Anticoagulant treatment and survival in cancer patients. The evidence from clinical studies

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The association between cancer and an increased incidence of venous thromboembolism (Trousseau syndrome) is well characterized and recent studies have shown that the hemostatic system plays a key role at different stages in the process of tumorigenesis. Anticoagulant drugs therefore appear to be an attractive strategy in cancer therapy, with an effect that would surpass the benefit of preventing thrombosis. This hypothesis was initially supported by the post-hoc analysis of clinical trials not primarily designed to evaluate the effect of anticoagulants, mainly low molecular weight heparins (LMWH), on cancer survival. Other studies regarding the addition of unfractionated heparin or oral anticoagulants to standard cancer treatment offered controversial results. However, recent investigations among cancer patients without deep venous thrombosis, with cancer-related mortality as the primary end point, suggest that at least in some patients LMWH may exert an antineoplastic effect *in vivo* and alter the natural history of malignant disease by increasing the response rates and, therefore, improving survival. Additional research on this field is needed to clarify the biological mechanisms involved and to answer yet unsolved questions such as the types of tumor and stages of disease most suitable for this treatment as well as how to optimize treatment regimens.

Key words: cancer, venous thromboembolism, low-molecular-weight heparin.

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The association between cancer and thrombosis was described for the first time in the nineteenth century.[1] Since then, great advances have been achieved in the field, leading to a better understanding of the pathophysiological mechanisms involved in the pathogenesis of this bi-directional association. On the one hand, cancer development induces a chronic hypercoagulable state that, added to other predisposing conditions in cancer patients (e.g. immobility, surgery, central venous catheters, antineoplastic treatments), leads to an increased risk of venous thromboembolism (VTE).[2] But on the other hand, the hemostatic system also plays a key role in the progression of malignant disease. In fact, cancer patients who develop VTE have a poorer prognosis over time in comparison with patients without thrombosis.[3] Furthermore, it has been reported that a persistent activation of the hemostatic pathway, with increased thrombin generation, is associated with an increased incidence of clinical malignancies, especially of the digestive tract.[4] In addition, plasma levels of coagulation activation markers are strong predictors of cancer survival.[5] During the last few decades there has been growing evidence pointing to possible benefits of anticoagulant treatment in cancer patients, in terms of cancer progression and survival, that would surpass the benefit achieved by the anti-thrombotic effect.[6] The hypothesis that anticoagulants influence cancer progression has been investigated in numerous experimental *in vitro* and *in vivo* studies, showing that these drugs (especially heparins) can interfere with cancer cell proliferation, tumor growth, angiogenesis, development of hematogenous metastasis, immune system reactions or drug resistance.[7-9] Experimental observations were supported by results obtained after post-hoc analysis of data obtained in some old studies on VTE treatment in cancer patients, and led to the design of new studies specifically aimed to evaluate the effect of anticoagulant drugs on cancer progression and survival in cancer patients. In particular, four new clinical studies with low molecular weight heparins (LMWH) have been published in the last year, renewing the interest in this field. This review will focus on the role of

Table 1. Classification of studies supporting the existence of an effect of anticoagulant drugs on cancer.

Studies providing indirect evidence
- Studies comparing LMWH vs UFH in the initial treatment of VTE

- Studies comparing LMWH vs OAT as secondary prophylaxis of VTE

- Studies comparing LMWH vs UFH as VTE prophylaxis after cancer surgery
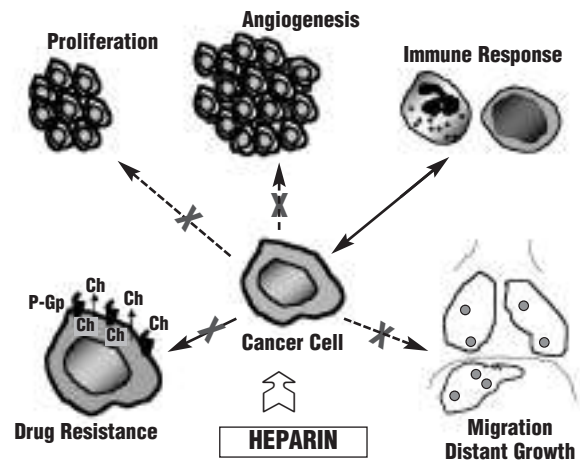
Studies providing direct evidence
- Evaluation of survival in cancer patients treated with standard treatment + oral anticoagulants or standard treatment + placebo/no treatment.

