Newly diagnosed multiple myeloma is associated with hypercoagulablity and high risk of VTE

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Background: Multiple myeloma (MM) and other plasma cell dyscrasias (PCD) as well as the associated immunomodulatory treatments are linked to increased risk of venous thromboembolism (VTE). The identification of patients at VTE risk and the optimization of VTE prevention is an unmet medical need. Elaboration of a risk assessment model (RAM) specific for patients with PCD, which includes biomarkers of hypercoagulability, could improve the management of VTE risk.

Aim: We conducted a longitudinal observational study, to explore the relationship of MM with cellular and plasma hypercoagulability aiming to identify the most relevant biomarkers for use in a RAM for VTE in combination with clinical risk factors.

Methods: Newly diagnosed patients with PCD (n=186) were recruited from July 2014 to Dec 2015; including 27 with monoclonal gammopathy of undetermined significance (MGUS), 40 with asymptomatic multiple myeloma (AMM), 79 with multiple myeloma (MM), 30 with AL-amyloidosis, 8 with Waldenstrom's Macroglobulinemia (WM) and 2 with solitary plasmacytoma. They were compared against 30 healthy age and sex-matched individuals (CG). A systematic compression ultrasound was performed at baseline and at 6-12 months. Blood samples were obtained at diagnosis and at 6-12 months (n=89). Samples of platelet-poor plasma (PPP) were assessed for thrombin generation (TG) with PPP-Reagent® (TF 5pM and 4 µM phospholipids), P-selectin, D-dimers (D-Di), activated FVII (FVIIa), Tissue Factor (TFa), fibrin monomers (FM), and procoagulant phospholipid-dependent clotting time (Procag-PPL). The upper and lower normal limits (UNL and LNL) were calculated by the mean±2SD.

Results: Median age was 67 years (37-89) and 49% of the population was male. Median time to follow up was 7 months (1-12 months). Among MM cases (n=79), symptomatic VTE rate was 10% (n=8) and mortality rate 7.5%. The events included 2 central venous catheter thromboses, 1 Pulmonary Embolism, 2 Deep Vein Thromboses, 2 Superficial Vein Thromboses and 1 Mesenteric Vein Thrombosis. Cases had significantly shorter PPL-ct, higher FTa and DDi, TG (increased Peak), heparanase and P-selectin compared to controls (p0.001). Along the MGUS- AMM- MM continuum, D-Di concentration (p0.0001), FM concentration (p0.05), lag time (p0.027) and MRI were highest in MM patients. Sixty percent of MM patients had Procoag-PPL: below the LNL, in 63% TFa levels were above the UNL, and 31% had MRI lower than LNL. After 6 months of treatment, FTa, DDi, MRI, peak thrombin and P-selectin levels decreased (p0.05) and TM and ATIII levels increased (p0.05).

Conclusion: In patients with PCD, increased procoagulant microparticles of cellular origin is a generalized phenomenon. In addition, patients with MM, are at high risk of VTE and present with significant TF pathway activation and increased TG. A significant fraction, but not all, of the patients present strong signs of plasma hypercoagulability. The finding of high inter-individual variability of TG underlines the heterogeneity of blood coagulation alterations in PCD patients. The data of the prospective part of this study will allow validation of the clinical significance of this finding.