Risk of thromboembolic events in metastatic colorectal cancer patients with single nucleotide polymorphisms in Factor V Leiden (FVL), Prothrombin, Plasminogen Activator Inhibitor-1 (PAI-1) and Methylenetetrahydrofolate Reductase (MTHFR)

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Several risk factors for thromboembolic events (TEE) are present in metastatic colorectal cancer (mCRC), as central catheter, chemotherapy and antiangiogenics (Elyamany, 2014). Single nucleotide polymorphisms (SNPs) related to hereditary thrombophilia are known, but their contribution to TEE risk in mCRC was never explored. In this study, we aimed at assessing the effect of FVL G1691A, prothrombin G20210A, PAI-1 4G, or MTHFR C677T and A1298C on TEE risk.

We included 179 mCRC patients from 2 Italian centers, with no previous history of TEE, not taking anticoagulants, treated with first-line chemotherapy and bevacizumab. DNA was extracted from peripheral blood; genotypes were determined by Real-Time PCR, using LightSNiP (TIB MOLBIOL) on LightCycler 480 (Roche). The percentage of patients with TEE was calculated from diagnosis of mCRC to death or last follow up. Clinical risk factors included age and obesity (BMI≥30).

All SNPs were in Hardy-Weinberg equilibrium (chi-squared test p>0.20). FVL and prothrombin G20210A were present only in heterozygosis in 4 (2.2%) and 7 (3.9%) patients, respectively. MTHFR C677T in heterozygosis in 95 (53.1%) and in homozygosis in 29 (16.2%) patients, respectively. MTHFR A1298C in heterozygosis in 82 (45.8%) and in homozygosis in 13 (7.3%), respectively. PAI-1 4G/4G in 41 (23%), 4G/5G in 98 (54.7%) and 5G/5G in 40 (22.3%). TEE occurred in 52 (29%) patients. Obesity and age were not associated with TEE (p=0.324 and p=0.488, respectively). TEE occurred in all 4 patients with A allele at FVL G1691A. TEE prevalence was higher in prothrombin G20210A carriers vs. non-carriers (71.4% vs. 27.3%; OR=6.65; 95%CI, 1.24-35.45; p=0.027), as well as in MTHFR C677T homozygous TT vs. CC (55.2% vs. 23.6%; OR=3.98; 95%CI, 1.52-10.39; p=0.005). MTHFR A1298C SNP was not associated with TEE risk (p=0.445), while a trend was observed for presence of PAI-1 4G allele (p=0.061). Recessive model for MTHFR C677T and dominant model for PAI-1 4G allele were statistically significant (OR=3.9; 95%CI , 1.71-8.87; p=0.001 and OR=2.8; 95%CI, 1.10-7.15; p=0.031, respectively). In multivariate model including age, obesity, MTHFR C677T and PAI-1 4G allele, both SNPs were significantly associated with risk of TEE (p=0.026 and p=0.028, respectively).

Given the low prevalence of SNPs usually associated with higher risk (FVL G1691A and prothrombin G20210A) and the preliminary association of frequent SNPs (MTHFR C677T and PAI-1 4G), studies on larger datasets are needed. A prospective study on TEE prophylaxis in carriers of risk SNPs is warranted.

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