Management of venous thromboembolism in patients with cancer

The association between venous thromboembolism and cancer has been recognized for over 140 years. This article reviews current prevention, diagnosis and treatment of cancer-related venous thromboembolism, and highlights emerging anticoagulants and the possible anticancer effects of anticoagulants such as low molecular weight heparins.

Venous thromboembolism is the formation of a blood clot or thrombus in a vein which may displace from its site of origin and form an embolus. The majority occur in the deep veins of legs, thus named deep vein thromboses and will usually present as a hot, painful, swollen, erythematous leg. If a deep vein thrombosis dislodges, it can travel via the venous system and embolize in the lungs forming a pulmonary embolus. A pulmonary embolus may be asymptomatic but usually presents with symptoms which include dyspnoea, chest pain and haemoptysis. Large pulmonary emboli can cause a sudden cardiovascular collapse leading to death. The 1-week survival rate after a pulmonary embolus is only 71%, and almost 25% of all cases of pulmonary embolus present as sudden death (Heit et al, 1999).

Venous thromboembolism affects 1 in 1000 patients annually (Silverstein et al, 1998) and accounts for an estimated 25 000 deaths in the UK each year (House of Commons Health Committee, 2005). The rate is higher in the cancer population with a prevalence of clinically apparent venous thromboembolism in up to 15% of oncology patients (Bick, 1978).

While the diagnosis and treatment of venous thromboembolism in the general population is relatively straightforward, the cancer patient with venous thromboembolism presents several challenges. First and foremost, there appears to be an under-appreciation of the prothrombotic risk that malignancy confers on a patient, even among oncologists, with a variation of practice worldwide (Kirwan et al, 2003; Wolf, 2003). Second, many of the co-morbidities associated with malignant disease have similar presentations to those of deep vein thromboses and pulmonary emboli leading to under-diagnosis, and common exclusionary tests such as D-dimers have limited use in the cancer setting. Finally, cancer patients receiving anticoagulation for venous thromboembolism will have a higher risk of bleeding and recurrent thrombosis than a non-cancer patient and these risks will increase with disease progression (Noble et al, 2008a). This article identifies the challenges in the management of venous thromboembolism in the cancer patient and discusses possible solutions to this complex yet common clinical problem.

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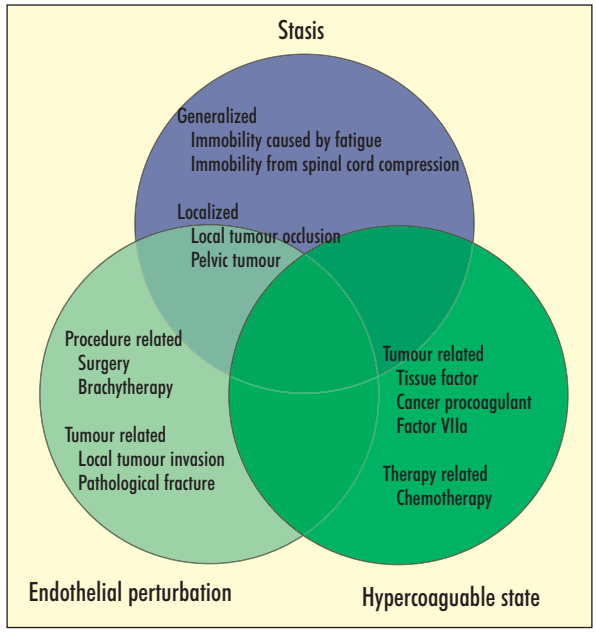
Pathogenesis of venous thromboembolism in cancer

