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► To cite this version:

Valerio de Stefano, Tommaso Za, Elena Rossi, Alessandro M. Vannucchi, Marco Ruggeri, et al.. Increased risk of recurrent thrombosis in patients with essential thrombocythemia carrying the homozygous JAK2 V617F mutation. *Annals of Hematology*, 2009, 89 (2), pp.141-146. 10.1007/s00277-009-0788-5 . hal-00535077

HAL Id: hal-00535077

<https://hal.science/hal-00535077>

Submitted on 11 Nov 2010

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Increased risk of recurrent thrombosis in patients with essential thrombocythemia carrying the homozygous JAK2 V617F mutation

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Received: 18 June 2009 / Accepted: 24 June 2009 / Published online: 7 July 2009
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Abstract Evidence suggests that the JAK2 V617F mutation is associated with an increased risk of first thrombosis in patients with essential thrombocythemia (ET). Whether this mutation is also a risk factor for recurrent thrombosis is currently unknown. To investigate the impact of the JAK2

V617F mutation on the risk of recurrent thrombosis in patients with ET, we carried out a multicentre retrospective cohort study. We recruited 143 patients with previous arterial (64.4%) or venous major thrombosis (34.8%) or both (0.8%); 98 of them (68.5%) carried the mutation.

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Thrombosis recurred in 43 of the patients (30%); overall, after adjustment for sex, age, presence of vascular risk factors, and treatment after the first thrombosis, the presence of the JAK2 mutation did not predict recurrence (multivariable hazard ratio, HR, 0.88, 95% CI 0.46–1.68). Indeed, the individuals homozygous for the JAK2 V617F (allele burden >50%) mutation had an increased risk of recurrence in comparison with wild-type patients (HR 6.15, 95% CI 1.51–24.92). In conclusion, a homozygous JAK2 V617F mutation is an independent risk factor for recurrent thrombosis in patients with ET.

Keywords Essential thrombocythemia · JAK2 V617F mutation · Recurrent thrombosis

Introduction

Arterial or venous thrombosis can be either the first manifestation or a complication associated with the clinical course of essential thrombocythemia (ET) [1]. Advanced age and prior history of thrombosis are the two most important risk factors for vascular complications [1–5]. More recently, leukocytosis has been reported to be an independent risk factor for thrombosis in ET [6–8]. The JAK2 V617F mutation has been demonstrated to be the main molecular marker of Philadelphia-negative chronic myeloproliferative neoplasms, occurring in the great majority of patients with polycythaemia vera and in about half of all of the patients with ET [9]. Certain evidence supports the hypothesis that the JAK2 mutation is associated with an increased risk of thrombosis in the carrier patients with ET [10, 11], especially in homozygote individuals [11, 12] and in those younger than 60 years [12]. Once the thrombosis occurs, expert-produced guidelines recommend cytoreduction and antithrombotic prophylaxis with antiplatelet drugs or oral anticoagulants [13]. Nevertheless, recurrences may take place [2, 3, 5]. We had previously demonstrated that age ≥ 60 years is an independent risk factor for recurrence in a cohort of patients with PV and ET who had suffered at least one major thrombotic event and that cytoreduction significantly protects against novel events [14]. The present study aims to investigate the impact of the presence of the JAK2 V617F mutation on the risk of recurrence.

Patients and methods

Study patients

With the collaboration of multiple haematological centres that are part of the Gruppo Italiano Malattie Ematologiche

dell'Adulto (GIMEMA), a retrospective study was conducted using the medical records of 259 patients with ET who were diagnosed at one of the GIMEMA facilities from January 1985 to December 2005. The main criterion for inclusion in the study was that all individuals had suffered at least one major thrombotic event related to their haematological disease. Details of the procedure used to recruit the cohort have been reported elsewhere [14]. The additional criterion for inclusion in the present analysis was to accept only patients tested for the presence of the JAK2 V617F mutation in granulocytes by allele-specific polymerase chain reaction according to Baxter et al. [15]. When available, information about the patient's mutant allele burden was recorded. Heterozygous or homozygous status was defined as a mutant allele burden $\leq 50\%$ or $>50\%$, respectively.

