Oncogenes and cancer-associated thrombosis: Is there a rationale for using molecular findings to assess thromboembolic risk in cancer patients?

L. Provenzano, M. Platania
Istituto Nazionale Tumori, Milan, Italy

**Background:** Cancer-associated thrombosis (CAT) is one of the most threatening complications of cancer. Many questions are as yet unsolved in this field, from pathogenesis to clinical management. One of the most interesting issues is the role of oncogenes and oncosuppressors as link between carcinogenesis and CAT. There is much evidence on in vitro capacity of some oncogenes to enhance the clotting system, but less clinical evidence of association between cancer mutational status and risk of thromboembolic events. The aim of this study was to explore the relationship between mutational status of genes commonly analysed and risk of CAT.

**Methods:** We retrospectively evaluated molecular cancer features of all consecutive patients admitted to the National Cancer Institute’s Department in Milan between October 2016 and November 2017. Patients with previous thrombotic events and patients under anticoagulant therapy at cancer diagnosis were excluded. All molecular investigations requested by clinicians were recorded. Due to death as competing risk, the Fine and Gray proportional regression model was used to detect statistical association and estimate relative risk.

**Results:** The resulting cohort consisted of 484 patients with solid tumors (most of all gastrointestinal - 47% - , lung - 18% - and breast - 15% - cancers). Molecular investigations were available for 375 (77%) patients, in particular Next Generation Sequencing (NGS) analysis for 148 (31%) patients. After a median follow up of 17 months, 118 patients (24%) exhibited clinical manifestations of thrombosis (i.e. deep vein
thrombosis, pulmonary thromboembolism, splanchnic thrombosis, disseminated intravascular coagulation, arterial thrombosis) and 117 (24%) patients deceased without thrombotic events. Statistically relevant data were observed for TP53, KIT and SMAD4 mutational status (respectively, HR = 0.50, 4.30, 3.19; p = 0.04, 0.04 and 0.03).

Conclusions: This is the first study using large molecular panel gene analysis for thrombosis risk prediction. Mutational status of some genes was statistically associated to the risk of thrombosis. Due to methodological limits and low prevalence of mutations, prospective and controlled studies are required.

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