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Antithrombotic therapy and survival in patients with malignant disease

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A broad range of studies suggest a two-way relationship between cancer and venous thromboembolism (VTE). Patients with cancer have consistently been shown to be at elevated risk for VTE; this risk is partly driven by an intrinsic hypercoagulable state elicited by the tumour itself. Conversely, thromboembolic events in patients without obvious risk factors are often the first clinical manifestation of an undiagnosed malignancy. The relationship between VTE and cancer is further supported by a number of trials and meta-analyses which, when taken together, strongly suggest that antithrombotic therapy can extend survival in patients with cancer by a mechanism that extends beyond its effect in preventing VTE. Moreover, accumulating evidence from *in vitro* and *in vivo* studies has shown that tumour growth, invasion, and metastasis are governed, in part, by elements of the coagulation system. On 22 May 2009, a group of health-care providers based in the United Kingdom met in London, England, to examine recent advances in cancer-associated thrombosis and its implications for UK clinical practice. As part of the discussion, attendees evaluated evidence for and against an effect of antithrombotic therapy on survival in cancer. This paper includes a summary of the data presented at the meeting and explores potential mechanisms by which antithrombotic agents might exert antitumour effects. The summary is followed by a consensus statement developed by the group.
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As reviewed elsewhere in this supplement, patients with cancer are at increased risk of venous thromboembolism (VTE), not only as a result of extrinsic factors (e.g., immobility, cancer treatment, surgery) but also as a result of an intrinsic hypercoagulable state caused by the tumour itself. Conversely, it has been shown that VTE often heralds an undiagnosed malignancy. Taken together, these data suggest that there is a two-way relationship between cancer and VTE. This link has been clearly established by numerous epidemiological studies; moreover, it has been shown that antithrombotic therapy – particularly with heparins – may extend survival in patients with cancer. Additional *in vitro* and *in vivo* data provide preliminary evidence that elements of the coagulation system itself are critical determinants of cancer growth, invasion, and metastasis. These data suggest that, beyond the intuitively obvious benefit of preventing VTE in patients with cancer, antithrombotic therapies may have a direct antitumour effect, thus prolonging life and perhaps suppressing metastasis.

On 22 May 2009, a group of health-care professionals based in the United Kingdom met in London, England, to examine recent advances in cancer-associated thrombosis and its implications for UK clinical practice. As part of the discussion, attendees reviewed clinical and experimental evidence suggesting an effect of antithrombotic therapy on survival in cancer patients. This paper includes a summary of the data presented at the meeting and explores potential mechanisms by which antithrombotic agents might exert antitumour effects. The summary is followed by a consensus statement developed by the group.

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EFFECTS OF ANTITHROMBOTIC THERAPY ON SURVIVAL IN CANCER

A number of clinical trials, of varying quality, have assessed the impact of antithrombotic therapy on cancer outcome. When considered together, the results of these studies suggest that antithrombotic agents – including warfarin, unfractionated heparin (UFH), and low-molecular-weight heparins (LMWH) – may prolong the survival of patients with malignant diseases.

Indirect evidence suggests that warfarin may have an impact on cancer occurrence. A prospective study randomised patients with VTE to either 6 weeks or 6 months of oral anticoagulation; patients were questioned yearly thereafter about any newly diagnosed cancer (Schulman and Lindmarker, 2000). An analysis, conducted after a mean follow-up of 8.1 years, found that cancer was diagnosed in 15.8% of patients who were treated for 6 weeks with oral anticoagulants, compared with 10.3% of those treated for 6 months (OR 1.6; 95% CI 1.1 – 2.4) (Schulman and Lindmarker, 2000). Notably, the difference between the 6-week and 6-month groups was driven primarily by the occurrence of new urogenital cancers (most commonly prostate cancer), which occurred in 6.7% of the 6-week group and in 2.8% of the 6-month group (Schulman and Lindmarker, 2000). More recently, Tagalakis *et al* (2007) examined the effect of warfarin in patients with urogenital cancer. This nested, matched case – control study included 19 412 new

cases of urogenital cancer diagnosed over a 22-year period in Canada (Tagalakis *et al*, 2007). Four years of warfarin use in the 5-year period immediately preceding the index date was associated with a rate ratio of 0.80; there was a trend towards a decreasing rate ratio for prostate cancer with increasing duration of warfarin use through 5 years (Tagalakis *et al*, 2007). Although interesting, neither of these studies indicate whether warfarin therapy prevents or merely delays the onset of cancer, nor whether it affects overall mortality.

