnosis, thrombosis, hemorrhages, progression into overt myelofibrosis, leukemic transformation, and death. All patients were treated with phlebotomies, to maintain hematocrit (Ht) below 45% and when appropriate, they received low dose aspirin. Eighty (54.8 %) PV patients were treated with hydroxyurea for high platelet count or symptomatic splenomegaly or after vascular complications.

The statistical tests adopted were Mann-Whitney U-test, $\chi 2$ test or Fisher's exact test as appropriate, Kaplan-Meier method for survivals, Log Rank test, Cox proportional hazard regression model.

Main clinical and laboratory data of our patients are summarized in table 1.

Twenty-one (14.5%) patients with IE and 39 (26.9%) with PV (p=0.01) experienced at least one thrombotic event. Five IE (3.4%) and 12 PV (8.3%) had a thrombotic event (p=NS) at presentation of erythrocytosis. The thrombotic events were 3 arterial and 2 venous in IE and 3 arterial and 9

venous in PV. During follow-up, 16 patients with IE (11%) and 27 with PV (18.6%) experienced thrombotic complications (p=0.047). Venous events were 2 (2 deep vein thrombosis -DVT) in IE and 15 (8 DVT, 3 pulmonary embolism, 4 splanchnic vein thrombosis) in PV (p=0,002). Arterial complications occurred in 13 IE (7 myocardial infarction -MI, 4 stroke, 2 transitory ischemic attack -TIA) and in 12 PV (5 MI, 1 stroke, 5 TIA and 1 peripheral arterial thrombosis) with no significant difference. Thrombosis free survival was significantly shorter in PV patients (p=0.005) (Fig 1). The thrombotic incidence rate was 3% patients/year in PV and 1.5% patients/year in IE (IRR = 2). IE displays a significant lower risk of developing thrombosis than PV also in age and sex adjusted multivariable analysis (HR 0.471, 95% CI 0.242 – 0.915; p=0.026).

During follow-up, 7 (4.8%) patients with IE (1 gastro-intestinal and 6 minor hemorrhage) and 22 (15.2%) with PV (6 major and 16 minor hemorrhage) suffered for bleedings with a significant difference between the two cohorts (p=0.005). In particular, 4 IE (5.4%) bleed compared to 19 PV (16%) (p=0.02) during the use of aspirin. Also Hemorrhagic Free survival was dramatically different (p=0.002)(Fig 2). The hemorrhagic incidence rate was 0.57% patients/year in IE and 2.01% patients/year in PV (IRR=0.28). Low dose aspirin was administered in 81.4% of PV and in 50.3% of IE (p=0.001). Cox multivariable analysis, including age, sex, platelet count at diagnosis and low-dose aspirin therapy, confirms the significant lower risk of bleedings in IE compared to PV (HR 0.27, 95% CI 0.091 – 0.792; p = 0.017).

Being few papers focusing on IE [2,3,4], we ignore the real outcome of this disease. We know that IE is an indolent form and it does not evolve into myelofibrosis or acute leukemia, unlike PV. IE is frequent in males suggesting that hormonal activity could play a significant role [3]: increased red blood cell mass is the most common adverse event associated with testosterone therapy in clinical practice and experimental data suggest that testosterone stimulates erythropoiesis by stimulating EPO and increasing iron utilization for erythropoiesis [5].

In the present cohort, IE patients have a lower risk of thrombosis (1.5/100 patients/year) than PV (3/100 patients/year) possibly because in PV platelets and WBC are frequently increased while they are normal in IE [3]. A significantly poorer thrombosis free survival of PV comparing IE confirms this observation. Interestingly, only 2 out of our IE patients suffered for venous thrombosis during follow-up with a lower incidence compared to PV patients while arterial events are similarly distributed among PV and IE. Recent data [6] suggest that red blood cells independently promote arterial thrombosis increasing the rate of platelet deposition and

thrombus growth: this may explain the occurrence of arterial thrombosis in IE and not only in PV patients.

A bleeding incidence rate in IE about 4 times lower than in PV (2.9/100 patients/year), not increased by the use of low-dose aspirin, has been observed in the present cohort. In agreement, the haemorrhage free survival is longer in IE patients compared to PV.

In conclusion, IE has a lower thrombotic and hemorrhagic risk than PV in spite of a stringent program of phlebotomies and a frequent use of low dose aspirin. Prospective, randomized study are needed to reinforce our results.

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Table 1: Main clinical and laboratory data of our patients with erythrocytosis

IE = Idiopathic Erythrocytosis, PV= Polycythemia Vera

	IE	***PV***	***P***
Patients, n	145	145	-
Males, n (%)	127 (87.6)	83 (57.2)	<0.001
Median age at diagnosis, years (5^{th} – 95^{th} Percentile)	56.5 (21.2 – 75.8)	61.7 (30.3 – 81.9)	0.006
Median follow up, years (5^{th} – 95^{th} Percentile)	6.6 (0.3 – 23.2)	7.4 (0.3 – 22.1)	n.s.
Median WBC, x 10^9/L (5^{th} – 95^{th} Percentile)	7.2 (5 – 11.9)	8.7 (5.7 – 17.3)	<0.001
Median Hb, g/L (5^{th} – 95^{th} Percentile)	179 (164 – 195)	175 (149 – 213)	0.03
Median Ht, % (5^{th} – 95^{th} Percentile)	52.8 (48.3 – 57.8)	53.1 (46.2 – 66.2)	n.s.
Median plts count, x 10^9/L (5^{th} – 95^{th} Percentile)	217 (132 – 320)	485 (209 – 882)	<0.001
Patients with at least a thrombosis, n (%)	21 (14.5)	39 (26.9)	0.01
Patients with at least a hemorrhage, n (%)	7 (4.8)	22 (15.2%)	0.005
Patients treated with low-dose aspirin, n (%)	73 (50.3)	118 (81.4)	0.001