- Evaluation of survival in cancer patients treated with standard treatment + UFH or standard treatment + placebo/no treatment.

- Evaluation of survival in cancer patients treated with standard treatment + LMWH or standard treatment + placebo/no treatment.

Figure 1. Potential coagulation-independent anticancer properties of heparins suggested by experimental studies. Ch: Chemotherapy; P-Gp: P-glycoprotein.

anticoagulant treatment and survival in cancer patients in the light of recent clinical trials. The literature contains studies providing both indirect and direct evidence about a potential effect of anticoagulants in cancer treatment (Table 1). Emphasis is placed on low molecular weight heparins.

Pathogenetic mechanisms in cancer and thrombosis

Cancer patients often show activation of blood coagulation and impairment of fibrinolysis that may result in the development of a thrombotic diathesis.[10,11] The pathogenesis of cancer-related thrombosis is complex and multifactorial. The mechanisms involved include the capacity of tumor cells to directly produce and release molecules with procoagulant or fibrinolytic activity: tissue factor, cancer procoagulant, urokinase-type plasminogen activator, tissue-type plasminogen activator, plasminogen activator inhibitor-1, among others.[12] Also, tumor cells interact with host cells (mainly endothelial cells, platelets and monocytes) inducing activation and release of different pro-coagulant mediators.[12] However, as mentioned above, the link between the hemostatic system and cancer is bi-directional. Tumor growth is dependent on angiogenesis, and it has been shown that components of the coagulation cascade (tissue factor, thrombin, fibrin) and platelets can influence tumor vessel development by both clotting-dependent and clotting-independent mechanisms, including upregulation of pro-angiogenic proteins such as vascular endothelial growth factor (VEGF) or cleaving protease-activated receptors.[13,14]

In addition, tumor-cell induced thrombin generation and platelet activation are involved in the process of metastasis. Cancer cells bind to activated platelets and fibrin inside the circulating blood preventing tumor cells from immune recognition and destruction. The tumor cell-fibrin-platelet complex is then able to bind to endothelial cells with subsequent extravasation and secondary distant growth.[8]

Therefore, anticoagulants would appear an attractive treatment for patients with cancer, although their effectiveness and mechanism of action are still far from being completely clarified.

Biological antineoplastic effects of anticoagulants

The biological antitumor effects of anticoagulant drugs have recently been reviewed[7,15] and will, therefore, be described only briefly. While vitamin K antagonists have been reported to exert an anticancer effect, mainly through their anticoagulant action, heparins also show coagulation-independent antineoplastic properties (Figure 1).

Heparins can influence proliferation of cancer cells through inhibition of proto-oncogene expression, inhibition of kinase phosphorylation, or induction of apoptosis. However, in several animal models of spontaneous metastasis, heparin failed to affect local growth of transplanted tumors.[7]

Angiogenesis is a complex multi-step process involving endothelial cell proliferation, migration, degradation of extracellular matrix and formation of new capillary structures. Heparins, especially LMWH, can interfere with binding of growth factors to their receptors. Small heparin fragments reduce vascular endothelial growth factor activity and compete with heparan sulfates in the extracellular matrix that store growth factors and prevent them from pro-

teolytic degradation. In addition, heparins can affect angiogenesis by altering the structure of fibrin matrices, and an inhibitory effect on proliferation and migration of endothelial cells has also been described. Moreover, heparins decrease tissue factor expression (tissue factor enhances angiogenesis by upregulating vascular endothelial growth factor expression). A recent report has shown that the inhibitory effect of a LMWH (tinzaparin) on endothelial tube formation is associated with the release of tissue factor pathway inhibitor.[16]

On the other hand, heparins can modulate activation of leukocytes, inhibit adhesion of leukocytes to endothelium and increase natural killer cell activity.[17] The biological importance of these effects of heparins on the immune system in cancer needs to be clarified.