An early trial of warfarin – the VA Cooperative Study #75 – directly examined the effect of warfarin on survival in patients with cancer. In this study, 431 patients with malignancies were randomised to either warfarin or placebo in addition to their standard cancer treatment (Zacharski *et al*, 1984). No differences in survival were observed between treatment groups for patients with advanced non-small-cell lung, colorectal, prostatic, or head and neck cancer (Zacharski *et al*, 1984). A trend towards improved survival was seen in patients with non-small-cell lung cancer after surgical resection or potentially curative radiation therapy. Notably, warfarin was associated with a significant improvement in survival ($P = 0.018$) in a small subset of 50 patients with small-cell lung cancer (SCLC); these patients also had a significantly increased time to disease progression compared with controls (Zacharski *et al*, 1984).

A similar three-arm trial by CALGB (Chahinian *et al*, 1989) randomised 328 patients with extensive SCLC to a standard chemotherapy regimen (MACC), to the regimen with concurrent warfarin, or to an alternating chemotherapy regimen. The overall response rate was significantly higher in the warfarin arm than in the others ($P = 0.012$), but although there was also a trend towards improved survival, this did not reach statistical significance (Chahinian *et al*, 1989).

Another trial, published by Maurer *et al* (1997), also attempted to confirm the results of the VA Cooperative Study in limited-stage SCLC patients. As in the previous study, patients were randomised to receive warfarin or no warfarin, in addition to cancer chemotherapy and radiation therapy. There were no significant differences between the warfarin and no-warfarin groups in terms of response rates, survival, failure-free survival, disease-free survival, or patterns of relapse (Maurer *et al*, 1997). However, the trial was confounded by a protocol amendment after accrual of 179 patients because of pulmonary toxicity with a reduction of the chemotherapy regimen from eight cycles to five cycles (Maurer *et al*, 1997).

Only one study has reported on the effects of UFH on survival. In this study, 277 patients with SCLC were randomised to either receive or not receive dose-adjusted subcutaneous UFH injections for 5 weeks, in addition to chemotherapy (Lebeau *et al*, 1994). In this study, heparin was associated with improved complete response rates (37 *vs* 23%; $P = 0.004$); improved median survival (317 days *vs* 261 days; $P = 0.01$); and better survival rates at 1 year (40 *vs* 30%), 2 years (11 *vs* 9%), and 3 years (9 *vs* 6%) (Lebeau *et al*, 1994). A subgroup analysis suggested that the effect on survival was only in patients with limited disease.

The effect of LMWH on survival has been more extensively studied. An early analysis of two studies, conducted by Green *et al* (1992), provided initial evidence that mortality was reduced in patients treated with LMWH, compared with those who received UFH. A meta-analysis of trials comparing UFH with LMWH, published in 1996, provided additional evidence that LMWH is associated with reduced mortality in patients with cancer (Siragusa *et al*, 1996). As expected, both UFH and LMWH were effective in preventing recurrent VTE. An analysis of four studies in patients with cancer found that mortality rates during the 16- to 90-day follow-up period of oral anticoagulant therapy were substantially lower among patients assigned to the LMWH group (12%) compared with the UFH group (26%) (RR 0.33; 95% CI 0.1 – 0.8; $P = 0.01$) (Siragusa *et al*, 1996). The mortality rate in patients without cancer was low and was not significantly different between the two groups. Notably, significant reduction in mortality in cancer patients who received LMWH was not observed during the initial 15 days of treatment. Instead, the majority of deaths occurred after ceasing LMWH or UFH, which suggests that the effect of LMWH in preventing mortality was not because of its antithrombotic effect (Siragusa *et al*, 1996). A second meta-analysis (1999) also found a striking 57% reduction in mortality with LMWHs compared with UFH in the small subgroup of patients with cancer (Gould *et al*, 1999).