The association between venous thromboembolism and cancer was first described by the French physician Armand Trousseau (1865) who observed that patients with idiopathic venous thromboembolism would later be diagnosed with gastric cancer. Trousseau observed that the thromboses often occurred in atypical sites and presented with a migratory thrombophlebitis. Ironically he died from gastric cancer after presenting with an axillary vein thrombosis. Virchow's triad (1856) describes the factors that contribute to the development of a thrombus, namely stasis, endothelial perturbation and hypercoaguability (*Figure 1*). While many of these factors are observed in general medical and surgical patients, cancer patients have additional risk factors related directly to the malignant process or its treatment. Prothrombotic factors such as tissue factor, cancer procoagulant and fac-

Figure 1. Virchow's triad as applied to malignancy.



tor VIIa are raised in cancer patients and the procoagulant effect increases with disease progression (Kakkar et al, 1995; Johnson et al, 1999a; Prandoni et al, 2002). In patients with advanced cancer, the rate of asymptomatic venous thromboembolism may be as high as 50% (Johnson et al, 1999b). Similar rates in cancer patients have been observed at post-mortem (Ambrus et al, 1975; Shen and Pollak, 1980). Cancer therapies also increase the thrombogenic risk. The thrombogenicity of surgery is well recognized; in the absence of thromboprophylaxis the risk of venous thromboembolism in patients undergoing surgery for cancer may be as high as 50% (Geerts et al, 2001). Chemotherapy also increases the incidence of venous thromboembolism although the additional risk, which is likely to vary with different agents, is yet to be quantified.

Clinical presentation of venous thromboembolism

For venous thromboembolism of malignancy to be appropriately treated, it must first be considered as a possible diagnosis and appropriately investigated. The common presenting symptoms of venous thromboembolism are similar to those of other common pathologies experienced by patients with cancer. While a painful swollen leg raises a high index of suspicion of deep vein thrombosis in a non-cancer patient, such symptoms are common in the cancer population, especially those with advancing disease (*Figure 2, Table 1*). Likewise dyspnoea, the commonest symptom associated with pulmonary embolus, is seen in a multitude of common conditions associated with cancer, e.g. pulmonary metastases, pneumonia, heart failure, pleural effusion or lymphangitis.

It is important to recognize that although many conditions may mimic venous thromboembolism, the presence of one such diagnosis does not negate the concurrent diagnosis of thrombosis. Acute conditions such as infection, heart failure and local venous obstruction will increase the prothrombotic state and likelihood of undiagnosed venous thromboembolism (Turpie, 2000).

Diagnosis of venous thromboembolism

In the non-cancer population there are several clinical models for determining the pre-test probability of a patient having a deep vein thrombosis (Tovey and Wyatt, 2003). These are useful in identifying those unlikely to have a thrombosis who therefore do not need confirmatory radiology. They rely on the use of D-dimers, specific cross-linked derivatives of fibrin which are produced when fibrin is degraded by plasmin and are thus raised in the presence of venous thromboembolism (Kelly and Hunt, 2002). Although sensitive for venous thromboembolism, high D-dimer concentrations also occur in infection, malignancy and postoperative states (Kelly et al, 2002). They are therefore of limited use in the cancer setting.

Doppler ultrasonography (*Figure 3*) is a widely available, cheap non-invasive test and thus the investigation of choice for symptomatic deep vein thrombosis. Meta-analysis suggests the sensitivity of ultrasonography to be 89% overall for symptomatic deep vein thrombosis and 97% for above-knee thrombus (Kearon et al, 1998; Fraser and Anderson, 1999).

Several tests are available for the diagnosis of pulmonary embolus including ventilation/perfusion lung scintigraphy (V/Q scan), pulmonary angiography and spiral

Figure 2. Swollen left leg caused by left deep vein thrombosis.

