Heparins, cancer and thrombosis: clinical and experimental studies
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SUMMARY AND GENERAL DISCUSSION
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Since the 1930's, a number of clinical and experimental studies have evaluated the effects of anticoagulants, such as heparins and vitamin K-antagonists, platelet aggregation inhibitors or fibrinolytic agents on cancer progression. These agents were tested for their anticancer properties, since it was assumed that blood coagulation plays an important role in the process of cancer spread. Indeed, experimental studies have indicated that platelets, thrombin and clot formation are important for intravascular arrest and survival of cancer cells in the circulation (1-3). Furthermore, cancer cells often express procoagulant factors and many patients with cancer have signs of intravascular coagulation activation (4;5). Conceivably, anticoagulants can interfere with the malignant process. However, results of studies in which anticoagulants were tested for their potential anticancer effects are not conclusive. Interpretation of the wide variety of results is difficult, since diverse tumor and animal models were used in experimental studies, and the methodology of clinical studies varied from rigorous to invalid. Moreover, it has been shown that anticoagulant agents, especially heparins, are endowed with a number of other biological properties besides their anticoagulant activity that may affect tumor growth and metastasis. This further complicates the interpretation of effects of anticoagulants such as heparins on cancer progression. Findings in recent clinical trials have created a renewed interest in the potential of heparins and other anticoagulants to affect cancer progression. In randomized trials, in which the efficacy and safety of low molecular weight heparin (LMWH) for the initial treatment of venous thromboembolism was compared with that of unfractionated heparin (UFH), an unexpected mortality reduction was observed in cancer patients who were treated with LMWH, as compared to UFH recipients. In a meta-analysis of these trials (chapter 2), we calculated and compared the mortality rates of patients with and without cancer of both treatment groups. The mortality rates of the two groups did not differ in patients without cancer, but a clinically relevant and statistically significant reduction in 3 month-mortality was found in the subgroup of LMWH-treated cancer patients, as compared with cancer patients who received UFH for their venous thromboembolism (odds ratio (OR) 0.61; 95% confidence interval (CI): 0.40-0.93). These findings cannot not be explained by differences in fatal thromboembolic complications or hemorrhages. To evaluate whether the improved mortality was indeed a result of LMWH-treatment and since randomization in these studies was applied without stratification for cancer, we adjusted the survival rates of both treatment groups for prognostic factors, such as age, sex, primary site, type and stage of cancer. After adjustment, the statistically significant beneficial effect on survival remained in the subgroup of cancer patients who were treated with LMWH (OR 0.39; 95% CI: 0.15-1.02). These clinical results thus suggest that either LMWH or UFH, or both agents, interfere with the malignant process and affect survival of patients with cancer.

It is unknown whether possible effects of heparins on the malignant process are related to their anticoagulant function. To elucidate potential mechanisms by which heparins may affect cancer
progression, we critically evaluated all animal studies in which heparins were tested as anticancer drugs (chapter 3). Most of these studies reported effects of UFH, or variants of UFH without anticoagulant capacities, on experimentally induced tumor growth or metastasis. The results of these studies are not conclusive. UFH did not affect growth of subcutaneously implanted tumors, but effectively inhibited spontaneous or experimentally aggravated metastasis in most studies, whereas in other experiments, treatment with UFH induced cancer spread. We also assessed the effects of heparins on various steps in cancer progression, including proliferation, migration and invasion of cancer cells, adherence of cancer cells to vascular endothelium, angiogenesis, and interactions between the immune system and cancer cells. The combined results of a number of in vitro and in vivo studies showed that UFH and related compounds, such as heparan sulfates, can interfere with all these processes in various ways, resulting in either stimulatory or inhibitory effects on cancer progression. Therefore, the ultimate effect of UFH on the malignant process is unpredictable. Moreover, since processes such as proliferation, migration, invasion and angiogenesis are important for both primary tumor growth and metastasis, it is difficult to understand why UFH affects metastasis but not growth of primary tumors in vivo.

In addition to experimental studies, we also analyzed all clinical studies that evaluated effects of UFH on survival of cancer patients, relative to placebo or no treatment (chapter 4). This analysis was performed to examine the possibility of a negative effect of UFH as an explanation for the findings in chapter 2, since the observed mortality reduction in LMWH-treated cancer patients was relative to treatment with UFH. We first classified the studies on methodological strength, to avoid possible bias as a result of invalid study methodology. In line with our conclusions with respect to experimental studies in chapter 3, this systematic clinical review revealed that, to date, there is no convincing evidence that UFH affects survival of cancer patients in one direction. Whereas trials with a less rigid methodology reported improved survival of UFH-treated patients with cancer, randomized studies showed no or possible detrimental effects of UFH. Similar conclusions were drawn on the basis of a systematic clinical review on effects of vitamin K-antagonists on survival of patients with cancer (chapter 5).