The effect of LMWH on survival in cancer was tested directly in the Fragmin Advanced Malignancy Outcome Study (FAMOUS) (Kakkar *et al*, 2004). In this study, 385 patients with advanced malignancies (histologically confirmed, advanced stage III or IV disease of the breast, lung, gastrointestinal tract, pancreas, liver, genitourinary tract, ovary, or uterus) were randomly assigned to receive either dalteparin (5000 IU administered once daily) or placebo (Kakkar *et al*, 2004). There were no restrictions on concomitant use of chemotherapy or radiotherapy. Patients were followed for 1 year for the primary end point of mortality; secondary outcomes included objectively confirmed VTE and bleeding (Kakkar *et al*, 2004). Rates of symptomatic VTE were low in both the dalteparin (2.4%) and placebo (3.3%) groups; bleeding was seen in 4.7% of dalteparin patients and in 2.7% of placebo patients (Kakkar *et al*, 2004).

At 1 year after randomisation, survival estimates in the dalteparin and placebo groups were 46 and 41%, respectively ($P = 0.19$; Figure 1A). At 2 years, survival rates were 27 and 18% for the dalteparin and placebo groups, respectively, and at 3 years the rates were 21 and 12%, respectively (Kakkar *et al*, 2004). *Post hoc* analysis of patients with a better prognosis who survived more than 17 months showed a survival advantage for the dalteparin group (Kakkar *et al*, 2004). At 2 and 3 years after randomisation, survival in the dalteparin and placebo groups was 78 *vs* 55% and 60 *vs* 36%, respectively ($P = 0.03$; Figure 1B). Median survival in the dalteparin group was 43.5 months, compared with 24.3 months in the placebo group (Kakkar *et al*, 2004).

The effect of LMWH on survival in patients with SCLC was evaluated directly in a study conducted by Altinbas *et al* (2004). In this small study, 84 patients were randomised to receive combination chemotherapy with or without dalteparin (5000 IU once daily during the 18 weeks of combination chemotherapy) (Altinbas *et al*, 2004). Tumour response rates were substantially higher among patients who received LMWH (69.2%) compared with those who did not (42.5%), but the difference between the two groups was not statistically significant ($P = 0.07$). Median progression-free survival was 10.0 and 6.0 months in the LMWH and no-LMWH groups, respectively ($P = 0.01$), with similar improvements in survival with LMWH observed in patients with both limited and extensive disease stages. Overall, the hazard of death was reduced by 44% among patients who received LMWH ($P = 0.012$) (Altinbas *et al*, 2004).

A second recent trial prospectively examined the effect of LMWH on survival in patients with advanced malignancies (Klerk *et al*, 2005). Patients with metastatic or locally advanced solid tumours who could not be treated curatively were randomly assigned to receive a 6-week course of weight-adjusted nadroparin (administered twice daily during the initial 14 days of treatment and once daily thereafter for an additional 4 weeks) or placebo (Klerk *et al*, 2005); concomitant chemotherapy or radiotherapy was permitted. The primary end point was all-cause mortality, the secondary end point was major and clinically relevant non-major bleeding (Klerk *et al*, 2005).

At 6 months, survival was 61% among patients randomly allocated to nadroparin, compared with 56% in the placebo group (Klerk *et al*, 2005). At 12 and 24 months, the corresponding values were 39 *vs* 27% and 21 *vs* 11% (Figure 2A) (Klerk *et al*, 2005). Among all patients, median survival was significantly longer in the

