Clinical course of isolated distal deep vein thrombosis in patients with active cancer: a large multicenter cohort study

F. Dentali1, S. Pegoraro1, S. Barco2, M. di Minno2, D. Mastroiacovo3, F. Pomero4, C. Lodigiani5, F. Bagna6, W. Ageno1, M. di Nisio7 (1Varese, Italy, 2Mainz, Germany, 3Naples, Italy, 4Avezzano, Italy, 5Cuneo, Italy, 6Rozzano-Milano, Italy, 7Chieti, Italy)

Thrombosis
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Objective: Although isolated distal deep vein thrombosis (IDDVT) is frequently associated with cancer, no study has specifically evaluated the long-term clinical course of IDDVT in active cancer patients. The aim of this study is to provide data on the rate of recurrent venous thromboembolism, major bleeding events and death in IDDVT patients with active cancer.

Methods: Consecutive patients with active cancer and an objective diagnosis of IDDVT (January 2011-September 2014) were retrospectively included. We collected information on baseline characteristics, IDDVT location and extension, venous thromboembolism risk factors, type and duration of anticoagulant treatment. The primary study outcome was the composite of objectively documented recurrent venous thromboembolism events. The primary safety outcome was major bleeding. All patients underwent regular follow-up visits or telephone contacts every six months up to 24 months after IDDVT diagnosis.

Results: 308 patients (mean age 66.2±13.2 years, females 57.1%) with solid (n=261) or hematologic (n=47) cancer were included in 13 centers. Cancer was metastatic in 148 (48.1%) patients. All but three patients (99.0%) received anticoagulant therapy which consisted of low molecular-weight heparin in 288 (93.5%) patients, fondaparinux in 15 (4.9%), and unfractionated heparin in 1. Vitamin K antagonists were used for the long-term treatment in 46 patients (14.9%) whereas all others continued the initial parenteral agent for a mean treatment duration of 4.2 months

(±4.6 months). During a total follow-up of 355.8 patients-year (mean 13.9 months), there were 47 recurrent objectively-diagnosed venous thromboembolism for an incidence rate of 13.2 events per 100 patients year. Seven (2.3%) patients had a major bleeding event and 138 (44.8%) died.

Conclusion: Cancer patients with IDDVT have a high risk of venous thromboembolism recurrence. Additional studies are warranted to investigate the optimal intensity and duration of anticoagulant treatment for these patients.
Platelet transcriptome analysis of mice with altered thrombin signaling

S. Schubert, F. Marini, C. Santos, H. Binder, W. Ruf (Mainz, Germany)

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Objective: Platelets are terminally differentiated blood components required for hemostasis and contributing to thrombosis. The RNA profile of platelets may provide indirect insights into alterations of megakaryocytes and the bone marrow or systemic diseases that result in platelets acquiring additional RNA cargo. Platelets are therefore circulating sentinels for pathological changes and easily accessible for profiling of their RNA content by next generation sequencing (NGS).

Our goal was to identify platelet signatures indicative of prothrombotic states. We therefore determined the platelet transcriptome of genetically modified mice that (1) have chronically impaired vascular control of thrombin associated with platelet hyper-reactivity due to a point mutation in thrombomodulin (TMProPro) or (2) altered thrombin responses due to loss of thrombin signaling (PAR4-/-) or binding to the extracellular domain of GPIba (GPIba-IL4 chimerea).

Methods: We determined total RNA profiles from wild-type, TMPProPro, PAR4-/- and GPIba-IL4 mice (n=6). Leukocyte-depleted platelet total RNA was subjected to deep NGS (>35 million reads). Reads were mapped to ENSEMBL GRCm38.76 and data were analyzed by featureCounts of the Rsubread package. Differential expression was analyzed with DESeq2.

Results: Principal component analysis showed highly reproducible NGS profiles for replicates of each genotype and a clear separation between receptor mutants. Differential expression analysis identified 190 differentially expressed transcripts selective for TMPProPro, 565 transcripts for PAR4-/- and 609 transcripts for GPIba-IL4 platelets. In addition, we found unique transcript changes common to TMPProPro and PAR4-/- (93), TMPProPro and GPIba-IL4 (158), and PAR4-/- and GPIba-IL4 (426) platelets, indicating common pathways influenced by thrombin signaling and binding to its receptors.

Conclusion: The transcriptome analysis of platelets from genetically modified mice yielded highly reproducible RNA profiles that provide insights into common and distinct pathways regulated by thrombin and its receptors expressed by the endothelium and platelets/megakaryocytes. The identified differentially expressed transcripts may be of utility to assess platelet function alterations due to chronically elevated thrombin levels and coagulation activation in diverse clinical settings predisposing to thrombo-embolic complications.