Heparins, cancer and thrombosis: clinical and experimental studies
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INTRODUCTION
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A causal relationship between cancer and venous thrombosis has been recognized at least since 1868. In that year, Trousseau published his observations on the development of cancer, shortly after an episode of venous thrombosis (1). Venous thromboembolic complications also frequently occur in patients with clinically manifest malignancy (2-4). In addition, many cancer patients have laboratory signs of coagulation activation in the absence of clinically evident thrombosis (5-7). It has been shown that cancer cells can activate the coagulation system directly, by production of procoagulant factors and by interactions with platelets, leukocytes and endothelial cells (8-10). Moreover, comorbid factors, frequently present in patients with cancer, such as surgical interventions, prolonged periods of immobilization and chemotherapeutic treatment further increase the risk of thromboembolism in these patients (11-14).

Because of this high risk to develop thrombosis, a substantial number of cancer patients are treated with anticoagulants for either prevention or treatment. For many years, unfractionated heparin (UFH) has been the standard initial treatment for venous thromboembolism, followed by a course of vitamin K antagonists for several months. In the last decade, the relative efficacy and safety of low molecular weight heparin (LMWH) for the initial treatment of venous thromboembolism has been compared to UFH in a large number of randomized clinical trials (15). In one of the first of these trials, an unexpected improvement in 6 months mortality was observed in cancer patients who were treated with LMWH, relative to UFH recipients (16). This mortality reduction could not be attributed to a reduction in the incidence of fatal thrombotic or bleeding complications. It was noted that 44% (8 of 18) of the cancer patients with deep vein thrombosis in UFH group died during the 6 months of observation, compared with only 8% (1 of 15) of cancer patients in the LMWH group. Similar observations were reported in subsequent studies (17;18). These findings have led to a renewed debate whether heparins and other anticoagulants may interfere with the progress of malignant disease.

The hypothesis that anticoagulant agents can affect cancer progression is supported by data from experimental studies, that have shown that the coagulation cascade can be activated by cancer cells or their products, and that this process plays a crucial role in cancer spread (19-23). Anticoagulant agents, such as vitamin K-antagonists, heparins, platelet aggregation inhibitors or agents that affect fibrinolysis were found to inhibit cancer spread in these experimental studies (24). However, it is still controversial whether coagulation activation per se is important for tumor growth or metastasis, since effects of heparins and other anticoagulants on cancer spread may be mediated by mechanisms independent of coagulation inhibition. Heparins are negatively charged polysaccharides that can bind to a wide range of proteins and molecules and affect their activity. As a consequence, heparins have a wide variety of biological activities other than their anticoagulant effects which may interfere with the malignant process. Indeed, in various studies, variants of heparins as well as coumarin
derivates without anticoagulant activity have been found to inhibit metastasis or cancer progression (25-28). However, heparins stimulated metastasis or cancer-related processes in other experiments (29-31).

In this thesis, we address the issue whether UFH and/or LMWH can affect the malignant process. Results of clinical and experimental studies are critically evaluated, and potential mechanisms by which heparins may interfere with cancer progression are discussed and investigated.

In **Chapter 2**, we calculated and compared the mortality rates of patients with and without cancer, who received LMWH or UFH for the initial treatment of venous thromboembolism, from published randomized clinical trials. Since randomization in these studies was applied without stratification for the presence of cancer, we adjusted the survival rates of both treatment groups for prognostic factors such as age, sex, primary site, type and stage of cancer, to evaluate whether the observations of an improved mortality in cancer patients was indeed a result of LMWH. A clinically and statistically significant beneficial effect on survival remained in the subgroup of cancer patients, who were treated with LMWH, as compared to UFH. To elucidate potential mechanisms by which heparins may affect cancer progression, we critically reviewed all experimental studies in which heparins were tested as anti-cancer drugs. The findings are reported in **Chapter 3**. It was shown that heparins can affect various steps in tumor growth and metastasis, and that these effects are not solely related to the anticoagulant function of heparins. Both stimulatory and inhibitory effects of heparins on tumor growth and related processes have been observed.

Since the findings, described in chapter 2, of an improved survival in cancer patients who were treated with LMWH were relative to survival rates of UFH recipients, it cannot be concluded from these data that UFH on its own either improves, worsens, or has no effects on prognosis. Therefore, in **Chapter 4**, we systematically analyzed all clinical studies on the effects of UFH on survival of cancer patients without venous thromboembolism, relative to placebo or no treatment, to examine the possibility of a negative effect of UFH as an explanation for the findings in chapter 2. A similar review, described in **Chapter 5**, was performed on effects of vitamin K antagonists on survival of patients with malignancy. These systematic analyses revealed that, to date, there is no convincing clinical evidence that either UFH or vitamin K antagonists affect survival of cancer patients.

Since results of some experimental studies have indicated that LMWH and UFH differentially affect angiogenesis (32-34), this hypothesis was examined in Chapter 6, 7 and 8. In **Chapter 6**, we investigated effects of UFH and LMWH on *in vitro* angiogenesis. In this study, we demonstrated that LMWH can inhibit angiogenesis *in vitro*, in contrast to UFH, that stimulated capillary-like structure formation in a fibrin matrix. In **Chapter 7 and 8**, we examined the effects of both heparins on cancer progression and tumor-associated angiogenesis in two experimental tumor models in rats. LMWH and UFH did not affect experimentally induced colon cancer metastasis or angiogenesis.
within the tumors. However, colon carcinoma metastases are poorly vascularized. Therefore, we investigated effects of both heparins on highly vascularized sarcomas in a second study. Again, no effects on tumor growth or angiogenesis were observed for either heparin.

In Chapter 9, we explain the study design and present the interim safety results of an ongoing, double blind randomized study on effects of LMWH on survival of cancer patients without thrombosis. In this study, patients with cancer and poor prognosis (i.e. an expected survival of less than 18 months) receive subcutaneous injections of LMWH or placebo for a period of 6 weeks. The 6 months mortality rates of both treatment groups will be compared. In the safety analysis, a 4% incidence of major bleeding was observed, which is within the expected range for LMWH-therapy. In Chapter 10, we evaluated the incidence of venous thrombosis in cancer patients, and discuss whether the treatment of thrombosis in these patients should be different from patients without malignancy, in view of the higher risk of both recurrent thrombosis and bleeding.

As discussed above, the thromboembolic event can be the first clinical manifestation of an underlying malignant process. Indeed, in a substantial number of patients, cancer becomes apparent in the early period following an episode of thrombosis, especially when the thrombotic event is idiopathic (35;36). These findings have raised the issue whether patients with idiopathic venous thromboembolism should be screened for an underlying malignancy. However, consensus about the appropriateness of screening for cancer in these patients has not been achieved. The controversy is related to the true prevalence of ‘occult cancer’ in this patient population and the unknown benefit of early detection on the ultimate outcome (37;38). In Chapter 11, we examined the potential efficacy of screening for cancer in patients presenting with venous thromboembolism. To achieve this objective, we analyzed data from two large population-based studies in Scandinavia in which more than 88,000 patients diagnosed with venous thromboembolism were followed for several years, to assess the subsequent diagnoses of cancer (39;40). Using these data, we calculated the number of thrombosis patients needed to screen to detect one extra particular type of cancer, in excess of the population-based expected number. The findings suggest that it may be worthwhile to screen for some types of cancer, including prostate, lung, ovarian and colon cancer.

REFERENCES

CHAPTER 1
INTRODUCTION


