Translational studies on coagulation and other aspects of hypoxic responses in small cell lung cancer

PhD thesis - Half time review seminar
January 17, 2019
Conference room, Kamprad, at 1 PM
Emelie Gezelius, MD
Division of Oncology and Pathology, Department of Clinical Sciences, Lund

Main supervisor: Mattias Belting
Co-supervisor: Hans Brunnström

Reviewers: Ana Carneiro, Helena Jernström
Background

Hypercoagulation is a hallmark of cancer and several coagulation factors are involved in malignant processes such as metastasis and angiogenesis. Pre-clinical and clinical studies have indicated that anticoagulants may have tumour-inhibiting effects, particularly in patients with small-cell lung cancer (SCLC).

The overall aim of my PhD project is to identify biomarkers that are predictive or prognostic of survival, development of venous thromboembolism (VTE) and response to low-molecular-weight heparin (LMWH), based on a randomized, phase 3 clinical trial investigating if addition of LMWH to standard treatment improves survival in SCLC.

Materials and methods

RASTEN is a randomized phase-III trial of LMWH (enoxaparin) in addition to standard therapy vs standard therapy in SCLC, with overall survival (OS) as primary outcome (paper I). Blood samples were collected continuously, and in the first sub-study we explored the role of coagulation biomarkers in predicting VTE risk and outcome, using four assays reflecting various facets of coagulation (paper II). In paper III we objectively measured adherence to LMWH using the ‘gold standard’ anti-factor Xa assay (anti-FXa) and the experimental Heparin Red® assay. Papers IV and V will examine biomarkers related to the hypoxic tumour microenvironment, including vasoactive peptides, using an advanced immunofluorescence assay and multiplex, proximity extension assay (PEA) technology.

Preliminary results

Paper I (published): The final analysis included 377 SCLC patients. The addition of LMWH did not improve OS despite a significant reduction in VTE.

Paper II (published): In control patients, increased total tissue factor was significantly associated with VTE incidence. Increased thrombin generation was significantly associated with decreased OS, especially in extensive disease.

Paper III (in submission): Heparin Red can be used to detect LMWH in clinical samples, and correlates to anti-FXa activity. We were not able to demonstrate a survival benefit in the subpopulation considered to be adherent, which supports the findings of the clinical trial.

Paper IV (in progress): The vasoactive peptides adrenomedullin and vasopressin appear to correlate strongly to SCLC survival, particularly in extensive disease.

Paper V (future project): We plan to explore the prognostic value of biomarkers related to specific signalling pathways in tumour biology and cardiovascular disease using extensive protein profiling.

Implications

The relationship between cancer and coagulation is highly complex. Based on our findings LMWH cannot be generally recommended in the management of SCLC. Moreover, our data underscore that predictive biomarkers are crucial to improve care for this patient group.
Published papers
