P1001 DNMT3A/TET2/ASXL1 MUTATIONS DETERMINE THROMBOTIC RISK IN POLYCYTHAEMIA VERA

**Topic:** 15. Myeloproliferative neoplasms - Biology & Translational Research

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**Background:** Polycythaemia vera (PV) is the myeloproliferative neoplasm with the highest incidence of thrombosis, with cardiovascular events being the main cause of death in these patients. Recent studies have identified clonal haematopoiesis (CHIP) in healthy individuals, which is associated with older age and an increased risk of developing both myeloid neoplasms and vascular events.

**Aims:** In a previous study we saw an association between the presence of mutations in DTA genes (DNMT3A, TET2 and ASXL1, the most frequently mutated genes in CHIP), and vascular events in patients with PV. We aimed to confirm this association in a consecutive series of PV patients from our centre and in an age-matched case control study with patients from various European centers.

**Methods:** All patients aged 18 years and above with a confirmed diagnosis of PV in our hospital were recruited consecutively between 2003 and 2018. NGS was performed on 200 ng genomic DNA extracted from peripheral blood at diagnosis. Sequencing was performed using a MiSeq (Illumina) with the 30-gene panel Myeloid Solution (SOPHiA Genetics). Only variants with an allelic frequency (VAF) ≥ 2% and annotated as pathogenic or probably pathogenic were considered. Additional mutations are defined as pathogenic mutations in any non-driver gene from the myeloid panel.

The case-control study included PV patients with a thrombotic event in their patient history and the results of a myeloid NGS panel available from 9 Spanish and 1 Polish hospital. Cases were gender- and age-matched with control patients (with a diagnosis of PV but no thrombotic event) from the consecutive series.

**Results:** A total of 79 patients with PV were analysed in our consecutive series. An association was observed between DTA mutation and thrombotic event (OR 4.3; p=0.002; χ²). An association was also observed between any non-driver mutation from the myeloid panel and thrombotic event (OR 7.7; p=<0.0001; χ²). However, no association was seen between non-DTA mutation and thrombotic events (p=0.231; χ²). The association between DTA mutation and thrombotic event was confirmed in multivariate analysis (p=0.021, Table 1). Thrombotic event was associated with age (p=0.020) and marginally with leukocyte count at diagnosis (p=0.065) but not with JAK2 VAF. We saw that when the JAK2 mutation comes before DTA, there is a tendency for the risk of thrombosis to be higher than for DTA first.

We also observed a positive association between cardiovascular risk factors (CVRF) and thrombotic events (Table 1), as expected. However, its significance was lost in the multivariate analysis. The DTA and CVRF variables are closely related, with a positive association between them (OR 6.77; p=0.009; χ²). Fifty eight of 79 patients (73.4%) were hypertensive; however, an association was still found between thrombotic event and DTA mutation in this group of hypertensive patients (p=0.033).
The association between DTA and thrombotic events in the uni and multivariate analyses was confirmed by the case-control study of 47 cases and 47 gender- and age-matched controls (OR 2.7; p=0.036; χ²).

Summary/Conclusion: We were able to confirm the previously observed association in PV between the presence of DTA mutations and higher risk of developing a vascular event. Thus, detection of DTA mutation by NGS could help predict thrombotic risk in PV patients, including those with pre-existing CVRF.

| Table 1. |
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| **UNIVARIATE ANALYSIS FOR THROMBOTIC EVENT** |
|          | OR  | CI 95%          | P value |
| CVRF     | 14.2| 1.76-115.434   | 0.002   |
| DTA      | 4.6 | 1.76-11.84     | 0.002   |
| TET2     | 2.6 |               | 0.08    |
| Non-driver No DTA | 0.88| 0.36-2.14     | 0.23    |

| **MUTIVARIATE ANALYSIS FOR THROMBOTIC EVENT** |
|          | CI 95%          | P value |
| Age      | 1.02           | 0.97-1.06 | 0.52    |
| CVRF     | 8.17           | 0.9-73.902 | 0.06    |
| DTA      | 3.28           | 1.2-8.99  | 0.021   |

DTA: DNMT3A, TET2, ASXL1; CVRF: cardiovascular risk factor.