The development of metastasis is also affected by heparins, through inhibition of adhesion of cancer cells to extracellular matrix proteins, such as fibronectin or laminin, or to endothelial cells (as a result of interfering with selectins) and cancer cell migration (inhibition of heparanases is probably involved).[7] Experimental animal models of metastasis have shown that shortly after intravenous injection of cancer cells there is a transient decrease in the circulating platelet count as a consequence of formation of tumor cell-platelet aggregates.[18] These aggregates allow tumor cells to survive (escaping the immune response) and facilitate their arrest in narrow capillaries within different organs developing distant metastasis. Animals pre-treated with LMWH showed less thrombocytopenia after tumor cell inoculation and developed fewer distant metastases than controls.[19]

Finally, a recent *in vitro* study reported an inhibitory effect of heparin on P-glycoprotein-mediated multidrug resistance, and so heparin would appear to be a potential chemosensitizer that may increase the efficacy of antineoplastic therapies.[20]

In conclusion, although there are some conflicting results, basic research provides strong data supporting an effect of anticoagulants (especially heparins) on tumor biology.

Anticoagulants in cancer patients: indirect evidence

Three different types of studies, not primarily designed to evaluate the effect on cancer mortality, suggest a possible effect of LMWH on cancer survival: a) LMWH versus unfractionated heparin (UFH) as initial treatment of VTE in cancer patients; b) LMWH versus oral anticoagulants as secondary prophylaxis of VTE in cancer patients; c) LMWH as VTE prophylaxis in cancer surgery.

LMWH vs UFH in the initial treatment of VTE

In 1992 Green *et al.* reported a significant difference

Table 2. Mortality during follow-up (3-6 months) in cancer patients with VTE after initial treatment with UFH or LMWH.

Meta-analysis	Mortality		Odds Ratio
	UFH	LMWH	(95% CI)
Green *et al.* 1992[21]	21/67 (31%)	7/62 (11%)	0.28 (0.1 - 0.7)
Siragusa *et al.* 1996[24]	23/81 (28%)	10/74 (14%)	0.33 (0.1 - 0.8)
Hettiarachchi *et al.* 1999[25]	71/323 (22%)	46/306 (15%)	0.61 (0.4 - 0.9)

in cancer-related mortality after analyzing the data from two randomized studies comparing LMWH and UFH in the treatment of proximal deep vein thrombosis.[21-23] Combining both studies, patients with cancer receiving LMWH had a survival advantage over those treated with UFH. After a follow-up of 3-6 months, there had been 21/67 (31%) cancer deaths in the standard heparin group and 7/62 (11%) in the LMWH group (p=0.005). That difference could not be attributed to fatal thrombotic or hemorrhagic events.

Similar data were obtained from two meta-analyses of all available randomized clinical trials in which LMWH was compared with UFH in the treatment of VTE[24,25] (Table 2). The most recent one included nine studies and over 3500 patients with VTE, 629 with cancer.[25] Patients were randomized to receive either subcutaneous LMWH or intravenous UFH for 5 to 10 days, followed by oral anticoagulants for at least 3 months. In patients without cancer, there were no differences in 3-month mortality between patients treated with LMWH (39/1481) or UFH (41/1471). However, 117 out of 629 cancer patients died within the first 3 months of follow-up (46/306 in the LMWH group and 71/323 in the UFH group). The pooled odds ratio for the 3-month mortality in cancer patients was 0.61 (95%CI 0.40 – 0.93) in favor of LMWH. Differences in 3-month mortality between the two groups remained after adjusting for some prognostic factors (age, gender, tumor characteristics), supporting the conclusion that the treatment had a real effect. Again, the differences observed could not be attributed to a higher incidence of fatal bleeding or thrombotic complications in the UFH group, which were equally infrequent in the overall population (1.1% versus 1.3%). Although no data regarding incidence of these fatal events in the cancer group were available, this low incidence makes a significant difference between cancer patients receiving LMWH or UFH unlikely. Of course, these results must be interpreted with caution. None of these

