Venous thromboembolism, coagulation and cancer
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In this thesis three aspects regarding the association of cancer and the coagulation system have been evaluated. In the first part the anticoagulant treatment of cancer patients with and without venous thromboembolism (VTE) was discussed. Part two addressed the incidence of cancer after a spontaneous venous thrombotic event, whereas the last part evaluated the presence and significance of microvesicles in cancer patients.

PART I - ANTICOAGULANT TREATMENT IN CANCER PATIENTS

Chapter 2 reviewed the two sided association of cancer and the coagulation system and provided a background for this thesis. The multi-causal character of the hypercoagulable state in cancer patients was highlighted, as well as the intense debate which is ongoing on the benefit of screening for cancer in patients with idiopathic venous thromboembolism. Furthermore, an in-depth overview of the mechanisms by which cancer cells utilize coagulation proteins for growth and how heparin interferes with this process was provided.

In Chapter 3 the development of new anticoagulants has been summarized with special attention to the use of anticoagulant therapy in cancer patients. The current standard anticoagulant treatment consisting of (low-molecular weight) heparin (LMWH) followed by vitamin K antagonists (VKA) is frequently complicated by bleeding and recurrent VTE. Cancer patients suffering from VTE are increasingly treated with long-term LMWH treatment alone. Different studies showed a lower recurrent VTE rate in cancer patients with VTE treated with LMWH for 3 to 6 months in comparison with standard treatment without an increased risk for bleeding. Furthermore, LMWH treatment appeared to benefit survival in cancer patients.

Chapter 4 presented a meta-analysis of five randomized trials that investigated the long term effect of (LMW) heparin on survival in cancer patients without VTE. This analysis showed an overall survival benefit in all cancer patients treated with (LMW) heparin at 12 months (relative risk 0.87, 95% CI; 0.80-0.95) and 24 months (relative risk 0.92, 95% CI; 0.86-0.99). The effect was the highest in those with small cell lung cancer and limited disease (relative risk 0.27, 95% CI; 0.10-0.69 at 6 months). However, the beneficial survival effect was at the cost of a higher incidence of bleeding with a relative risk of 2.21 (95% CI 1.02-4.78).
Chapters 5 and 6 evaluated two new anticoagulant drugs in the treatment of VTE in cancer patients. In Chapter 5, the efficacy and safety of fondaparinux, a synthetic pentasaccharide, was compared to LMWH in the initial treatment of deep vein thrombosis (DVT) and to unfractionated heparin (UFH) in the initial treatment of pulmonary embolism (PE) in cancer patients. Regarding overall survival and bleeding, fondaparinux was comparable to LMWH and UFH in cancer patients, respectively. Also no significant differences in the recurrent VTE rates were observed. Chapter 6 addressed the efficacy and safety of a long-acting pentasaccharide, idraparinux, in the long-term treatment of cancer patients with DVT. No safety or survival differences were observed between cancer patients with DVT treated with idraparinux for six months compared to standard therapy, consisting of (LMW) heparin followed by vitamin K antagonists. There was a trend for less recurrent VTE in the idraparinux group during the six month treatment period (hazard ratio 0.39, 95% CI; 0.14-1.11).

The preliminary results of the INPACT study were described in Chapter 7, a randomized controlled trial that investigated the effect of nadroparin, a LMWH, on the overall survival in patients with advanced cancer. A total number of 503 patients with non-small cell lung cancer, hormone refractory prostate cancer or locally advanced pancreatic cancer were included. They were randomized to nadroparin, or to no nadroparin and all received standard anti-cancer treatment. The interim-analysis in July 2009 did not show a survival benefit in the patients treated with nadroparin. In the nadroparin recipients the median survival was 12.5 months compared to 11.9 months in the no-treatment arm (hazard ratio 0.92, 95% CI; 0.73.-1.16.). A comparable bleeding rate was observed.

PART II - VENOUS THROMBOSIS AND CANCER

Chapter 8 described the results of a prospective controlled cohort study, in which an extensive cancer screening strategy, consisting of a chest and abdominal CT scan and a mammography in women, was compared to a limited strategy in patients presenting with an idiopathic VTE. The limited strategy consisted of a standardized history taking, a thorough physical examination, basic laboratory tests and a chest X-ray. A total number of 630 patients were included. The additional value of the extensive screening strategy was low with 6 malignancies in 302 screened patients, whereas in 30% abnormalities were observed on the CT scans or the mammography, which required additional tests to exclude cancer. The incidence of newly diagnosed cancer during the first years after
presentation of idiopathic VTE was comparable between the two groups and the applied screening strategy did not benefit the survival in the patients included in the extensive screening arm (hazard ratio 1.22, 95% CI; 0.69-2.22). Therefore, we concluded that extensive screening for cancer in patients with idiopathic VTE is not warranted.

Chapter 9 evaluated the cost-effectiveness of screening for cancer in patients with idiopathic VTE in the framework of the study reported in Chapter 8. This analysis confirmed that CT-scans of the abdomen and chest cannot be used to detect malignancy in these high risk patients due to the low sensitivity (33%) and specificity (70%). The performance of the CT-scan in this study illustrated the disadvantages of the use of whole body CT-scans in asymptomatic, low risk populations.

The aim of Chapter 10 was to determine the incidence of cancer in primary care patients presenting with idiopathic superficial thrombophlebitis (SVTP). A total number of 250 idiopathic SVTP patients were included in a cohort study and the incidence of cancer during a two year follow up period was compared to the incidence of cancer in a cohort of gender, age and general practitioner matched controls and to the incidence in the overall Dutch population. This study did not show an increased incidence of cancer in patients presenting with idiopathic SVTP in primary care compared to the control cohort. The incidence was 2% (95% CI 1-5%) in the patients and 2% (95% CI 1-4%) in the controls. Also no difference was detected compared to the overall Dutch population (standardized morbidity ratio 1.1, 95% CI; 0.5-2.7).

PART III - MICROPARTICLES AND CANCER
The predictive value of microparticle-associated procoagulant activity for the development of VTE in cancer patients was studied in Chapter 11. The procoagulant activity was measured in 43 cancer patients by a phospholipid-dependent coagulation test, a factor Xa-generation assay and a fibrin generation test (FGT). The last two tests were also performed in the presence of anti-tissue factor or anti-factor VII(a). In five patients a VTE was reported during a six month follow up period. Receiver operating characteristic analyses showed that the FGT had the highest area under the curve (0.83, 95% CI; 0.68-0.98, p=0.017). A cut off level of 909 seconds resulted in a sensitivity of 80% and a specificity of 84%. Therefore, we concluded that the microparticle-associated procoagulant activity may identify those cancer patients at high risk for the development of VTE.
Chapter 12 reviewed the significance of circulating microvesicles, mainly consisting of microparticles, in cancer patients. In these patients, microvesicles have mainly been associated with their prothrombotic state. This review, however, also addressed their significance in cancer progression. Several in vitro and in vivo studies showed a significant contribution of microvesicles in the different stages in cancer growth, such as cellular survival, angiogenesis and the process of metastases.