237 A JAK2V617F Variant Allele Frequency Greater Than 50% Identifies Patients with Polycythemia Vera at High Risk for Venous Thrombosis

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Background:

Thrombosis is the main cause of morbidity and mortality in pts with Polycythemia Vera (PV). Current risk stratification is based on 2 variables: age >60y and history of thrombosis. Additional thrombotic risk factors in PV are generic cardiovascular risk factors and leukocytosis. JAK2V617F (JAK2VF) variant allele frequency (VAF) at diagnosis is highly heterogeneous. A VAF>75% was associated with higher rate of all thrombosis after diagnosis (Vannucchi AM et al, Leukemia 2007), and a VAF ≥ 60% correlated with increased rate of venous thrombosis (VT) in high-risk pts (Guglielmelli P et al, ASH 2018); however, predictive role of JAK2VF VAF is still debated.

Aim:

To evaluate the impact of JAK2VF VAF on rate of arterial and venous thrombosis in PV pts.

Patients and methods:

A cohort of 576 strictly 2016 WHO-defined PV pts followed at Univ. of Florence (1981-2020) were included. All pts were annotated for JAK2VF VAF, determined <3 years from diagnosis, and thrombosis at diagnosis and follow-up (FU). Arterial thromboses (AT) included stroke, transient ischemic attacks, retinal artery occlusion, coronary artery disease, and peripheral arterial disease; VT included cerebral venous thrombosis, deep vein thrombosis, pulmonary embolism. Splanchnic vein thromboses (SVT) were excluded. Only first occurring event was considered. Cox proportional hazard regression model was used for univariate and multivariable analysis. Kaplan-Meier (KM) analysis was used for time-to-event assessment, compared by log-rank test.

Results:

Median age was 61.4 y (range, 16.2-91.8), 58.2% were male; 62% were high-risk based on current classification. Median JAK2VF VAF was 41.5% (range, 0.3-100). A total of 76 (13.2%) pts had an AT event before/at PV diagnosis and 49 (8.5%) pts had an AT during FU. As regards VT, 64 (11.1%) and 39 (6.8%) pts had a VT before/at or after PV diagnosis, respectively. We found that JAK2 VAF as a continue variable was correlated with the risk of VT in FU (p=0.003) but not with AT (p=0.8). ROC analysis to determine the best cut-off level for JAK2 VAF predicting VT had an AUC of 0.72 and a best cut-off value of VAF=50%. VT at FU were significantly enriched in pts with VAF >50%: 14.5% versus 2.4%, p=<0.0001. VT -free survival (VT-FS) by KM was significantly shorter in the presence of a JAK2 VAF >50% (HR 4, CI 1.9-8.6, p<0.0001) (Figure 1A), whereas no difference was found for AT (HR 0.9). In addition to JAK2VF VAF>50%, univariate analysis for VT-FS identified history of VT (HR 2.9; CI 1.4-6.1, p=0.006), leukocytosis ≥11x10 9/L (HR 1.9; CI 1.1-3.4, p=0.02) and palpable splenomegaly (HR 1.9, CI 1-3.6; p=0.04) as risk factors. Multivariable analysis confirmed VAF>50% (HR 3.8, CI 1.8-8.1, p=0.0006) and previous VT (HR 2.4, CI 1.1-5.1; p=0.02) as independent risk factors for future VT. In contrast, univariate analysis for AT-free survival (AT-FS) identified history of AT (HR 2.5; CI 1.3-4.9,

p=0.007), diabetes (HR 3.3; CI 1.6-6.5, p=0.0007), hyperlipidemia (HR 3.1; CI 1.7-5.6, p=0.0003) and hypertension (HR 2, CI 1.1-3.8; p=0.03) as predictors of future AT; age >60y showed only a trend (p=0.08). Multivariable analysis for AT-FS identified diabetes (HR 2.4, CI 1.2-5; p=0.02), hyperlipidemia (HR 2.3; CI 1.2-4.3, p=0.01) and previous AT (HR 2.1, CI 1-4.2; p=0.04) as independent predictors of future AT.

Validation:

Our findings were validated in an independent cohort of 315 2016-WHO defined PV pts from Policlinico Gemelli, Catholic Univ., Rome. After exclusion of 26 pts with SVT, analysis was conducted on 289 pts, 38 of them with thrombosis as heralding event (21 AT and 17 VT). Multivariable analysis confirmed JAK2VF VAF >50% (HR 2.3, CI 1.03-5.0, p=0.04) and previous VT (HR 4.5, CI 2.0-10.1; p=0.0003) as independent risk factors for future VT. In pts with VAF >50%, the rate of VT at FU was 19.9% vs 7.7%, P=0.005. KM curve showed that VT-FS was significantly shorter in pts with a JAK2VF VAF >50% (HR 2.2, CI 1.2-4.2; p=0.01) (Figure 1B). Of note, impact of JAK2 VAF>50% on VT at FU was statistically significant particularly in conventionally low-risk pts, accounting for an HR of 9.4 (CI 1.2-72) and HR 3.6 (CI 1.3-10) in Florence and Rome cohorts, respectively.

Conclusions:

These data support JAK2VF VAF as a strong independent predictor for future venous thrombosis in PV, in association with history of prior venous events, reinforcing that AT and VT are associated with unique risk factors in pts with PV.