studies was designed to evaluate the effect of the anticoagulant drug on cancer mortality; in fact, cancer patients were only a small percentage of the whole population included in the different studies, so the possibility of bias due to uncontrolled distribution of confounding factors related to malignancy cannot be ruled out. Moreover, it is difficult to establish how short-term LMWH treatment can reduce cancer mortality. As a consequence, clear conclusions about the benefits of LMWH on long-term survival could not be drawn. Interestingly, however, recent *in vitro* studies have shown that the heparin chain length is responsible for the variable effects of heparins on the hemostatic properties of endothelium and angiogenesis.[26,27] LMWH showed a stronger inhibition of endothelial cell proliferation and formation of tubular-like structures than did UFH or a pentasaccharide.

LMWH vs oral anticoagulants in the secondary prophylaxis of VTE

In order to investigate whether LMWH was more effective and safer than oral anticoagulant therapy in preventing recurrent thromboembolism in patients with cancer who had suffered a first episode of VTE, 676 patients were randomized to receive either dalteparin or a coumarin derivative for 6 months, in the setting of a multicenter trial, the CLOT study.[28] Dalteparin was more effective than oral anticoagulants in reducing the risk of VTE recurrence (27/336 patients in the LMWH group and 53/336 patients in the oral anticoagulant group; $p=0.002$) without increasing the risk of bleeding (14% and 19%, respectively). Mortality rates at 6 months were 39% in the LMWH group and 41% in the oral anticoagulant group ($p=0.53$), most of them related with cancer progression. A further post-hoc analysis, performed to determine any treatment-related difference in mortality at 12 months in patients with solid tumors, showed mortality rates during the 12-month follow-up period of 59% in both the dalteparin group (174/296 patients) and warfarin group (182/306 patients). However, there were differences if patients with or without known metastasis were analyzed separately.[29] The probability of mortality at 12 months in patients with known metastasis was similar in the dalteparin and warfarin groups (72% and 69%, respectively). In contrast, in the subgroup of patients with non-metastatic solid tumor at randomization (n=150 patients) the cumulative mortality at 12 months was 20% (15/75) for those treated with LMWH and 35% (26/75) for those treated with oral anticoagulants (hazard ratio, 0.50 [95% CI 0.27–0.95], $p=0.03$). This difference in mortality could not be attributed to treatment group differences in fatal pulmonary embolism, and did not change after adjustment for other possible confounding variables such as age, tumor type, cancer treatment, ECOG status or type of thrombotic episode. Once again, caution is required since results were observed after a post-hoc analysis of a population not defined *a priori* and the number of patients without known metastasis included was relatively small (75 in each treatment group). In addition, the population recruited was heterogeneous and some potential confounding factors such as time from diagnosis of the malignancy or previous antineoplastic therapies were not considered. Furthermore, patients in the CLOT trial were cancer patients with an objectively diagnosed VTE, thus conclusions could only be applied to that population. However, the results are in line with those of recent trials designed to investigate the influence of LMWH on cancer survival (*FAMOUS and MALT trials, see later*).

In a previous study with a similar aim, 146 patients with cancer and an objective diagnosis of VTE were randomized to receive anticoagulant treatment with a fixed dose of LMWH (enoxaparin 1.5 mg/Kg/day) or oral warfarin (adjusted to achieve an international normalized ratio –INR- between 2.0 and 3.0), for 3 months.[30] During the study treatment period, patients assigned to receive warfarin experienced a higher incidence of recurrent VTE and major hemorrhages (composite end-point) than those treated with LMWH (21.1% vs 10.5%; relative risk: 2.02, 95%CI, 0.88–4.65) ($p=0.09$). Mortality during the 3-month study period was also higher in the warfarin group (22.7%) than among patients receiving LMWH (11.3%). However, this difference in mortality rate was mainly due to fatal bleeds, cancer-related death and cancer progression being similar in both groups. After a 6-month follow-up period, cancer progression was observed in 36.0% of patients randomized to warfarin and in 33.8% of patients initially treated with enoxaparin. No difference was observed regarding overall mortality at 6 months either (38.7% in the warfarin group and 31.0% in the LMWH-treated patients) ($p=0.25$).

