Cancer, thrombosis and low-molecular-weight heparins
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Citation for published version (APA):
CHAPTER 13

Anticoagulants and cancer survival

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Published in:

Semin Thromb Haemost 2006;32:810-3

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Abstract

The association between cancer and activation of blood coagulation has been described since Trousseau’s time. The hypercoagulable state often encountered in cancer patients not only acts as an important risk factor for thrombosis, but also may play a role in tumor progression and metastatization. An antineoplastic effect of anticoagulants in this setting has often been hypothesized. The results of recently conducted clinical trials suggest that cancer patients could have a benefit from the administration of low-molecular-weight heparin, particularly in those with non advanced disease. Additional clinical trials are needed to provide an important step forward in this challenging setting.

The relationship between cancer and venous thromboembolism has been documented since Trousseau’s time and has been documented and confirmed since then (1). Basic research progressively has improved our knowledge on the mechanisms and functions of coagulation activation in human malignancies. The results of these studies have shown that (1) tumor cells are able to activate blood coagulation in different ways; (2) these capacity parallels tumor cell malignant transformation; (3) fibrin formation in tumor tissue as the final of clotting activation appears involved directly in tumor growth and dissemination (2,3); and oncogenic events (4) regulate tissue factor expression in cancer cells (4) or drive other genetic programmes linking cancer to hemostasis (5). The interaction between the hemostatic system and cancer cells is associated with two conditions. First the hypercoagulable state generated in this pattern acts as a high-risk condition for the development of thromboembolic complications. Second, the activation of blood coagulation influences the biology of the tumor by implicating itself in tumor progression and in the development of metastases (2,3). Because of the possible involvement of the hemostatic system in tumor growth and progression, one of the most exciting issues related to anticoagulant therapy is the potential for an antineoplastic effect in patients with cancer. The interest in the possible antineoplastic effect of anticoagulants has over time converged onto low-molecular-weight heparins (LMWH). These drugs might affect the natural history of cancer either by counteracting cancer growth and dissemination or by increasing the response to anticancer therapy. Data from clinical trial in the thromoprophylaxis and treatment settings of VTE in cancer patients, have suggested that heparins may have a beneficial effect on survival in these patients, with a major role of LMWH compared to unfractionated heparin. Although published studies look promising and provide an important step forward in the development of this field, additional clinical trials are needed to assess this challenging topic.

The effect of anticoagulants on cancer

Along with experimental studies shedding more light on antimalignant properties of antithrombotic agents, a growing body of evidence coming from clinical trials suggests that adjunctive therapy with anticoagulants may improve prognosis in cancer patients. From a clinical research view point, the first report on a possible beneficial effect of anticoagulants in cancer progression was about vit K antagonists (VKAs) and dates back to the 1960s (6). The first clinical evidence in support of anticoagulants having an antineoplastic effect was reported in a prospective randomized trial testing warfarin for survival of cancer patients by Zacharsky et al (7), and showed that warfarin administration significantly affected the mortality in patients with small cell lung cancer (SCLC). However, subsequent randomized clinical trial on warfarin in patients with other types of cancer did not achieve the same results, and a systematic review of studies on VKA and mortality in cancer, by Smorenburg et al (8), concluded that there Was not enough evidence to support long term therapy with VKA to prolong survival in patients with established cancer.

Since these report were published, a large number of studies focused on the impact of heparin (first unfractionated heparin (UFH) and then LMWH) on mortality in patients with cancer. In fact, during during the 1980s and early 1990s some retrospective evaluations of cohorts of cancer
patients enrolled in randomized clinical trials of peri-operative prophylaxis with UFH versus no prophylaxis have reported a beneficial effect of UFH on overall survival (9). They found that not only did patients who received heparin therapy for VTE prophylaxis have a significantly lower 3-years mortality rate in comparison to patients who did not receive prophylaxis, but also death from metastatic cancer in the group of patients undergoing prophylaxis was notably reduced. In a randomized prospective multicenter study by Labeau et al (10) among patients with SCLC undergoing chemotherapy and receiving or not receiving concomitant therapeutic doses of UFH, it was shown that the response rate was significantly higher among patients receiving UFH together with chemotherapy than among those receiving chemotherapy alone (37% versus 23%, p=0.004). The median survival was also significantly longer in the UFH group. However, this benefit was statistically significant only in the subgroup of patients with a limited disease (p=0.03). A systematic review of all methodologically correct clinical trial that compared UFH with placebo or non treatment in patients with cancer without thromboembolism, found no convincing evidence of either positive or negative effects of UFH on survival of patients with malignancy (11).

