Thrombosis is a frequent complication of cancer, and the presence of a tumour confers a prothrombotic state. Despite modern interventions, venous and (rarely) arterial thromboembolic disorders are still among the most common complications of cancer, and are a cause of substantial morbidity and mortality in these patients. The severity, number of complications, and recurrence rates of thromboembolic disease are also substantially greater. Recurrent thromboembolism is more likely to occur in patients with cancer as in healthy individuals, even when established on oral anticoagulant therapy, and these patients tend to need longer stays in hospital, respond less well to oral anticoagulant therapy, and have a poorer prognosis.

Some cancers are more likely to be prothrombotic than others, but this feature is also influenced by disease staging, immobility, and being in hospital, as well as by interventions such as surgery or chemotherapy. What is less known are the thromboembolic risks associated with new treatment strategies for cancer. Two such strategies, the inhibition of angiogenesis and matrix metalloproteinases, are worthy of some further discussion.

**Anti-angiogenic therapy: a realistic goal?**

Angiogenesis inhibitors are a relatively new concept in cancer treatment. Angiogenesis is the formation of new blood vessels from pre-existing vasculature, and is essential for solid tumour growth and progression (1, 2), and is a complex dynamic process consisting of extracellular matrix remodelling, endothelial cell proliferation and capillary differentiation, characterized by tumour expression of pro-angiogenic proteins, including vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), interleukin-8 (IL-8), placenta-like growth factor (PLGF), transforming growth factor-β (TGF-β), platelet-derived endothelial growth factor (PD-EGF), and pleiotrophin, among others (3).

Angiogenesis inhibitors are a group of drugs with very different biological properties and modes of action in vivo, compared to conventional cytotoxic chemotherapy. They work on the principle of targeting vascular endothelial cells, and suppressing tumour angiogenesis, either “directly” by blocking the ability of the cells to proliferate, or “indirectly” by blocking the pro-angiogenic proteins and receptors that induce angiogenesis in these cells.

Indeed, various angiogenesis inhibitors have already been developed to target vascular endothelial cells, and block tumour angiogenesis, with various degrees of success. Last year, a prospective randomised trial of an antibody against VEGF, bevacizumab (Avastin), in 110 patients with metastatic renal cancer showed that VEGF inhibition significantly prolonged the time to tumour progression with minimal toxicity (4). More recently, in a larger randomised Phase III clinical trial, reported on 1st June at the American Society of Clinical Oncology in Chicago, bevacizumab given in combination with conventional chemotherapy, significantly improved survival of patients with metastatic colorectal cancer (5).
**Matrix metalloproteinase inhibition: general principles and current status**

Targeting cells which maintain and support cancer growth, such as the matrix metalloproteinases (MMPs), rather than tumour cells directly, is a new concept that is equally promising. Inhibition of MMP activity represents a novel, non-toxic approach towards improving the therapy of aggressive, metastatic disease (6, 7). MMPs, and in particular MMP-2 and MMP-9, are the principal secreted proteases required for degradation of extracellular matrix, the process of which is essential for tumour invasion, metastasis, growth and angiogenesis (8). Indeed, angiogenesis has been shown to be reduced in MMP-2-deficient mice (9), and metastasis eliminated by inhibiting MMP-9 transcription in a rat sarcoma tumour model (10).

One of the main advantages to MMP inhibition is that, unlike tumour cells, these cells are genetically stable, and are therefore less likely to accumulate mutations that would allow them to acquire drug resistance in a rapid manner.

So far, all tested MMP inhibitors (MMPIs) have failed to reach primary end points in Phase III clinical trials, although secondary analyses suggest benefits in particular patient groups. While 5 different MMPIs went into Phase III clinical trials for various tumours (11), no MMPI is presently licensed for cancer therapy. Two of the drugs, tanomastat and prinomastat, are not currently in clinical trials; tanomastat development was halted after interim analysis of a Phase III trial in patients with small cell lung cancer indicated that treated patients were doing significantly worse than placebo-treated patient, and prinomastat failed to demonstrate efficacy in any of the Phase III trials in which it was tested. The three drugs still in Phase III clinical trials are neovastat, marimastat, and BMS-275291. Neovastat is being used in renal cancer patients who have immunomodulatory therapy, marimastat in patients with pancreatic cancer, and BMS-275291 in patients with non-small cell lung cancer.

The clinical development of these agents has also been hampered by problems related to determination of effective dosages and side effects that necessitate dose lowering or drug discontinuation. The main side effects of MMPIs have been reported as rashes and musculoskeletal pain and stiffness, with clinical effects being so severe that dose lowering is essential.

