B1

Paraneoplastic antigen Ma2 autoantibodies as a blood biomarker for diagnosis, prognosis and detection of early recurrence of small intestine neuroendocrine tumors

Tao Cui[1], Monica Hurtig[2], Graciela Elgue[3], Su-Chen Li[1], Giuseppe Pelosi[4], Ahmed Essaghir[5], Jean-Baptiste Demoulin[5], Giulia Veronesi[6], Mohammad Alimohammadi[2], Kjell Öberg[2], Valeria Giandomenico[1]

[1] Department of Medical Sciences, Endocrine Oncology, Uppsala University, Uppsala SE-75185, Sweden; [2] Department of Medical Sciences, Uppsala University Hospital, Uppsala SE-75185, Sweden; [3] Division of Clinical Immunology, Uppsala University, Uppsala SE-75185, Sweden; [4] University of Milan, School of Medicine, Milan, Italy; Diagnostic Histopathology Unit, European Institute of Oncology, Milan IT-20141, Italy; [5] Université Catholique de Louvain, de Duve Institute, Brussels B-1200, Belgium; [6] Division of Thoracic Surgery, European Institute of Oncology, Milan IT-20141, Italy

Background: Small intestine neuroendocrine tumors (SI-NETs) belong to a rare group of cancer. Most patients have developed metastatic disease at the time of diagnosis, for which there is currently no cure. The delay in diagnosis is a major issue in the clinical management of the patients and new markers are urgently needed. We have previously identified paraneoplastic antigen Ma2 (PNMA2) as a novel SI-NET tissue biomarker. This finding prompted us to evaluate whether the detection of Ma2 autoantibodies in the blood stream is useful for the clinical diagnosis and recurrence of SI-NETs.

Methods: A novel indirect enzyme-linked immunosorbent assay (ELISA) was set up to detect Ma2 autoantibodies in blood samples of patients with SI-NET at different stages of disease. In total, 124 blood samples of SI-NET patients were included in the study. Ma2 autoantibodies in the blood from SI-NET patients were verified by western blot and sequential immunoprecipitation. The analysis was extended to 66 blood samples of typical and atypical lung carcinoids (TLC and ALC) to evaluate whether Ma2 autoantibodies in the blood stream may become a general biomarker for NETs.

Results: The novel Ma2 autoantibody ELISA showed high sensitivity, specificity and accuracy with ROC curve analysis underlying an area between 0.734 and 0.816. We observed that SI-NET patients expressing Ma2 autoantibody levels below the

cutoff had a longer progression and recurrence free survival compared to those with higher titers. We also detected higher levels of Ma2 autoantibodies in blood samples from TLC and ALC patients than from healthy controls, as previously shown in small cell lung carcinoma samples.

Conclusion: Here we show that high Ma2 autoantibody titers in the blood of SI-NET patients is a sensitive and specific biomarker, superior to chromogranin A (CgA) for the risk of recurrence after radical operation of these tumors.