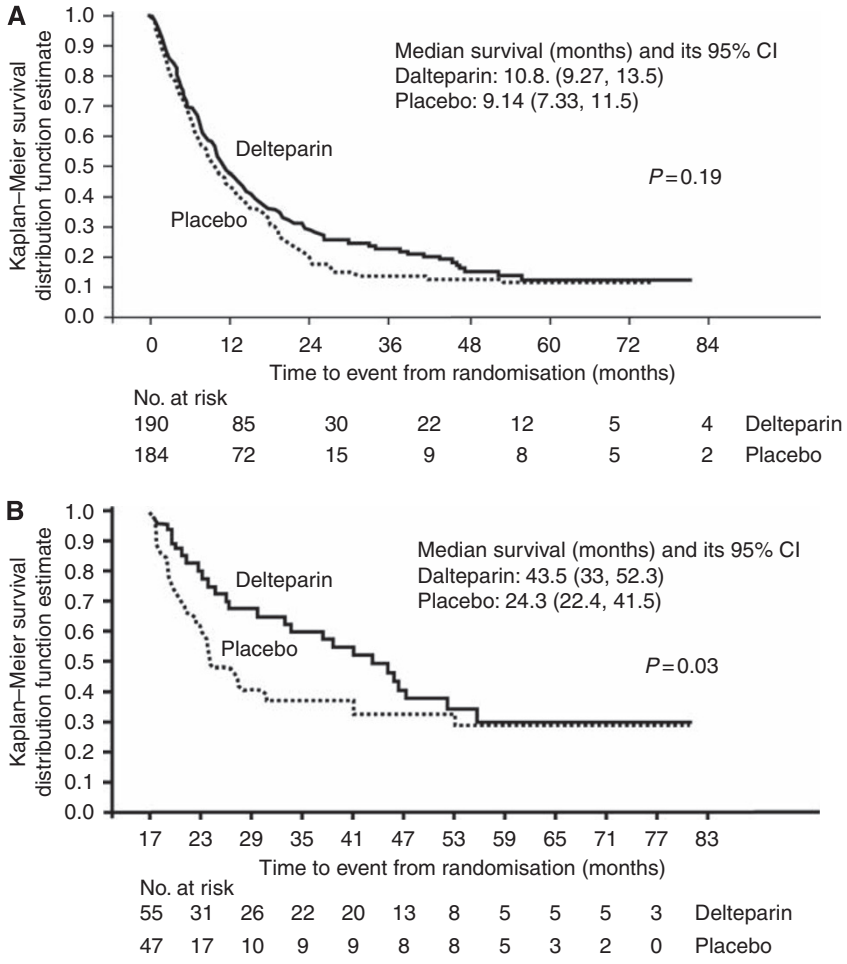

Figure 1 (**A**) Survival curves for the intent-to-treat population enrolled in the FAMOUS trial; (**B**) survival curves for the subgroup of patients with better prognosis who survived beyond 17 months after randomisation (Kakkar *et al*, 2004).

nadroparin group (8.0 months) than in the placebo group (6.6 months; hazard ratio 0.75; 95% CI 0.59–0.96; $P=0.021$). After adjustment for life expectancy, WHO performance status, concomitant treatment, and type and histology of cancer, the relationship between nadroparin and improved survival remained statistically significant (hazard ratio, 0.76; 95% CI 0.58–0.99) (Klerk *et al*, 2005).

Consistent with the results seen in the FAMOUS trial, the effect of nadroparin on survival was most apparent among patients with a better prognosis at enrollment (defined as an estimated life expectancy of $\geqslant 6$ months; Figure 2B) (Klerk *et al*, 2005). In this group, the hazard ratio was 0.64 (95% CI 0.45–0.90; $P=0.010$), compared with 0.88 (95% CI 0.62–1.25) in those with a life expectancy of <6 months. Median survival in the good-prognosis group was 15.4 months and 9.4 months for the nadroparin and placebo groups, respectively. There was no significant difference in the rate of major bleeding between the nadroparin group (five events) and the placebo group (one event; $P=0.12$) (Klerk *et al*, 2005).

In contrast to these data, a trial conducted by Sideras *et al* (2006) found that LMWH did not influence survival times in patients with advanced cancer. This small study, including 141 participants, initially randomised patients with advanced cancer to treatment with LMWH or saline. Because of low accrual, the placebo injection arm was eliminated and the study became open label, with patients receiving either LMWH plus standard clinical care or standard clinical care alone (Sideras *et al*, 2006). Median survival was 10.5 months in the combined standard care and placebo groups and 7.3 months in the combined LMWH arms. When the two arms from the initial, blinded phase of the study were examined, the median survival times were 6.2 months in the LMWH arm and 10.3 months in the placebo arm (Sideras *et al*, 2006).

