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Myeloproliferative disorders

JAK2 46/1 HAPLOTYPE AND JAK2 VARIANT ALLELIC FREQUENCY CORRELATE WITH THE DEVELOPMENT OF POLYCYTHEMIC PHENOTYPE IN JAK2-MUTATED ESSENTIAL THROMBOCYTEMIA PATIENTS

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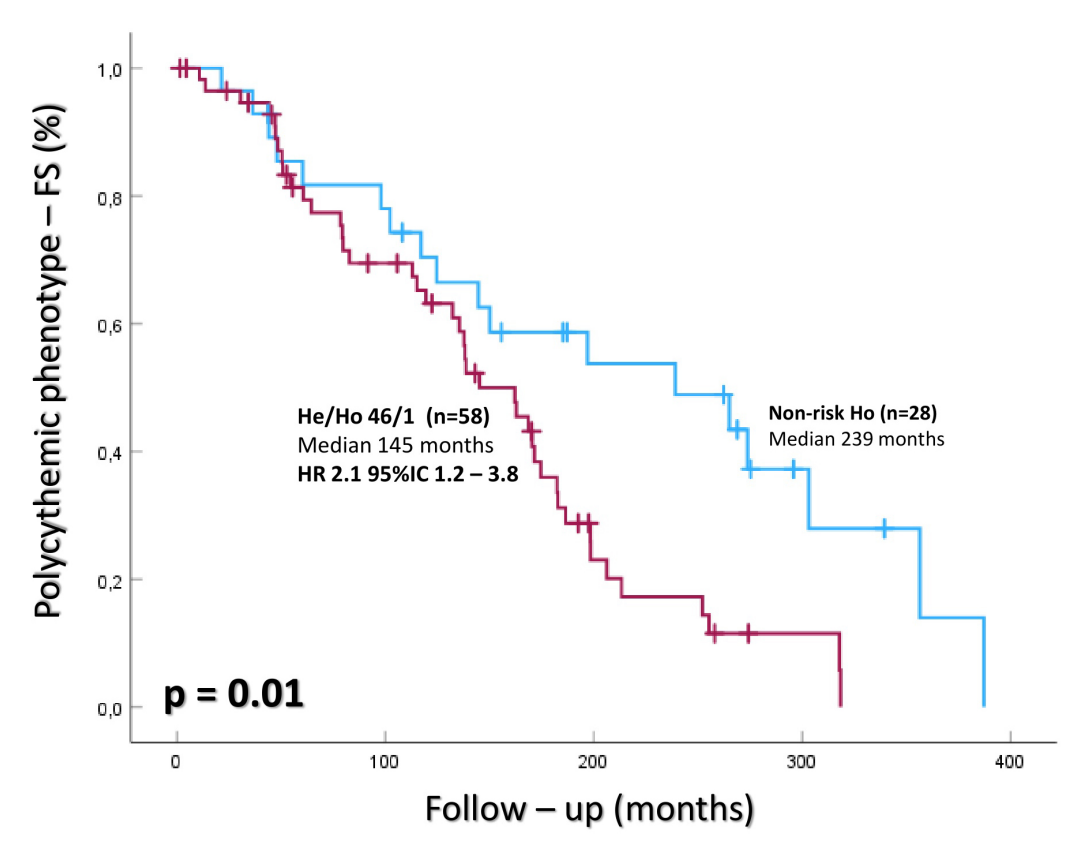
Introduction: Appearance of a polycythemic phenotype (PP) in patients (pts) with JAK2 mutated Essential Thrombocythemia (ET) strictly diagnosed according to ICC/WHO criteria represents an uncommon occurrence. The JAK2 46/1 (GGCC) haplotype (46/1), spanning 250–280 Kb on chr9p24.1, has been associated with higher blood counts and the acquisition of JAK2V617F homozygosity. We investigated clinical and molecular features of ET pts who developed PP, focusing on potential role of 46/1 and JAK2V617F variant allele frequency (VAF), that in turn was reported positively associated with higher hemoglobin levels.

Methods: We identified 69 JAK2V617F ET pts from CRIMM database who presented PP after diagnosis (dg), confirmed by either (or both) a new bone marrow biopsy showing trilinear proliferation consistent with PV dg or a progressively increasing hematocrit (Hct) level despite ongoing cytoreduction and/or in the presence of iron deficiency. Propensity score matching selected 165 pts (MC group) matched by age at dg, sex, JAK2V617F VAF at dg, and follow-up (FU) duration. The 46/1 was assessed by PCR allele discrimination, JAK2V617F VAF was quantified by ddPCR at dg and during FU. Targeted NGS of 40 myeloid genes was performed at ET dg in 81; in 35 PP pts, paired samples were also available at the time of PP appearance.

Results: A total of 234 pts were analyzed. In PP and MC group median age at dg was respectively 44 and 46 years (y), median FU 178 and 162 months (mo); 26 (37.7%) and 66 (40%) pts were male. Median time to PP was 120 mo. No differences were observed in hematologic/clinical features, myelofibrosis-free survival (FS), blast phase-FS, overall survival between PP and MC groups. MC had higher incidence of venous thrombosis (VT, 20% vs 7.2%, p=0.019) and bleeding events (25% vs 12%, p=0.02) although VT-FS showed borderline significance (p=0.08). There was no significant difference in Arterial Thrombosis (AT, 25.5% vs 21.7% p. 0.62) and AT-FS (p 0.12) between the 2 groups. At PP timepoint, median JAK2V617F VAF was significantly higher than at dg (36% vs 23%, p <0.01); the calculated annual increase of VAF was + 6.4%; no significant difference was seen in MC group. By abstract submission, 46/1 status was available for 86 pts (60 PP and 26 MC); 43 pts (50%) were heterozygous (He) and 15 (17.4%) homozygous (Ho), no differences were observed between groups. Median time to PP was 239 mo for non-risk haplotypes and 145 mo for pts harbouring at least one 46/1 allele (p= 0.01, HR 2.1 95%IC 1.2 – 3.8, Figure 1). No differences were observed in additional mutations in myeloid genes at dg between groups. During FU, among PP group 9 pts (25.7%) acquired ≥1 additional mutation; notably, 42.9% 46/1 Ho pts acquired an additional mutation during FU vs 17.9% in no-46/1 ho.

Discussion: Our findings suggest that 46/1 haplotype associates with more rapid development of PP, paralleled by accumulation of JAK2 mutant alleles and acquisition of additional mutations.


Polycythemic phenotype – FS (%)
1,0
0,8
0,6
0,4
0,2
0,0
He/Ho 46/1 (n=58)
Median 145 months
HR 2.1 95%IC 1.2 – 3.8
Non-risk Ho (n=28)
Median 239 months
p = 0.01
0
100
200
300
400
Follow – up (months)