Definition of the events and of the risk factors

A thrombotic event related to a patient's existing haematological disease was defined as an event that occurred following diagnosis and referral to the specialised haematological centre, or one that occurred no earlier than 2 years preceding the diagnosis. Thrombotic events that occurred more than 2 years prior to the haematological disease diagnosis were considered remote thromboses.

The major thrombotic events of interest were ischaemic stroke, transient ischaemic attack (TIA), acute myocardial infarction, unstable angina pectoris, peripheral arterial thrombosis, retinal artery or vein occlusion, deep venous thrombosis (including thrombosis of cerebral and splanchnic veins), pulmonary embolism and superficial venous thrombosis. Our definition of acute coronary syndrome encompasses acute myocardial infarction as well as unstable angina pectoris. We consider cerebrovascular disease to include ischaemic stroke as well as TIA. Splanchnic venous thrombosis included occlusion of the hepatic, portal, mesenteric, and splenic veins. Diagnosis of a first or subsequent major thrombotic event was accepted only if objectively proven or in the case of medical documentation that unambiguously confirmed the occurrence of angina or a transient ischaemic attack, as previously described [14]. Microcirculatory events (including vascular headaches, dizziness, visual disturbances, sensations of burning pain in the palms of the hands and soles of the feet, distal paraesthesia and acrocyanosis) were not considered events of interest.

Statistical methods

Differences in proportions were estimated using the Fisher's exact test (statistical significance threshold set at $p < 0.05$). The relative risk with a 95% confidence interval (CI) was calculated using a 2×2 contingency table.

The interval between the initial thrombosis and a recurrent thrombotic event (uncensored observations) or the duration until death or the time elapsed until the patient's final visit to the centre (censored observations) was analysed in order to estimate the probability of recurrence as a function of time, according to the method proposed by Kaplan and Meier. The probability of recurrence was compared between groups using the log-rank test (statistical significance threshold at $p < 0.05$) and the relative risk of recurrence was estimated as a hazard ratio (HR) using a Cox proportional hazards regression model. The HR was adjusted using recurrence as the dependent variable and selecting as covariates gender, presence of the JAK2 V617F mutation, age at the time of the initial thrombosis (≥ 60 or < 60 years), presence of one or more vascular risk factors (smoking habit, hypercholesterolemia, hypertension, diabetes mellitus and chronic atrial fibrillation), history of remote thromboses and type of treatment following thrombosis. Treatments used within our sample included antithrombotic prophylaxis using antiplatelet agents or long-term oral anticoagulants, and any type of pharmacological cytoreductive treatment.

Statistical analyses were performed using the GraphPad PRISM 3.0 software (GraphPad Software, Inc., San Diego, CA, USA) for univariable methods and using GB-STAT V6.5 (Dynamic Microsystems, Silver Spring, MD, USA) for multivariable testing.

Results

Study patients

We recruited 143 patients with ET and a previous history of thrombosis for which their information about JAK2 mutational status was available. The baseline clinical features of the patient cohort are shown in Table 1. The JAK2 V617F mutation was detectable in 98 of the patients (68.5%) (Table 1); the mutant allele burden had been estimated for 47 of them and was homozygous in five of them.

First thrombosis

Sites

Two thirds of the initial thromboses were arterial: thrombosis occurred consistent with cerebrovascular disease in 52 patients (36.2%), acute coronary syndrome in 31 (21.5%) and peripheral arterial occlusion in 16 (11.0%). The first event was a venous thrombosis in 45 of the patients (31.3%), of whom 20 individuals (13.9%) had cerebral ($n = 2$) or abdominal vessel ($n = 18$) involvement.