A recent systematic meta-analysis of randomised trials suggests that LMWH, on balance, improves overall survival in cancer patients, including those with advanced disease (Lazo-Langner *et al*, 2007). This meta-analysis included four studies, enrolling 898 patients with solid tumours who were randomly allocated to either LMWH or placebo (Lazo-Langner *et al*, 2007). Three studies used dalteparin (5000 IU daily) for 18 weeks, 1 year, or 2 years; one used 6 weeks of weight-adjusted nadroparin, with a high dose during the first 2 weeks (Lazo-Langner *et al*, 2007).

At 1 year, the pooled results of the studies showed a 30% reduction in the hazard of death in favour of the LMWH group ($P=0.05$; Figure 3); for patients with less advanced disease, there was a 25% reduction in the hazard of death ($P=0.04$) (p 731). At 2 years, LMWH reduced mortality in all patients by 43% ($P=0.03$), and by 41% ($P=0.004$) in patients with advanced disease. LMWH conferred a statistically significant improvement in survival at both 12 and 24 months (Lazo-Langner *et al*, 2007).

In summary, there is accumulating evidence that anticoagulant therapy may increase survival in some patients with cancer. Further studies are currently ongoing to confirm the effects of anticoagulant therapy in a range of tumour types. The largest of

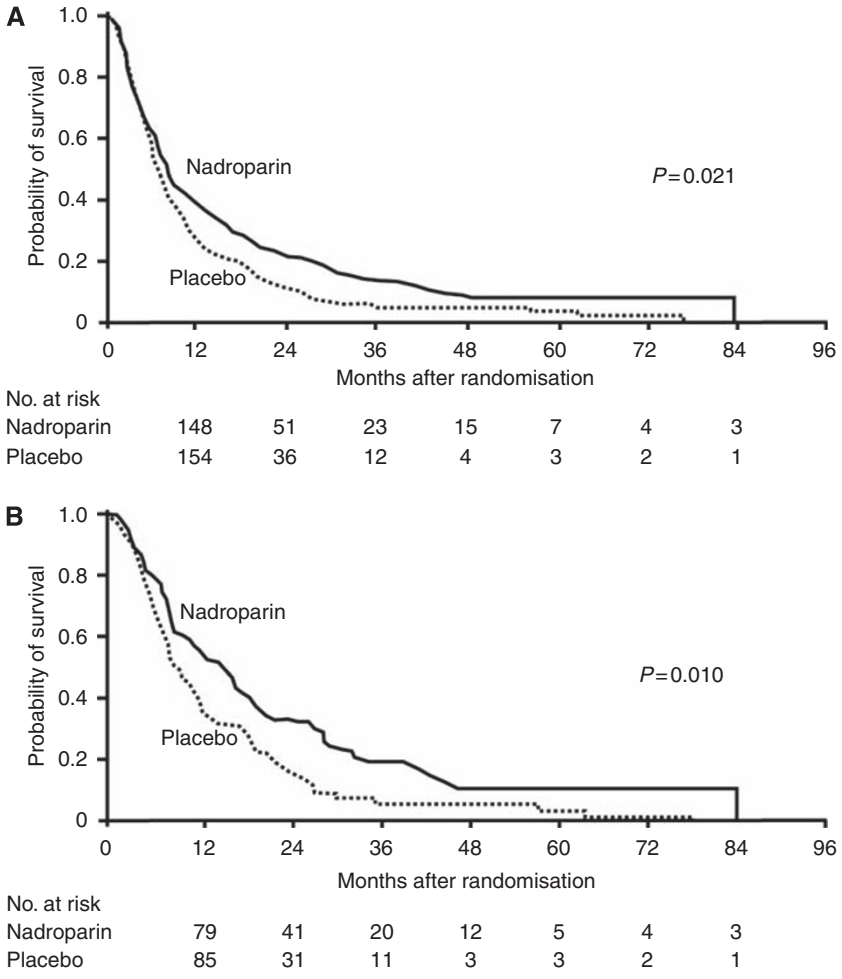

Figure 2 (**A**) Probability of survival in all patients with advanced solid malignancy according to assignment to nadroparin or placebo; (**B**) probability of survival in patients with advanced solid malignancy with a life expectancy of ⩾6 months at enrollment, according to assignment to nadroparin or placebo (Klerk *et al*, 2005).