These results do not really argue against those observed in the CLOT trial. In fact, the study lacked enough power to address an effect of treatment on cancer spread or mortality. Patients were followed for 6 months and differences in mortality may become evident after longer follow-up. Besides, more than 50% of patients had metastatic disease, in which the effect of LMWH on survival seems to be lower according to the CLOT trial.

LMWH for VTE prophylaxis after cancer surgery

In a prospective, randomized, double-blind clinical trial, 324 patients undergoing breast or pelvic cancer surgery received antithrombotic prophylaxis with

either a LMWH, certoparin (n=160), or UFH (n=164) until day 7 post-operatively.[31] Mortality after 650 days was lower in the certoparin group (5.7%) than in the UFH-treated patients (15.6%) (*p*=0.006). However, after a longer follow-up, 1050 days, mortality in the LMWH and the UFH group was no longer significantly different between groups (11.4% and 18.4%, respectively; *p*=0.136). In the subgroup analysis, among patients with breast cancer, there was no treatment-related difference in mortality either after 650 days or at day 1050 (*p*=0.367 and *p*=0.812), whereas mortality at day 650 in patients with pelvic cancer was reduced by almost 70% by LMWH prophylaxis: 8.7% vs 28.6%; RR 0.30 (95%CI 0.11 – 0.85) (*p*=0.013). Mortality at day 1050 in patients with pelvic cancer treated with LMWH group was still half of that in those receiving UFH (15.2% vs 28.6%), although this difference was not statistically significant (*p*=0.10). Again, these findings were independent of whether the patient did or did not develop VTE. Although this study included quite a homogeneous group of cancer patients, the results observed differed according to the type of tumor, suggesting that stratification by tumor cell type and stage is crucial.

On the other hand, in the Enoxacan II study, 332 patients undergoing planned curative surgery for abdominal or pelvic cancer were randomly assigned, after 6 to 10 days of anti-thrombotic prophylaxis with enoxaparin 40 mg daily, to receive either enoxaparin or placebo for an additional 21 days.[32] Extended treatment with LMWH was associated with a significant reduction in the rates of VTE, both at the end of the double blind phase and at 3 months, without increasing the rates of bleeding or other complications. Mortality during the 3-month follow-up was 3.6% in the placebo group and 1.8% in the enoxaparin group, although the study lacked enough statistical power to evaluate differences in mortality between the groups. After a 1-year follow-up no difference in mortality was observed (7.7% and 9.5%, respectively).[33]

Anticoagulants in cancer patients: direct evidence

Direct evidence comes from studies specifically aimed to investigate the effect of anticoagulants on cancer mortality. According to the type of anticoagulant, these studies can be divided into three groups: a) trials evaluating survival in cancer patients undergoing oral anticoagulant therapy; b) trials evaluating the effect of UFH on cancer survival; c) trials investigating the role of LMWH on cancer survival.

Oral anticoagulant therapy and survival in cancer

Although there were previous reports concerning a beneficial effect of vitamin K antagonists on mortali-

ty in patients with cancer, the first randomized clinical trial evaluating the role of warfarin on cancer survival in patients with different types of cancer, was published by Zacharski *et al.*, in the early eighties (Veterans Administration Cooperative Study N° 75).[34] No differences in survival were observed between warfarin-treated and control groups for non-small cell lung, colorectal, head and neck and prostate cancers. However, warfarin treatment was associated with a significantly longer time to disease progression (*p*=0.016) and improvement in survival (*p*=0.018) in patients with small cell lung cancer.