Treatment

Following thrombosis, the great majority of the patients received therapy with antiplatelet agents and/or cytoreduction

Table 1 Baseline characteristics of the patient cohort

Patients with ET (no.)	143
JAK2 V617F mutation—no. (%)	98 (68.5)
Sex (M/F)—no. (% of male sex)	56/87 (39.1)
Median age at diagnosis—years (range)	55 (19–88)
Median age at thrombosis—years (range)	57 (21–86)
First arterial thrombosis—no. (%)	99 ^a (69.2)
JAK2 V617F mutation—no. (% of arterial thromboses)	62 (62.6)
First venous thrombosis—no. (%)	46 ^a (32.1)
JAK2 V617F mutation—no. (% of venous thromboses)	35 (76.0)
Presence of at least one vascular risk factor—no. (%)	75 (52.4)
Smoke—no. (%)	21 (14.6)
Hypertension—no. (%)	55 (38.4)
Hypercholesterolemia—no. (%)	22 (15.3)
Diabetes mellitus—no. (%)	9 (6.2)
Chronic atrial fibrillation—no. (%)	7 (4.8)
History of remote thromboses—no. (%)	9 (6.2)
Inaugural thrombosis at diagnosis or during the 2 years before—no. (%)	92 (64.3)
Thrombosis during the follow-up—no. (%)	51 (35.7)
Patients receiving one treatment or more than one treatment following the initial thrombosis:	
Antiplatelet agents—no. (%)	110 (76.9)
Long-term oral anticoagulation—no. (%)	30 (20.9)
Any pharmacological cytoreduction—no. (%) ^b	104 (72.7)

ET essential thrombocythemia

^a In one patient, the inaugural event involved both arterial and venous vessels

^b Cytoreductive treatment includes hydroxyurea, pipobroman, busulphan, interferon or anagrelide

(Table 1). In total, 110 patients (76.9%) received antiplatelet agents, while 30 of the patients (20.9%) were prescribed long-term treatment (over a year) with anti-vitamin K agents. Five patients (3.4%) received both antiplatelet and anti-vitamin K medication. Of the 104 patients who received pharmacological cytorreduction, 85 (81.7%) were prescribed hydroxyurea. Other cytorreductive agents were pipobroman (1.9%), busulphan (1.9%), interferon (8.6%) and anagrelide (5.8%). Cytorreduction was not prescribed in the remaining 39 patients, due to a physician-in-charge decision. In total, 94 patients (65.7%) received a combined treatment that included both a cytorreductive agent and an antithrombotic drug.

Recurrent thrombosis

Sites

The first recurrence of a thrombotic event involved arterial vessels in 26 of the patients (60.4% of recurrences) and venous vessels in 17 (39.6%) of the patients. Recurrence was in the form of an ischaemic stroke in two of the patients, TIA in 12 of the patients, myocardial infarction in four of the patients, unstable angina in two of the patients, peripheral arterial thrombosis in five of the patients, splenic infarction in one of the patients, deep venous thrombosis of the legs in five of the patients, pulmonary embolism in two of the patients, superficial venous thrombosis in seven of the patients, portal vein thrombosis in two of the patients and cerebral venous thrombosis in one of the patients.

Rate

In total, 43 of the patients (30.0%) encountered one first recurrence over a total observation time of 922 patient-years following the first thrombosis (median 5.5), with an incidence of events of 4.6% patient-years. The observation time exceeded 5 years for 82 of the patients (57.3%) and exceeded 10 years in the case of 26 individuals (18.1%). The cumulative probability of recurrence was 14.1% (95% CI 8.2–20.0) at 2 years after the first thrombosis, 26.9% (95% CI 18.7–35.1) at 5 years and 42.2% (95% CI 31.0–53.4) at 10 years. The rate of recurrences was 28.5% among those patients who had the JAK2 V617F mutation (28 of 98) and 33.3% among those without (15 of 45, $p=0.56$). Of the former group, recurrence was observed in all the five homozygous patients (100%, $p=0.007$ versus wild-type patients and $p=0.001$ versus heterozygotes) and in 13 of the 42 heterozygous patients (30.9%, $p=0.82$ versus wild-type patients). The rate of the JAK2 V617F mutation was 82.3% among the patients with venous recurrences (14 of 17) and 53.8% among those with arterial recurrences (14 of 26, $p=0.10$).

Risk factors for recurrent thrombosis

Patients left untreated after the first episode

When the analysis was restricted to the 39 patients who did not receive cytorreduction following the initial thrombotic event, we recorded 14 recurrences (11 involving arterial vessels, 35.8%, and three involving venous vessels, 7.6%). The incidence of events was 6.2% patient-years. The presence of the JAK2 V617F mutation did not produce any increase in the risk of recurrence (multivariable HR 0.74, 95% CI 0.20–2.71).