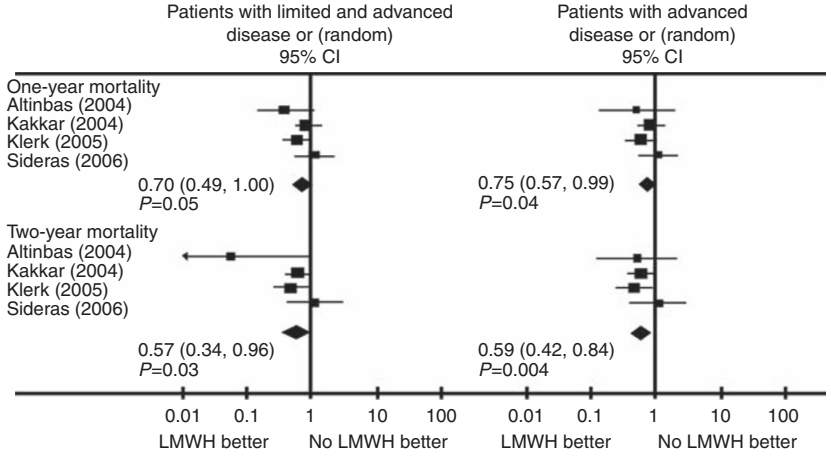

Figure 3 One- and 2-year mortality in cancer patients randomised to LMWH *vs* placebo/no intervention (Lazo-Langner *et al*, 2007).

these is the FRAGMATIC (FRAGMin Added to standard Therapy In patients with lung Cancer) trial (Wales Cancer Trials Unit, 2009), which is currently enrolling patients with pathologically confirmed lung cancer (of all histological types and all stages) who will be randomly allocated to standard care or standard care plus 6 months of treatment with dalteparin. This trial aims to recruit 2200 patients and is powered to detect a 5% increase in 1-year survival. The GASTRANOX Study (ClinicalTrials.gov, 2009) is enrolling up to

740 patients with advanced gastric cancer who will be randomly allocated to LMWH enoxaparin (1 mg kg^{-1} day^{-1}) for 6 months with chemotherapy or chemotherapy alone. The primary end point of the trial is the composite of all-cause mortality and symptomatic VTE.

POTENTIAL MECHANISMS FOR THE EFFECT OF ANTITHROMBOTIC THERAPY ON SURVIVAL IN CANCER

The results of individual clinical trials and meta-analyses, on balance, seem to indicate that antithrombotic therapy – and particularly LMWH – has an effect on survival in patients with cancer. Although this observation is relatively consistent across studies, it is difficult to understand how a short course of LMWH can provide a substantial survival advantage in patients with cancer. Recent data suggest that antithrombotic therapy may have a direct tumour biology-modifying effect.

A large number of circulating proteins, usually in inactive form, are involved in the haemostatic cascade. The activation of these factors culminates in the formation of the fibrin network of the clot and is countered by the fibrinolytic cascade, which, when activated, results in thrombus degradation. Cancer itself seems to elicit a systemic hypercoagulable state. Production of a wide range of procoagulant molecules, including tissue factor (TF) and cancer procoagulant (CP), a cysteine protease growth factor, has been demonstrated in patients with cancer, as well as increased levels of procoagulant markers, including TF, activated factor VII (FVIIa), prothrombin-activation peptide, and thrombin–antithrombin complexes (a comprehensive review can be found in Petralia *et al* (2005). Recent evidence suggests that the production of procoagulant molecules in patients with cancer is more than a mere side effect of cancer growth; instead, data suggest that these factors have an integral role in malignancy through eliciting tumour growth, invasion, metastasis, and angiogenesis. These data provide a potential link between the use of anticoagulant therapies and improved survival in patients with cancer.

Tissue factor, a cell-surface bound, transmembrane glycoprotein, has been shown to be expressed on a variety of tumours derived from the epithelium. Tissue factor interacts with FVIIa to form the TF–VIIa complex – the primary activator of coagulation (Petralia *et al*, 2005). This complex seems to have a role in cell adhesion and migration through the recruitment of actin-binding protein 280 (filamin A), an intracellular protein implicated in cell motility (Ott *et al*, 1998). *In vitro*, immobilised ligands for TF specifically support cell adhesion, spreading, and intracellular signalling, suggesting that the interaction between the cytoplasmic domain and filamin A may support tumour cell metastasis and vascular remodelling. Cancer procoagulant is also expressed by a wide range of tumours. It has the ability to initiate the haemostatic cascade directly by activating FX independently of the TF–VIIa complex.