The effects of LMWH on cancer progression are less well studied than those of UFH. However, since LMWHs are small fragments of UFH, it is conceivable that LMWHs also affect diverse steps in tumor development and metastasis and that some of these effects are different from those of UFH. In chapter 6, 7 and 8, we examined the hypothesis that LMWH and UFH differentially affect angiogenesis, a crucial step in cancer progression. In chapter 6, we studied effects of LMWH and UFH on in vitro angiogenesis. For these experiments, human microvascular endothelial cells were seeded on top of a fibrin matrix, that was altered by addition of either LMWH or UFH during polymerization. The cells were stimulated with angiogenic growth factors to induce the formation of capillary-like tubular structures. Turbidity measurements and electron microscopy showed that the presence of LMWH during polymerization of the fibrin matrix led to a more transparent rigid
network with thin fibrin bundles, while the presence of UFH resulted in a more opaque malleable network with thick fibrin fibers. The formation of capillary-like tubular structures was retarded in matrices polymerized in the presence of LMWH, whereas matrices polymerized in the presence of UFH facilitated tubular structure formation. 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 also investigated the effects of both heparins on a highly vascularized sarcoma. Again, no effects on tumor growth or angiogenesis were observed for either type of heparin. Consequently, we concluded that the effects of heparins on tumor growth and tumor-associated angiogenesis in vivo are probably limited.

As discussed, UFH has numerous biological activities. Therefore, it can affect malignancy progression by various mechanisms. Observed effects in experimental models may be a result of one particular activity of UFH, or may be related to the tumor model or animal model used, rather than a reflection of the overall effect of UFH on cancer progression. Hence, data from in vitro experiments or animal experiments on effects of UFH on cancer progression or related processes should be interpreted with caution. It is likely that similar conclusions can be drawn for LMWH. These findings stress the importance of methodologically valid clinical trials to establish unequivocally effects of heparins on survival of patients with cancer. Therefore, we are conducting a randomized placebo-controlled clinical trial to evaluate whether LMWH, irrespective the mechanism, can improve survival of cancer patients without venous thromboembolism. In this trial, a total of 300 patients with various types of 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. Therapeutic dosages of LMWH are given during the first two weeks, whereas in the subsequent four weeks, the initial dose is halved. To evaluate effects of LMWH on survival, the 6-months mortality rates of both treatment groups will be compared. The results of this study and other to the question related clinical randomized trials that are in progress at the moment will give a final answer whether LMWH-treatment can improve survival of cancer patients. In this thesis, the study design and interim safety analysis of the first 151 patients that were included are presented (chapter 9). A 4% incidence of major bleedings was observed, which is within the expected range of LMWH-therapy. Since this safety analysis remained blinded, no conclusions can be drawn yet about effects of LMWH on mortality.

The findings of an improved survival of cancer patients with venous thromboembolism who were treated with LMWH, as compared to UFH, as described in chapter 2, have also initiated the discussion whether treatment of thrombosis in patients with malignancy should be altered. In chapter 10, we analyzed the incidence of venous thrombosis in cancer patients, and discussed whether treatment of thrombosis in these patients should be different from patients without
malignancy. It was shown that for most types of cancer, with the exception of breast cancer, there is a lack of prospective studies documenting the precise incidence of thromboembolic complications in cancer patients. Anticancer treatment, such as chemotherapy or hormonal therapy, increases the risk of thrombosis in patients with breast cancer. We also evaluated studies that reported incidences of recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with malignancy. Patients with cancer were found to have an increased risk of recurrent venous thrombosis during anticoagulant treatment, as compared to patients without cancer. In addition, some trials showed that the risk of bleeding during anticoagulant treatment is enhanced in patients with malignancy, and that therapy with vitamin K-antagonists is often difficult to manage. These findings indicate that treatment of venous thromboembolism in cancer patients should be improved and alternatives in treatment considered. LMWH has been found to be at least as effective and safe as UFH for the initial treatment of venous thromboembolism. In view of the observed mortality reduction in cancer patients treated with LMWH, LMWH is recommended as initial treatment for venous thromboembolism in patients with malignancy. Moreover, prolonged treatment of LMWH may be considered in stead of conventional therapy with vitamin K-antagonists. At present, the efficacy and safety of long-term use of LMWH for treatment of venous thromboembolism in cancer patients is investigated in a multi-centre randomized clinical trial.

Finally, in Chapter 11, we examined the potential efficacy of screening for cancer in patients presenting with venous thromboembolism. 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 (6;7). However, it is still controversial whether patients with idiopathic venous thromboembolism should be screened for underlying malignancy, because the true prevalence of ‘occult cancer’ in this patient population is unknown. Moreover, the benefit of early detection on the ultimate outcome is unclear (8;9). Recently, 2 two large population-based studies from Scandinavia were published, in which more than 88,000 patients diagnosed with venous thromboembolism were followed for several years to assess the subsequent incidence of cancer (10;11). 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, in patients presenting with idiopathic venous thromboembolism.

REFERENCES