The Cancer and Leukemia Group B (CALGB) conducted a prospective randomized trial in patients with extensive small cell lung cancer comparing two chemotherapy regimens.[35] In one group of patients, warfarin, aimed to maintain a prolongation of the prothrombin time between 1.5 to 2 times the control value, added to chemotherapy was associated with significantly increased objective response rates (*p*=0.012). Failure-free survival and overall survival improved in the warfarin-treated group, although the differences observed did not reach statistical significance (*p*=0.054 and *p*=0.098, respectively). On the other hand, an overall increased incidence of hemorrhage in the warfarin group was observed, although the rate of life-threatening hemorrhages was low (4%).

Another randomized study by the same group evaluated the effect of warfarin (to keep the prothrombin time between 1.4 and 1.6 times the control values) together with chemotherapy and radiation therapy in patients with limited stage small cell lung cancer.[36] No significant differences were noted in either response rates (89% in warfarin-treated patients and 88% in controls; *p*=0.86), or overall survival (median 21.4 months in warfarin-treated patients and 18.6 months in controls, *p*=0.12). A trend towards a higher disease-free survival in the warfarin group was observed (median 24.9 months versus 13.7 months, *p*=0.09) only in a subgroup of patients who received more intensive chemotherapy treatment.

Two other studies did not find any beneficial effect of warfarin on survival in patients with breast cancer or colorectal cancer.[37,38] A recent meta-analysis showed that one-year mortality rates of patients with various types of cancer was not significantly influenced by the addition of vitamin K-antagonists to chemotherapy (odds ratio 0.89; 95% CI: 0.70 – 1.13).[39] After stratification by cancer type, the odds ratio for 1-year mortality was 0.75 (95% CI: 0.44 – 1.16) in favor of warfarin in the subgroup with small cell lung cancer, and 1.40 (95% CI: 0.65 – 3.00) in favor of no additive treatment in colorectal cancer. Thus it is not possible to conclude that oral anticoag-

ulants have a beneficial effect on cancer survival. In addition, there is special concern about the use of vitamin K antagonists in cancer patients because of the higher risk of bleeding complications in this population, and the difficulty of maintaining adequate INR levels,[40] which has prompted an increased use of LMWH instead of oral anticoagulants in cancer patients with VTE.

Interestingly, an antineoplastic effect of warfarin was suggested by Schulman *et al.* in a randomized study analyzing the duration of oral anticoagulant therapy after a first episode of VTE.[41] A new cancer was diagnosed during follow-up in 15.8% of patients treated with oral anticoagulants for 6 weeks, compared with 10.3% in patients treated for 6 months (odds ratio 1.6; 95% CI: 1.1–2.4). This difference became evident only after two years of follow-up, suggesting that the effect may be limited to small cancers. However, a more recent prospective study that randomized patients with a first episode of idiopathic VTE to receive oral anticoagulants for 3 months or 1 year found no difference in the incidence of newly diagnosed overt cancer (6.2% and 8.7%, respectively).[42]

UFH and survival in cancer

In a French study, 277 patients with small cell lung cancer were randomized either to receive UFH (n=138) or not (n=139). Subcutaneous injections of heparin calcium (500 IU/Kg/day) were administered for a period of 5 weeks, in addition to chemotherapy and delayed thoracic radiotherapy.[43] There were no differences between the groups in terms of overall response rates, but a difference was obtained in complete response rate in favor of the heparin group (33% vs 21%; p=0.03). The median survival was 317 days in the heparin-treated patients and 261 days in the control group (p=0.01). The calculated odds ratio of total 3-year mortality was 0.64 (95% CI 0.25 – 1.62) in favor of heparin. However, after subgroup stratification according to the stage of the disease (limited or extensive), the difference observed was statistically significant only in the former group (p=0.03). Hemorrhagic adverse events were not increased in the heparin group, although patients with high bleeding risk were not included. Thus, in this study, UFH seemed to improve survival in patients with small cell lung cancer, although the effect seems restricted to patients with limited forms of disease.