Patients treated with cytorreductive therapy after the first episode

Among the 104 patients treated with cytorreduction therapy after the first thrombosis, 29 recurrences occurred: 15 involved arterial vessels (51.7%) and 14 involved venous vessels (48.3%). The incidence of events was 4.1% patient-years. The presence of the JAK2 V617 mutation was associated with a risk of recurrence similar to that found in the untreated patients (multivariable HR 0.87, 95% CI 0.40–1.88).

Overall patient cohort

After adjustment for gender, age at the time of the initial thrombosis, presence of vascular risk factors, history of remote thromboses and antithrombotic or cytorreductive treatment following the initial thrombosis, the risk for recurrence was not affected by the presence of the JAK2 V617 mutation (multivariable hazard ratio, HR, 0.88, 95% CI 0.46–1.67). Our estimate of the recurrence risk associated with the mutation did not substantially change after stratification of the patients by age <60 years (HR 1.28, 95% CI 0.57–2.82) or >60 years (HR 0.71, 95% CI 0.33–1.51) at the time of the initial thrombosis, neither when the analysis was restricted only to those patients who had suffered arterial (HR 0.85, 95% CI 0.38–1.85) or venous first thrombotic events (HR 1.21, 95% CI 0.31–4.61).

The homozygous patients had showed an increased risk of recurrence in comparison with the wild-type patients (multivariable HR 6.15, 95% CI 1.51–24.92); with respect to the heterozygous patients, the risk was increased, but without reaching statistical significance (HR 2.94, 95% CI 0.73–11.78). The heterozygous patients had a risk of recurrence quite similar to that of the wild-type patients (HR 0.99, 95% CI 0.45–2.14) (Fig. 1). Recurrence among the homozygous patients was TIA ($n=1$), deep venous thrombosis ($n=1$) or superficial venous thrombosis ($n=1$) of one leg, portal venous thrombosis ($n=1$) and cerebral venous thrombosis ($n=1$). At the time of recurrence, four of

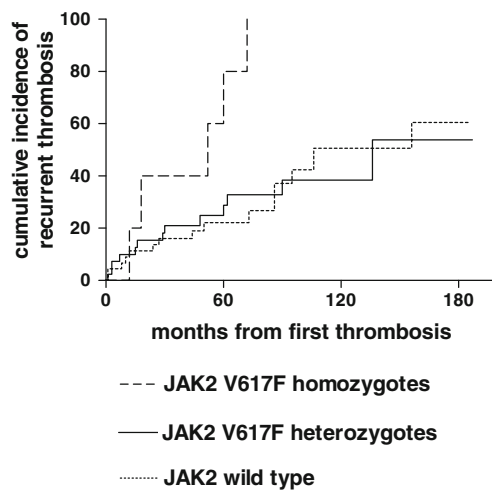


Fig. 1 Cumulative probability of recurrence in patients with the JAK2 V617F mutation in comparison to those without

them were receiving cytoreduction with hydroxyurea ($n=2$) or interferon ($n=2$) and aspirin (in one case together with ticlopidine); the latter was on long-term oral anticoagulant treatment. All the homozygous patients except one were younger than 60 years (median age 34, range 19–76).

Discussion

In essential thrombocythemia (ET), the thrombotic risk is greater in those patients who are older than 60 years and in those who have a history of a previous thrombosis. Both of the aforementioned patient groups are included in the high-risk category [1–5]. Recently, the identification of the somatic JAK2 V617F mutation allowed significant advances with respect to the diagnostic certainty for these conditions [9]. The phenotype of patients who suffer from ET is influenced by the JAK2 V617F allele burden. Specifically, patients with the mutation display a higher leukocyte count and haemoglobin level than those without, and the effect is particularly pronounced in the case of homozygotes [10, 16]. Moreover, the presence of the JAK2 mutation has been reported to be associated with enhanced platelet and leukocyte activation as well as with plasma hypercoagulability [17, 18]. This could be a plausible basis underlying an increased risk for thrombosis in those patients who have the mutation as compared to those without. However, this issue remains a matter of debate. A meta-analysis conducted on 2,436 patients with ET estimated that risk of thrombosis in the presence of the mutation is increased 1.7-fold for arterial events and 2.5-fold for venous events [11]. In a recent investigation on patients with ET, the risk of a thrombosis associated with the mutation was found increased only among the individuals younger than 60 years, especially those with a