In this issue of Thrombosis and Haemostasis, Behrendt and Ruiz (12) report another possible (worrying) adverse effect with this class of drugs - an increased risk of venous thromboembolism (VTE) as a consequence of treatment with the MMPI prinomastat, in combination with conventional chemotherapy, when used for the treatment of non-small cell lung cancer (NSCLC).

**Increased thromboembolic risk with new anticancer drugs**

Is an increase in thromboembolic risk a worrying problem with new anticancer drugs? Furthermore, what are possible mechanisms for this increased risk, especially since there appears to be an intimate link between cancer and thrombosis in general, and more specifically, between factors such as VEGF and thrombosis (via tissue factor) and MMPs and fibrinolysis, which may play important roles in the pathophysiology of thrombogenesis in cancer.

Recently, 2 clinical trials have reported that combined treatment with a VEGF inhibitor plus chemotherapy was associated with an increased risk of VTE. Firstly, in a Phase I trial (13) of combined SU5416 (VEGF receptor-1 and -2 inhibitor) plus gemcitabine/cisplatin for advanced solid tumours, 4 out of 19 treated patients developed thromboembolic events (specifically, 4 deep vein thromboses [DVT] with or without pulmonary embolism [PE]). Secondly, in a Phase II trial comparing bevacizumab plus fluorouracil (FU)/Leucovorin (LV) with FU/LV alone, DVT or PE occurred in 6 out of 67 patients receiving combination therapy, and 0 out of 35 receiving FU/LV alone (14). The current study by Behrendt and Ruiz (12), using retrospective univariate and multivariate analysis, report the first evidence that combined treatment of an MMPI (15mg prinomastat) plus chemotherapy can approximately double the risk of VTE in stage IIIB, IV or recurrent non-small cell lung cancer (NSCLC). The risk was highest when given with gemcitabine, and was also associated with the placement of a central venous catheter.

**Possible mechanisms**

The use of central venous catheters, perhaps used for the administration of certain chemotherapeutic agents, are certainly risk factors for VTE, with the development of thrombotic complications characterized by fibrin and platelet deposits within and around the catheter. The size and composition of the catheter itself, as well as extrinsic venous compression by tumour, may also be factors predisposing to catheter-related thrombosis. Associated comorbidity (for example, heart failure, atrial fibrillation, etc) and immobility, would add further to thromboembolic risk.

However, the contributory role (and possible prothrombotic mechanisms) of anticancer therapies in increasing thromboembolic risk tends to be slightly neglected. This area is also more confusing in cancer therapy by the frequent use of combination therapy, so that the precise role(s) of individual drugs in contributing to thromboembolism may be difficult to define.

In the study by Keunen et al (13), the increase in thromboembolic events due to a VEGF inhibitor could not be explained by a direct pharmacokinetic interaction among the drugs, as there are no common metabolic pathways linking the three drugs, SU5416, cisplatin, and gemcitabine. The authors
hypothesized that endothelial cells become activated during combination therapy and shift toward a prothrombotic profile, and may push their prothrombotic risk above a certain threshold which makes VTE a very realistic prospect.

Additionally, the presence of cancer (16, 17), the use of certain chemotherapeutic agents and central venous catheters further raise this profile, and may push their prothrombotic risk above a certain threshold which makes VTE a very realistic prospect.

Finally, it should be noted that whilst the risk for VTE is quite defined in cancer, the development of arterial or systemic thromboembolism is less frequent, although not unknown (17). Whether chemotherapeutic agents increase the risk of arterial thromboembolism is again less certain, but perhaps the limited survival of cancer patients does not permit the more frequent development of arterial complications. Furthermore, the true epidemiology of venous (or arterial) thromboembolism is likely to be confounded by the increasing use of concomitant antiplatelet or anticoagulant drug therapy as thromboprophylaxis in these patients.

Clearly, with more treatment strategies being developed in our fight against cancer, we feel that a greater appreciation of the prothrombotic effects of new anticancer drugs is needed, and certainly, more attention is needed to the development of venous (and hopefully, arterial) thromboembolism when such drugs are used in clinical trials. However, we should also optimise our provision of thromboprophylaxis for such patients. Recent data on new classes of antithrombotic agents, such as the oral direct thrombin inhibitors, for the treatment and prophylaxis against VTE (and recurrent VTE) are welcomed, as these agents are given in a fixed dose, without the need for anticoagulant intensity monitoring – unlike warfarin (18).

References

1. Folkman J. What is the evidence that tumors are angiogenesis dependent? J Natl Cancer Inst 1990; 82: 4-6