Another two randomized trials investigated the effect of adjuvant intraportal infusion with heparin and 5-fluorouracil in resectable colon cancer.[44,45] Overall, 632 patients were randomized to no adjuvant treatment (n=224), or intraportal infusion of 5-fluorouracil together with continuous prophylactic UFH (5000–10000 UI/24 h) for seven days post-operatively (n=214), or intraportal UFH alone (n=194). Three-year mortality rates were 16% in the control group, 24% in the UFH alone group and 13% in the UFH/5-fluorouracil group. The calculated odds ratio of UFH compared with no treatment after surgery for colon cancer was 1.66 (95% CI 1.02-2.71). Therefore, in these series UFH seemed to show a detrimental effect on cancer survival.

A meta-analysis of the previous studies, which also separately evaluated four studies that either were not randomized or included post-hoc analysis for the long term effects of UFH on cancer patients,[46] showed that 3-year mortality rates of patients who received UFH or no UFH perioperatively for resectable gatrointestinal cancer were 24% (187/786) in the heparin group and 30% (195/649) in the untreated group. The calculated odds ratio was 0.65 (95% CI 0.51-0.84) in favor of UFH prophylaxis.

It is, therefore, difficult to address whether there is either improved survival or worse prognosis in patients with malignancy receiving UFH.

LMWH and survival in cancer

A summary of recent studies aimed to evaluate the effect of LMWH on cancer survival is provided in Table 3. In the FAMOUS trial (Fragmin Advanced Malignancy Outcome Study), 385 patients with advanced solid cancer were randomized to receive either dalteparin (5000 U/day) or placebo for up to one year.[47] Survival estimates at 1, 2 and 3 years after randomization were 46%, 27% and 21% for the dalteparin group and 41%, 18% and 12% for patients receiving placebo (p=0.19). The incidence of symptomatic VTE or bleeding was low during the study period (2.4% and 4.7%, respectively, in the LMWH group and 3.3% and 2.7%, respectively, in the placebo group). However, analysis of a subgroup of patients, not defined *a priori*, with a better prognosis (survival beyond 17 months, 55 patients in the dalteparin group and 47 in the placebo group) revealed a significant advantage for LMWH-treated patients, with a median survival time of 43.5 and 24.3 months, respectively (survival estimates at 2 and 3 years after randomization were 78% and 60% for the dalteparin group vs 55% and 36% for the placebo group; p=0.03). Thus, a potential antitumor effect of LMWH could not be excluded.

Another recent multicenter randomized study compared LMWH versus placebo in patients with non-curable solid malignant tumors (the MALT trial).[48] A total of 302 patients were randomized to receive a therapeutic dose of a LMWH (nadroparin) for 2 weeks followed by 4 weeks of half this dose, or placebo for 6 weeks. Patients were followed for a minimum period of 3 months, and cumulative mor-

Table 3. Clinical trials evaluating the role of LMWH in cancer treatment.

Study	LMWH	Dose	Treatment Period	n	Type of Cancer	Stage	Effect
Kakkar et al., 2004[47]	Dalteparin	5000 UI/day	1 year	385	Solid	Advanced	Survival not improved*
Klerk et al., 2004[48]	Nadroparin	Therapeutic Half dose	2 weeks 4 weeks	302	Solid	Advanced	Increased survival#
Altinbas et al., 2004[49]	Dalteparin	5000 UI/day	18 weeks	84	Lung (small cell)	Limited and advanced	Increased response¶ rate and survival

*Benefit in subgroup of patients with better prognosis (survival beyond 17 months); #in subgroup of patients with life expectancy > 6 months; ¶in patients with limited disease.

tality from all causes was the primary efficacy outcome. The overall hazard ratio was 0.75 (95% CI 0.59 – 0.96) in favor of LMWH, with the median survival being 8.0 months in the LMWH group and 6.6 months in the placebo group. The difference between these groups became more evident in an *a priori* defined subgroup of patients with better prognosis, who had a life expectancy of at least 6 months, in whom the hazard ratio was 0.64 (95% CI 0.45 – 0.90) in favor of LMWH, while the difference observed in those with a life expectancy of less than 6 months was less pronounced (hazard ratio, 0.88; 95% CI, 0.62 – 1.25). The incidence of major hemorrhage during study treatment was 3% among the LMWH recipients and 1% in the placebo group (p=0.12).

