P1026 COMPARATIVE GENOMIC PROFILING OF MYELOPROLIFERATIVE NEOPLASMS PRESENTING WITH AND WITHOUT SPLANCHNIC VEIN THROMBOSIS

Topic: 16. Myeloproliferative neoplasms - Clinical

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Background:
Splanchnic vein thrombosis (SVT) is the initial manifestation in 5% of myeloproliferative neoplasms (MPN). MPN patients presenting with SVT are usually younger, have less abnormal blood counts and lower JAK2V617F allele burden than other MPN patients. However, it is unknown whether they have a different genomic background.

Aims:
To describe the clinical and genomic profile of MPN presenting with SVT and to compare it with a matched group of MPN without SVT.

Methods:
Samples of 190 MPN patients were selected: 64 MPN presenting with SVT (SVT+) and 126 MPN without SVT (SVT-). SVT+ and SVT- were matched according to sex, age, MPN clinical subtype and driver mutation. Next Generation Sequencing was performed using Myeloid Solution by Sophia Genetics, which includes 30 genes recurrently mutated in MPN. Variants were selected using Sophia DDM software and were subsequently classified into 5 categories: 5 (definitely pathogenic), 4 (likely pathogenic), 3 (uncertain), 2 (likely benign), and 1 (benign). Only variants included into 4 and 5 categories were taken into account. Patients were classified according to the genomic classification proposed by Grinfeld and colleagues.

Results:
One hundred and three patients were women (54.2%) and 87 patients were men (45.8%), without significant differences between SVT+ and SVT- groups. Median age was 44 years (range: 15-85) and 50 years (range: 15-87) in SVT+ and SVT-, respectively (p not significant). Regarding MPN clinical subtype in SVT+ group, 39 (60.9%), 15 (23.4%) and 10 (15.6%) corresponded to Polycythemia Vera (PV), Essential Thrombocythemia (ET) and MPN unclassifiable, respectively. In the SVT- group, 75 (59.5%) and 51 (40.5%) corresponded to PV and ET, respectively.

Genomic classification in the SVT+ and SVT- groups is shown in Table 1. The proportion of patients with high molecular risk (TP53 disruption/aneuploidy, chromatin/spliceosome mutation, or homozygous JAK2 mutation) was 14.1% and 26.2% for SVT+ and SVT-, respectively (p=0.06). Median number of pathogenic mutations was 1 (range: 1-4) in both SVT+ and SVT- groups. Pathogenic mutations in TET2, DNMT3A and ASXL1 were present in 10%, 3.7% and 3.7%, respectively, without significant differences between both groups.

With a mean follow-up of 10.1 years for cases and 9.7 years for controls, 27 patients died (13 SVT+ and 14 SVT-). Median survival was 24 years and not reached for SVT+ and SVT-, respectively (p=0.1). On multivariate analysis, SVT+ group showed a higher risk of death (HR: 2.4, 95%CI: 1.1-5.5, p=0.03) after correction by age, sex and genomic classification. Transformation to myelofibrosis and acute leukemia was low and similar in both groups.

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4.7% vs. 5.6% for myelofibrosis in SVT+ and SVT-, respectively (p not significant); and 0% vs. 2.4% for acute leukemia (p not significant). On multivariate analysis, patients with TP53 disruption/aneuploidy, chromatin/spliceosome mutation, or homozygous JAK2 showed a higher risk of disease progression to myelofibrosis or acute leukemia (HR: 14.5, 95%CI: 3.1-68.7, p=0.001) regardless of the presence of SVT at diagnosis, age and sex.

**Table 1. Genomic classification of cases presenting with SVT and MPN without SVT**

| MPN genomic category                  | SVT+ group (n=64) MPN presenting with SVT, n (%) | SVT- group (n=126) MPN without SVT, n (%) |
|---------------------------------------|-------------------------------------------------|------------------------------------------|
| MPN with TP53 disruption or aneuploidy| 1 (1.6%)                                        | 3 (2.4%)                                 |
| MPN with chromatin of spliceosome mutation | 2 (3.1%)                                      | 7 (5.6%)                                |
| MPN with homozygous JAK2 mutation     | 6 (9.4%)                                        | 23 (18.3%)                               |
| MPN with heterozygous JAK2 mutation   | 55 (85.9%)                                      | 93 (73.8%)                               |

MPN, myeloproliferative neoplasms; SVT, splanchic vein thrombosis. Table 1 shows the prevalence of the represented genomic categories in the case and the control groups. The prevalence of the genomic categories is similar in both groups, with a higher proportion of MPN with homozygous JAK2 mutation in the SVT+ group and a higher proportion of MPN with homozygous JAK2 in the SVT- group. These differences were statistically non-significant.

**Summary/Conclusion:**

MPN presenting with SVT and MPN-matched controls showed a low molecular complexity. Genomic classification was helpful in identifying a small proportion of MPN patients presenting with SVT who are at high risk of disease progression. SVT at MPN diagnosis is associated with a higher risk of death independent of sex, age and genomic classification.