homozygous burden, and was further enhanced by the presence of inherited thrombophilia [12]. To date, no study has addressed the question of whether the presence of JAK2 V617F is associated with an increased risk of recurrent thrombosis. We investigated, in the frame of a previously reported multicenter retrospective cohort [14], 143 patients with ET who had a previous history of thrombosis and who had been genotyped for the JAK2 V617F mutation, which was observed to be present in 68% of the cases. In our patient sample, the cumulative probability of recurrence was 41% at 10 years following the first thrombotic event, with an incidence of 4.5% patient-years. This is in agreement with the actuarial estimate of the recurrent major cardiovascular events reported in a previous cohort of 142 patients with ET [3]. A multivariable analysis adjusted for the number of potential confounding factors showed that the presence of the JAK2 V617F mutation had no effect on the risk of recurrence while considering the entire cohort or restricting the analysis to those patients whose first thrombosis was arterial or venous. Similarly, no risk-related effects were identified when the multivariable analysis was limited only to those patients who did not receive an appropriate cytoreduction therapy following the first thrombosis. Indeed, homozygous patients had a risk of recurrence that was six-fold increased and three-fold increased with respect to the wild-type and heterozygous counterparts, respectively. This is consistent with previous investigations that reported an increased thrombotic risk among the patients homozygous for the mutation [7, 10, 12]. The importance of the JAK2 V617F mutant allele burden in modulating the thrombotic risk has also been reported in polycythaemia vera, in which the patients with a greater mutant allele burden are those at higher risk for thrombotic events [19]. Interestingly, the risk appeared scarcely contrasted by cytoreduction or antithrombotic prophylaxis, since all the homozygous carrier patients suffered a recurrent thrombosis during treatment; moreover, all of them except one were younger than 60 years, confirming the importance of the JAK2 mutational status as risk factor among the young patients [12]. In conclusion, the presence of the JAK2 V617F mutation is not a risk factor for recurrent thrombosis in patients with ET, unless the patient is homozygous for the mutant allele burden. In our study, we acknowledge that the JAK2 mutational status was available only for a percentage of the total patient cohort, and this could have reduced the statistical power of our analysis. In spite of such a limitation, the homozygous JAK2 V617F mutant allele burden emerged as a strong independent risk factor for recurrent thrombosis, suggesting that special care should be warranted for carriers. The impact of such information for the management of antithrombotic secondary prophylaxis needs to be explored using larger prospective trials.

Appendix

Investigators and institutions of the Chronic Myeloproliferative Neoplasms—Working Party of the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) that participated in this research.

Chairman: T. Barbui; *Study Coordinator:* V. De Stefano; *Participating Centers:* Institute of Hematology, Catholic University, Rome: V. De Stefano, E. Rossi, T. Za, A. Fiorini, G. Leone; Department of Hematology, University of Florence, Florence: A.M. Vannucchi, P. Guglielmelli, L. Pieri, A. Bosi; Hematology Department and Hemophilia and Thrombosis Center, San Bortolo Hospital, Vicenza: M. Ruggeri, F. Scognamiglio, F. Rodeghiero; Hematology Division and Bone Marrow Transplantation Unit, San Gerardo Hospital, University of Milano-Bicocca, Monza: E. Elli, E.M. Pogliani; Department of Hematology–Oncology, Ospedali Riuniti, Bergamo: C. Micò, G. Finazzi, T. Barbui; Hematology Unit, Santa Maria Nuova Hospital, Reggio Emilia: A. Tieghi, L. Gugliotta; Department of Biomedical Sciences, Section of Hematology, University of Catania, Catania: R.R. Cacciola, E. Cacciola, R. Giustolisi; Institute of Hematology, Department of Cellular Biotechnology and Hematology, University La Sapienza, Rome: C. Santoro, M. G. Mazzucconi; Institute of Hematology and Oncology L. and A. Seràgnoli, University of Bologna, Bologna: A. Lucchesi, N. Vianelli.

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