Tissue factor expression has been shown to dramatically change tumour behaviour. In animal models, overexpression of TF in cancer cells has been shown to significantly upregulate over 40 genes and downregulate nearly 230 genes involved in transcription, translation, intercellular signalling, cell growth, and apoptosis (Wang *et al*, 2004). Tissue factor expression correlates with histological grade and heralds the transformation from benign to malignant phenotype (Kakkar *et al*, 1995). Overexpression of TF in experimental models of pancreatic adenocarcinoma enhances *in vitro* invasion and primary tumour growth (Kakkar *et al*, 1999). Similarly, overexpression in a mouse sarcoma model resulted in increased levels of proangiogenic vascular endothelial growth factor (VEGF) and suppression of thrombospondin, an antiangiogenic regulatory protein (Zhang *et al*, 1994). In human breast cancer, TF expression has been shown to correlate with an invasive phenotype and initiation of angiogenesis (Contrino *et al*, 1996). Tissue factor expression in hepatocellular cancer is strongly associated with VEGF-induced angiogenesis and venous invasion (Poon *et al*, 2003), potentially mediated by an interaction with integrin αIIIβI. Moreover, TF-expressing cells seem to be protected from apoptosis induced by serum deprivation and loss of adhesion, suggesting a potential mechanism by which TF may promote metastasis (Versteeg *et al*, 2004).

These data are consistent with the known role of TF in enhancing wound healing, in which it indirectly induces proliferation of human vascular endothelial cells and promotes endothelial cell alignment through the production of thrombin (Carney *et al*, 1992; Haralabopoulos *et al*, 1997). Protease-activated receptor-1 (PAR-1) is a receptor for thrombin that is overexpressed in a range of tumour cell lines, particularly metastatic cell lines. Thrombin–PAR signalling has been shown to upregulate expression of TF and urokinase plasminogen in prostate cancer, increase invasiveness of breast and pancreatic cell lines, and enhance procoagulant activity in colon cancer (Petralia *et al*, 2005).

Together, it is clear that there is a role for elements of the haemostatic system in cancer progression that extends beyond their role in fibrin generation. These data also suggest mechanisms through which antithrombotic treatments, such as LMWH, may have a direct impact on tumour phenotype, as well as influence survival in patients with cancer, beyond their effect in suppressing VTE.

CONSENSUS STATEMENT

Although the association between cancer and an increased risk of thromboembolism is well understood, the evidence that anticoagulant therapy may improve survival in cancer patients has been slow to accumulate. The results of studies have been quite heterogeneous in both the patient population and the anticoagulant used. Many of the studies have also been underpowered to show clinically significant improvements in survival. However, it does seem that there is a beneficial effect even from quite short courses of treatment, and it seems that heparins may be more effective than coumarins, and that this effect may be more marked in patients with better prognosis. The beneficial effects do not seem to come at the expense of a significant risk of adverse effects, haemorrhage in particular.

Together, these findings suggest that, although there may be a short-term benefit in preventing thromboembolism in a group of patients at increased risk, there may also be a longer-term effect on the cancer itself. This hypothesis is supported by a number of *in vitro* and animal studies indicating a link between key factors in the coagulation cascade and tumour growth and metastasis.

In addition to continuing investigation of the detailed mechanisms of the complex interactions between growing tumour cells and the coagulation cascade, there are a number of important questions to be answered before routine anticoagulant therapy is integrated into cancer therapy:

- How large and how consistent is any survival benefit?
- Which patients (tumour type, stage, prognostic category) are most likely to benefit from therapy?
- Which anticoagulant is most effective?
- What duration of treatment is needed?
- How large is the risk of significant adverse effects?

We would therefore urge participation in the ongoing clinical trials and in planning of future studies to make the most of this fascinating and potentially important area of cancer treatment.

Conflict of interest

AK Kakkar has received consulting fees from Bayer, Sanofi-aventis, Boehringer Ingelheim, Pfizer, Bristol-Myers Squibb, and Eisai. F Macbeth has received grant support from CRUK and Pfizer.

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