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Myeloproliferative disorders

MOLECULAR CHARACTERIZATION OF A COHORT OF PATIENTS WITH POLYCYTHEMIA VERA: A SINGLE-CENTER STUDY

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Introduction: Polycythemia vera (PV) is a chronic myeloproliferative neoplasm mainly driven by *JAK2* mutations. Additional myeloid gene mutations (MyMut) have been reported, sometimes with prognostic relevance, but the molecular landscape at diagnosis and its impact on disease phenotype or outcome remain unclear.

Methods: We included patients (pts) with a diagnosis (dx) of PV according to WHO/ICC 2022 criteria with at least a DNA sample collected at dx or during the chronic phase in the absence of disease progression, and with comprehensive hematologic, clinical, and outcome data. Molecular and bioinformatic analyses were performed using a targeted NGS panel (SOPHiA DDM Myeloid Solution) on the SOPHiA DDM platform.

Results: A total of 637 PV pts were analyzed, 355 (55.7%) were males with a median age of 61.3 years (range 14.4–91.8). 138 pts (21.7%) progressed to post-PV Myelofibrosis (MF), 15 (2.4%) to blast phase (BP) during the PV chronic phase, 222 (34.9%) pts had at least an event of thrombosis (138 (62.2%) at dx or within the 5 preceding years, and 109 (49.1%) during follow-up), including both arterial (n=121) and venous (n=125). Death occurred in 109 (17.1%). Almost all pts (99.4%) harbored a *JAK2* mutation: *JAK2 V617F* in 625 (98.1%) cases and *JAK2* exon 12 mutations in 8 (1.3%). 4 pts resulted *JAK2* WT. Additionally, 11 pts (10 V617F, 1 exon 12) harbored a *JAK2* mutation combined with a non-canonical *JAK2* variant. Other MyMut were found in 283 pts (44.4%), with 8.9%, and 2.4% of pts harboring 2 or ≥3 mutations, respectively. *JAK2*-negative pts showed mutations in *ASXL1* (n=1), *DNMT3A* (n=1) and *ZRSR2* (n=1). The most frequently mutated genes (≥5 pts) were: *TET2* (21.4%, mean VAF 23.9%), *ASXL1* (12%, mean VAF 24.4%), *DNMT3A* (9.9%, mean VAF 17.8%). The most common co-mutation patterns were: 9.4% pts carried both *TET2* and *ASXL1* mutations, 8% *TET2* and *DNMT3A*, 4.8% *ASXL1* and *EZH2*, 5.8% *ASXL*1 and *IDH2*. Correlation analyses showed that the presence of at least 1 MyMut correlates with worst prognosis, as shown in Figure 1. In particular, genes more significantly associated with shortened overall survival (OS) were *DNMT3*A (p=0.012), *TET2* (p<0.001) and *U2AF1* (p=0.002). In addition, *ASXL1* (p<0.001), and *EZH2* (p=0,002) were associated with progression to secondary myelofibrosis –postPV, while *DNMT3A* (p<0.001) resulted inversely correlated with MF progression.

Conclusions: These findings demonstrate that almost half of PV pts show a complex molecular landscape already at diagnosis, and that both survival and progression to MF may be influenced by the presence of additional mutations in myeloid-associated genes. Comprehensive molecular profiling at diagnosis may improve risk stratification and future prognostic models in PV.

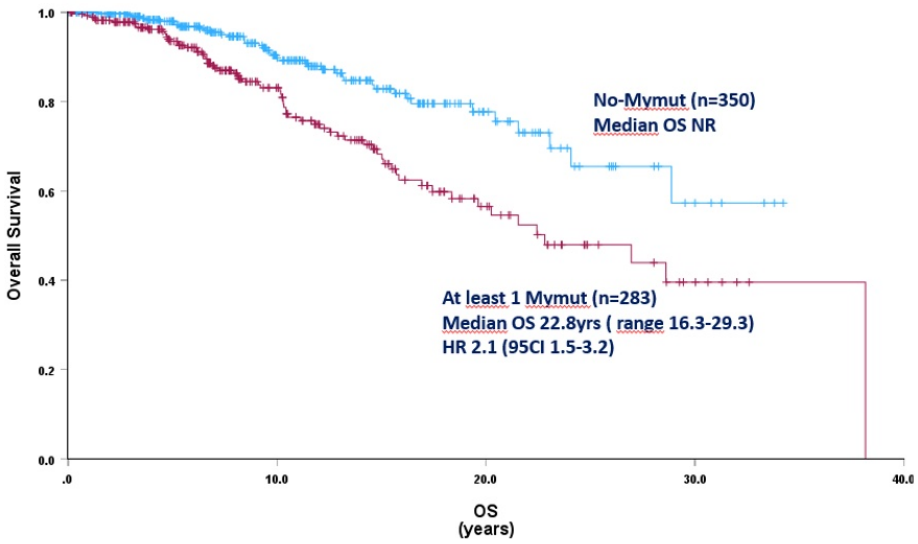

Figure 1: The impact of at least 1 MyMut on OS.