Although the beneficial effect of UFH on cancer survival have been questioned, by contrast, several studies support a positive impact of LMWH on cancer prognosis. Two meta-analysis of all clinical trials testing the efficacy of LMWH versus UFH for the initial treatment of VTE showed reduction in mortality among cancer patients receiving LMWH (12,13). This indication, together with the known advantage of LMWH administration and the feasibility of long term treatment, has provided an impetus for researchers to continue investigating heparin’s potential role as an antineoplastic agent by designing prospective randomized clinical trial addressing as primary end-point the survival of cancer patients without VTE receiving LMWH, stratified by tumor cell type, stage and other prognostic variables (1).

Recent Clinical Trials addressing the topic

In a pilot study Wojtukiewitz et al (14) evaluated the effect of a LMWH (enoxaparin 20 mg/die subcutaneously) in 27 patients with melanoma. The survival rate for patients with stage III and IV receiving enoxaparin compared favourably with those investigated in the past and receiving only chemotherapy. Given the promising benefit based upon this investigation, additional studies have been proposed to highlight the topic. Recently, the publication of at least three randomized clinical trials testing LMWH for improvement of survival in cancer patients as a primary end point have further enhanced research knowledge on the topic. The Fragmin Advanced Malignancy Outcome Study (FAMOUS) (15) was the first prospective, randomized placebo-controlled trial to examine possible effects of a LMWH (dalteparin) on survival among patients with cancer, but without underlying thrombosis. In this study 385 patients with advanced solid malignancies of various types, without any evidence of thrombosis, were randomly assigned to receive either 5000 anti Xa Units of dalteparin subcutaneously daily or placebo along with standard cancer therapies in both groups. Dalteparin was associated with a survival advantage at 1,2 and 3 years, although the difference form placebo was not statistically significant: 46% of dalteparin patients compared with 41% of placebo patients were alive at 1 year (p=0.19). In a post hoc subgroup analysis of good prognosis patients it was found that LMWH was associated with a significant increase in survival.

The effectiveness of LMWH (dalteparin 5000 Anti Xa u/die subcutaneously for 18 weeks) in patients with SCLC, administered in combination with chemotherapy versus chemotherapy alone, was evaluated by Altimbas et al (16). In the overall trial population, the tumor response rate was significantly higher in patients receiving chemotherapy plus LMWH compared with chemotherapy alone (69.2 versus 42.5% p=0.07). The median progression free survival was significantly longer with the addition of LMWH (10 versus 6 months with chemotherapy alone, p=0.01). The survival advantage was more pronounced in patients with limited disease. The present study, although small in size, discloses promising results by assessing that patients with SCLC could benefit from the administration of LMWH, at prophylactic dosages, and that anticoagulant administration in this setting is safe even during chemotherapy.
The Malignant and Low Molecular Weight Heparin Trial (MALT) (17) is a randomized, placebo-controlled clinical trial, which enrolled 302 patients with various solid malignancies, without evidence of VTE. Patients with metastatic or locally advanced solid tumors were eligible for the study. Patients randomly assigned to the treatment arm initially received full treatment doses of nadroparin for 2 weeks, and then received half of the treatment dose for other 4 weeks. The control group received placebo for 6 weeks. A modest but significant survival benefit was observed among patients treated with LWWH when compared with those who did not receive LMWH. Moreover, the beneficial effect of LMWH on cancer survival was more evident among patients in whom life expectancy at entry was at least 6 months. Nadroparin treatment was associated with a similar improvement in survival, whether or not chemotherapy was administered concomitantly.

The same results have been indicated in a study assessing efficacy and safety of long term LMWH administration versus oral anticoagulants as secondary prevention in patients with cancer and acute VTE, in which LMWH was administered for 6 months. In a post-hoc analysis of this randomized clinical trial, an advantage in survival in patients receiving long-term LMWH was observed, particularly among those patients with limited disease at entry (18,19).

**Conclusion**

The results of these studies raise the question of how LMWHs may be achieving the potential effect in prolonging survival in this setting. The results suggest that LMWH may help modulate certain processes in cancer evolution and may provide a survival benefit, especially among patients with a better life expectancy at entry, although data from these studies have increased interest in a possible prolongation of cancer patients survival when LMWH is administered, the available evidence remains limited. These trials are heterogeneous for many reasons: for example FAMOUS and MALT studies included patients with different types of cancer at different stages, who had undergone different treatments. The study by Altinbas et al (16) included only patients with SCLC, but at different stages. The effect of LMWH may not be the same with different cancer types, and the stage also may be important in this setting. Moreover, these patients were administered different LMWH, different treatment regimens, and different duration of treatment.

Hence the potential important role of LMWH on survival in patients with advanced solid malignancy deserves additional clinical evaluations. Clinical trial should be undertaken to identify the types and stages of cancers that are most likely to respond to this form of therapy. Finally, there is a need to assess potential differences between LMWHs in this setting, and to optimize dosages and durations of LMWH treatment.
References