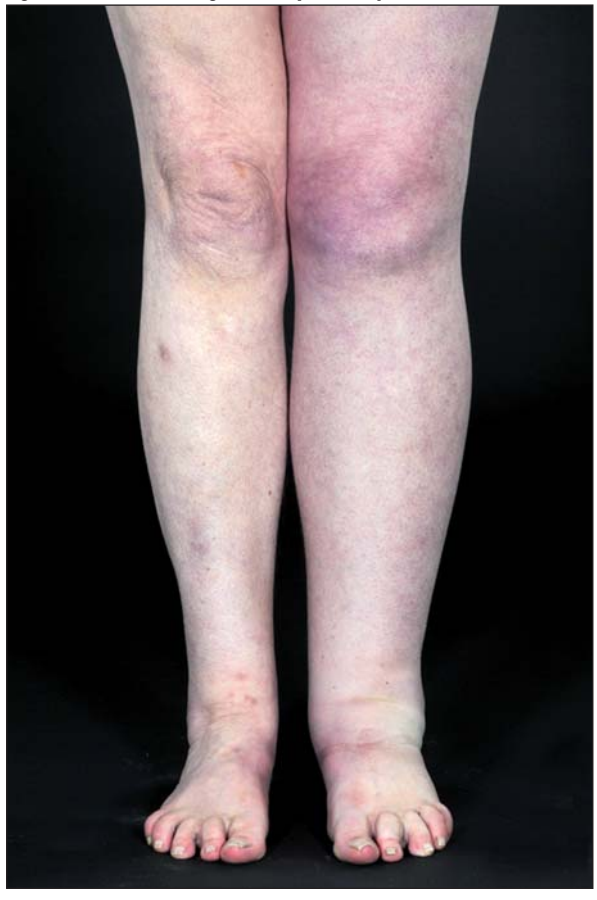


Table 1. Common causes of swollen legs in the cancer patient

Unilateral	Deep vein thrombosis
	Cellulitis
	Nodal disease in groin
	Lymphoedema
Bilateral	Deep vein thrombosis
	Hypoalbuminaemia
	Heart failure
	Medicines, e.g. steroids, nifedipine
	Lymphoedema
	Pelvic disease causing reduced venous outflow

computed tomographic pulmonary angiography (CTPA). Pulmonary angiography is considered the gold standard investigation but is invasive, technically demanding and associated with major complication and mortality rates of 0.5% and 0.1% (Hudson et al, 1996; Nilsson et al, 1998). V/Q scans are relatively simple to perform and non-invasive but when used in isolation can be non-diagnostic in up to 70% of suspected pulmonary emboli (PIOPED Investigators, 1990). Interpretation of scans can be further complicated in cancer patients with coexisting pulmonary pathology. CTPA has a sensitivity of 70% and a specificity of 90% in the diagnosis of pulmonary embolus (Remy-Jardin et al, 1996) and is readily available in most hospitals, making it the investigation of choice.

Treatment of venous thromboembolism

The current treatment for venous thromboembolism consists of 3–6 months' anticoagulation with warfarin after initial anticoagulation with low molecular weight heparin (Baglin et al, 2006). Despite its efficacy and safety in the general medical or surgical patient with venous thromboembolism, warfarin use in the cancer population is associated with bleeding rates as high as 21.6% (Prandoni, 1997; Hutten et al, 2000). Initial warfarinization, in itself, is challenging and following standard anticoagulation protocols has produced international normalized ratios greater than 4.5 in over 60% of patients and greater than 8 in 30% (Noble, 2004). Maintaining a stable international normalized ratio is similarly difficult for reasons including:

- Poor nutritional status
- Liver metastases
- Variable oral intake and drug absorption
- Drug–drug interactions.

The most commonly used drugs in oncology that interact with warfarin are listed in *Table 2*. Antibiotics (e.g. ciprofloxacin, penicillin and fluconazole) increase the international normalized ratio and alternatives should be used where possible. Steroids have an unpredictable relationship with warfarin but are clearly an essential drug in many cancer patients. Likewise omeprazole, frequently used to minimize gastric acid production, can increase the international normalized ratio and an alternative proton pump inhibitor should be considered. Teams should be aware of potential interactions, monitor more frequently and alter the warfarin dose accordingly whenever steroids are introduced or changed.