Altinbas *et al.* have recently reported the results of a randomized clinical trial of combination chemotherapy with and without LMWH in small cell lung cancer, aimed to determine whether the addition of LMWH improved cancer outcome.[49] Eighty-four previously untreated patients were randomized, 42 to each treatment group: chemotherapy with cyclophosphamide, epirubicin and vincristine alone (3-weekly cycles for six cycles) or chemotherapy plus dalteparin (5000 U daily) until disease progression or until the end of the chemotherapy. An objective response was observed in 69.2% of patients receiving LMWH and in 42.5% of those treated with chemotherapy alone (p=0.07). This difference was more evident for patients with limited disease (n=48) (91.4% versus 60.0%, p=0.02) compared with patients with extensive disease at diagnosis (n=36) (37.4% versus 13.3%, p=0.59). Differences in the 1- and 2-year progression-free survival rates were favorable to chemotherapy+LMWH, 30.4% and 3.4% versus 11.7% and 0% (p=0.01). The 1- and 2-year overall survival rates were 51.3% and 17.2% for patients treated with chemotherapy+LMWH and 29.5% and 0% for patients receiving chemotherapy alone (p=0.01). The median survival was 13.0 months (95% CI 9.83-16.17) and 8.0 months (95% CI 6.14-9.86), respectively (p=0.01). In this study, differences in progression-free survival and overall survival were observed in both subgroups of patients, either with limited or extensive disease. The addition of LMWH to antineoplastic treatments appeared to be safe, since toxicity consisted of a single episode of mild bleeding during the treatment period in one patient treated with LMWH, but larger multicenter studies are necessary to confirm these promising results.

Indeed, although the results from these studies seem to support an antineoplastic effect of LMWH, several points deserve discussion. First, the tremendous heterogenity among all clinical studies. Both the FAMOUS and the MALT trials included patients with different kinds of tumors, different stages, time from diagnosis or previous treatments, while the study performed by Altinbas included only patients diagnosed with a single type of cancer, but at different stages (which eventually were associated with different responses after the addition of dalteparin). The effect of LMWH may not be the same on different cancers. LMWH could be associated with an improved survival in limited and advanced stages of some type of cancer, while exert no effect, or be limited only to early phases in other tumors. Secondly, the treatment regimens administered were diverse. While Altinbas *et al.* and the FAMOUS trial used prophylactic doses of LMWH during the study period, in the MALT trial patients initially received a higher dose of LMWH. The duration of the treatment period was different in all the trials, ranging from 6 weeks in the MALT study to 1 year in the FAMOUS trial. Lastly, it cannot be excluded that a different effect is obtained depending on the molecule used. Each LMWH has its own characteristics regarding molecular weight and distribution of the length of heparin chains, which could be responsible for differences in the *in vivo* effect of the different agents, as suggested by *in vitro* studies.

Conclusions

The real effect of anticoagulant treatment on cancer survival still remains to be determined. Although some individual studies found a beneficial effect in

selected cases, overall it is not possible to conclude that UFH or oral anticoagulant have a positive effect on cancer survival. However, the evidence suggesting that LMWH have an antineoplastic effect seems more consistent. Results from individual studies and some meta-analyses show that at least some patients with VTE and cancer treated with LMWH have a better survival than patients treated with UFH or warfarin. A similar effect has been described in cancer patients without a history of VTE. The addition of LMWH to standard treatment regimens is safe and could improve survival in some types of cancers.

However, we are only at the starting point of an attractive field. Basic research aimed to clarify the mechanisms involved in the antineoplastic effect of LMWH is urgently needed, and appropriately designed clinical trials to assess unsolved questions regarding the tumor biology-modifying effect of LMWH (type of tumor and stages likely to respond, treatment regimen, potential differences between molecules) are required.

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