In addition to an increased risk of bleeding, cancer patients are more likely to develop further thrombotic events on warfarin than non-cancer patients. Up 27% of cancer patients will develop secondary venous thromboembolism despite therapeutic warfarinization (Hutten et al, 2000).

Although several trials have addressed long-term therapy for venous thromboembolism with oral anticoagulant *vs* low molecular weight heparin, only three have looked at patients with cancer. Meyer et al (2002) randomized patients with cancer and venous thromboembolism to 3 months of treatment with either low molecular weight heparin enoxaparin (1 mg/kg) or warfarin. The composite outcome of major bleeding and recurrent venous thromboembolism was observed in 15 out of 71 (21.1%) patients receiving warfarin, compared to seven of the 67 (10.5%) receiving low molecular weight heparin (P=0.09). The Long-term Innohep Treatment evaluation (LITE) trial randomized 200 patients with acute venous thromboembolism and cancer to receive either unfractionated heparin followed by warfarin for 84 days at a targeted international normalized ratio of 2.5 or the low molecular weight heparin tinzaparin (175 IU/kg) for 85 days (Hull et al, 2006). The rate of recurrent venous thromboembolism at 3 months was 6% in the low molecular weight heparin group compared to 10% in the warfarin group and at 1 year was 7% and 16% respectively (P=0.044).

Lee et al (2003) reported the results of the CLOT trial, which was a large multicentre trial comparing treatment with low molecular weight heparin dalteparin with oral anticoagulant therapy in patients with active cancer presenting with acute venous thromboembolism. Each arm included 338 patients who were well matched for gender, age, outpatient treatment and performance status. Twenty-seven patients in the low molecular weight heparin group experienced recurrent venous throm-

Figure 3. Doppler ultrasound showing thrombus in peroneal vein.

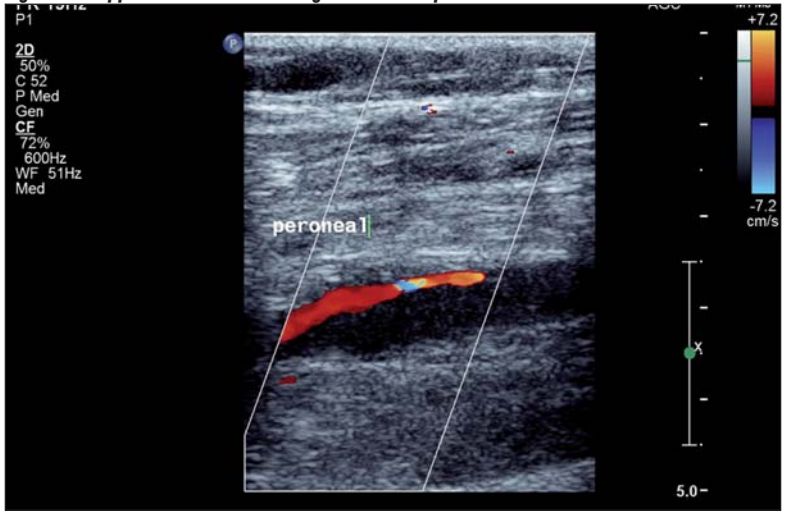


Table 2. Drugs commonly used in oncology that alter international normalized ratio

Fluconazole
Ciprofloxacin
Omeprazole
Dexamethasone
Penicillins

boembolism compared with 53 in the oral anticoagulant group. Patients receiving long-term low molecular weight heparin treatment had a significantly lower cumulative risk of recurrent venous thromboembolism at 6 months than those who received long-term oral anticoagulant therapy (8.8% *vs* 17.4%, 52% risk reduction, P=0.0017). Major bleeding was seen in 19/338 (5.6%) patients receiving low molecular weight heparin compared with 12/338 (3.6%) in the oral anticoagulant group (P=0.27). Corresponding data for any bleeding were 13.6% and 18.5% respectively (P=0.09).

Consequently low molecular weight heparin has been recommended for long-term anticoagulation in cancer patients (Baglin et al, 2006; Mandala et al, 2006; Lyman et al, 2007; Segal et al, 2007; Kearon et al, 2008). Qualitative research suggests the treatment to be acceptable to patients, and to some, preferable to warfarin (Noble and Finlay, 2005). A systematic review and meta-analysis suggests low molecular weight heparin to also be the anticoagulant of choice in patients with advanced malignancy (Noble et al, 2008a).

In addition to better efficacy with respect to recurrent venous thromboembolism, low molecular weight heparin has several benefits over warfarin in cancer patients:

- The dose is calculated according to patient weight and so there is less need to monitor anticoagulation
- The efficacy does not appear to be altered by changes in nutritional status
- Administration is not affected by absorption problems or poor oral intake
- The efficacy is not altered by new medicines, in particular with respect to drug–drug interactions.

Length of anticoagulation

Baglin and colleagues (2006) recommend patients with temporary risk factors and a low risk of recurrence should receive 3 months of anticoagulation. For patients with idiopathic venous thromboembolism or permanent risk factors at least 6 months' anticoagulation is recommended. Other guidelines recognize the ongoing thrombotic tendency in cancer patients and recommend a patient remain anticoagulated long term, or as long as active cancer is present, although this has not been formally evaluated (Buller et al, 2004; Mandala et al, 2006). Patients with advanced or incurable cancer should, in theory, receive lifelong anticoagulation since the prothrombotic state will not only remain, but potentially increase with disease progression. While long-term low molecular weight heparin has been shown to be acceptable in advanced cancer patients, participants studied had been on anticoagulation for an average of 4 weeks and the qualitative effects of longer term treatment have not been formally evaluated. In practice patients with advanced cancer live for a median of 97 days and decisions to anticoagulate beyond 6 months are rarely required (Noble et al, 2007).

Primary thromboprophylaxis

The past 5 years have seen a growing appreciation of the importance of thromboprophylaxis in hospitalized patients. In response to the House of Commons Health Committee on the prevention of venous thromboembolism for hospitalized patients (2005) the Chief Medical Officer appointed an expert working group to design a venous thromboembolism risk assessment model (Department of Health, 2008). Among the many conditions listed, active cancer was identified as an independent risk factor for venous thromboembolism warranting prophylaxis in cancer inpatients.

The growing body of clinical evidence supporting the prevention of venous thromboembolism in hospitalized cancer patients is reflected in general and cancer-specific national guidelines which recommend that immobile hospital inpatients with cancer receive low molecular weight heparin thromboprophylaxis (Grade Ia) (Scottish Intercollegiate Guidelines Network, 2002; Snow et al, 2007; Khorana, 2007; Geerts et al, 2008).

Despite the availability of guidelines, compliance varies worldwide. The ENDORSE (Epidemiologic International Day for the Evaluation of Patients at Risk of Venous Thrombosis in the Acute Hospital Care Setting) study (Cohen et al, 2008) revealed that 51% of almost 70 000 patients in 358 hospitals across 32 countries were considered to be at risk of venous thromboembolism but only 39.5% of medical patients at risk (including those with cancer) received thromboprophylaxis.

Specific to the cancer population there may be underrecognition of the additional risk factors resulting from the malignant process, even among cancer specialists (Kirwan et al, 2003; Wolf, 2003). Low molecular weight heparin is an acceptable intervention to cancer patients (Noble et al, 2006), yet there may be attitudinal barriers to thromboprophylaxis by clinicians, particularly for patients with metastatic disease.

A qualitative study identified the perception of some physicians that a fatal pulmonary embolus may be a 'nice' or 'quick and easy' mode of death compared to other cancer-related pathologies (Noble et al, 2008b). However, the published evidence does not support this belief; in a study of 92 patients where pulmonary embolus was confirmed at autopsy as the cause of death only 27 (30%) patients died within 10 minutes of the onset of symptoms and of these only nine died abruptly with no preceding symptoms (Havig, 1977). The clinical experience of patients taking longer than 10 minutes to die was of a 'gradual deterioration dominated by dyspnoea, tachycardia and fever'. A correct diagnosis of pulmonary embolus was made in only 10% of patients with most being treated with diuretics, digoxin and antibiotics for presumed infection or heart failure. This suggests that in the majority of patients who died from a pulmonary embolus, the death was neither sudden nor symptom free. In addition, the diagnosis was not made in 90% of cases and so appropriate treatment or symptom control was not given.

Future anticoagulants

The past year has seen the introduction of several new oral anticoagulants. Dabigatran, a direct thrombin inhibitor, and rivaroxaban, a factor Xa inhibitor, have recently been licensed for primary thromboprophylaxis in orthopaedic surgery. They are yet to be evaluated in the cancer population in either the primary or secondary thromboprophylaxis setting but their oral route of administration could make them an attractive option to patients, particular if long-term use is required. Furthermore, while low molecular weight heparin is superior to warfarin in the management of cancer-related venous thromboembolism, there still remains a group of patients experiencing recurrent thrombosis on low molecular weight heparin fuelling speculation of low molecular weight heparin resistance in part being the result of tumour-related thrombin release. An oral direct thrombin inhibitor may theoretically offer additional benefits in the cancer population.

Anticancer effects of low molecular weight heparin

In addition to being the drug of choice in the treatment of cancer-related venous thromboembolism, accumulating clinical evidence suggests that low molecular weight heparin improves overall survival in cancer patients who do not have a thrombus (Kakkar et al, 2004; Klerk et al, 2005). A complex feedback mechanism exists between tumour cells, coagulation proteases and vascular endothelial cells, making a hypothesis of low molecular weight heparin having anti-cancer effects entirely plausible. In addition, the overall survival observed in these studies cannot simply be explained by a reduction in fatal pulmonary embolism since the survival benefit continued long after low molecular weight heparin was discontinued, suggesting that low molecular weight heparin can directly influence tumour cell biology. There is also an accumulating body of in-vitro experimental evidence to suggest that both heparin and warfarin have direct antineoplastic effects (Smorenburg and Van Noorden, 2001). Several studies are now underway to explore the survival benefits of low molecular weight heparin in specific tumour types including pancreatic (FRAGEM study) and lung cancer (FRAGMATIC).

KEY POINTS

- Venous thromboembolism is a common complication of cancer.
- Anticoagulation for cancer-related venous thromboembolism has a higher incidence of bleeding and recurrence compared to the general population.
- Low molecular weight heparin is recommended for the treatment of cancer-related venous thromboembolism.
- Hospitalized cancer patients are at high risk of venous thromboembolism and should receive pharmacological thromboprophylaxis.
- Low molecular weight heparin may have anti-cancer properties and research is ongoing.

Conclusions

Venous thromboembolism is a common occurrence in cancer, which may cause significant morbidity or even mortality at any stage of the cancer journey. The past 10 years have seen substantial developments in its prevention and treatment with low molecular weight heparin superseding warfarin as the anticoagulant of choice in venous thromboembolism treatment. Nevertheless, particular challenges remain in the management of patients with haemorrhagic risks and those resistant to low molecular weight heparin therapy.

While the emergence of new oral anticoagulants offer opportunity to further improve venous thromboembolism management, their use is yet to be evaluated in representative cancer populations. Furthermore, advances in oncological therapies have improved survival such that patients are living longer with metastatic disease. The management of venous thromboembolism in the palliative population, particularly with respect to thromboprophylaxis, is yet to be established and worthy of further research. Finally, the complex relationship between the thrombotic process and cancer progression offers exciting opportunities to investigate novel therapies in the treatment of cancer. **BJHM**

Conflict of interest: Dr Noble is co-investigator on the FRAGMATIC study which has received an investigator grant from Pfizer. He a trustee of Lifeblood: the Thrombosis Charity to which he donates any speakers' honoraria.

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