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Treatment and secondary prevention of venous thromboembolism in cancer

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Patients with cancer who develop venous thromboembolism (VTE) are at elevated risk for recurrent thrombotic events, even during anticoagulant therapy. The clinical picture is further complicated because these patients are also at increased risk of bleeding while on anticoagulants. In general, there are four key goals of treatment for VTE: preventing fatal pulmonary embolism (PE); reducing short-term morbidities associated with acute leg or lung thrombus; preventing recurrent VTE; and preventing the long-term sequelae of VTE (e.g., post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension). A fifth goal – minimising the risk for bleeding while on anticoagulation – is particularly warranted in patients with cancer. Traditionally, pharmacological treatment of VTE has two phases, with the transition between phases marked by a switch from a rapid-acting, parenterally administered anticoagulant (such as unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), or fondaparinux) to an oral vitamin K antagonist (e.g., warfarin). Recent clinical trials of established agents and the advent of new pharmacological options are changing this paradigm. Low-molecular-weight heparin continued for 6 months is more effective than warfarin in the secondary prevention of VTE in cancer patients without increasing the risk of bleeding and is now the preferred treatment option. Given the impact of VTE on short-term and long-term outcomes in patients with cancer, a group of health-care providers based in the United Kingdom gathered in London in 2009 to discuss recent data on cancer-associated thrombosis and to evaluate how these recommendations can be integrated or translated into UK clinical practice. This article, which is the third of four articles covering key topics in cancer thrombosis, focuses on treatment and secondary prevention of VTE in cancer patients.
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It has been clearly established that patients with cancer have an increased risk of venous thromboembolism (VTE) compared with patients without cancer. Venous thromboembolism, comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is an important cause of morbidity and mortality in cancer patients and its treatment is particularly difficult because standard therapy is less effective in preventing recurrences and causes more bleeding than is the case in non-cancer patients with VTE. The need to perform surgery or invasive procedures in patients with cancer receiving anticoagulants, as well as the frequent presence of thrombocytopenia due to chemotherapy or haematological malignancy, widespread use of in-dwelling central lines, administration of multiple interacting drugs, and varying dietary intake during the course of cancer therapy, all add to the particular challenges faced in VTE treatment.

Randomised clinical trials over the past decade have substantially altered the management of VTE in patients with cancer, leading to improved outcomes and quality of life. Unfractionated heparin (UFH) and vitamin K antagonists (e.g., warfarin) have been the mainstay of management of VTE since the mid-twentieth century, followed by the widespread replacement of UFH by low-molecular-weight heparins (LMWH) since the 1990s. The appearance of new classes of oral anticoagulants that directly inhibit specific clotting factor targets, such as thrombin and factor Xa, may further transform the management of VTE in patients with cancer in the years to come.

Venous thromboembolism is a major cause of death in patients with cancer receiving chemotherapy (Khorana *et al*, 2007). Compared with patients without cancer, patients with cancer have a three-fold elevated risk of recurrent DVT or PE, following an initial episode of VTE. For example, in a prospective study, Prandoni *et al* (2002) observed a 12-month cumulative incidence of recurrent thromboembolism of 20.7% in 181 cancer patients, compared with 6.8% in patients without cancer. Both groups were managed in the same standard manner with initial heparin followed by warfarin. Levitan *et al* (1999) showed that the cumulative probability of re-admission to the hospital with DVT among patients initially hospitalised for DVT and malignant disease was approximately three-fold higher than those initially hospitalised with DVT alone. A more recent retrospective study, conducted by Elting *et al* (2004) using medical records from 529 consecutive cancer patients, found an overall rate of recurrence of 17%, ranging to as high as 32% in patients with inferior vena caval (IVC) filters. Similarly, in 2006, Blom *et al* (2006) found that the risk of VTE within the first 6 months after a first thrombotic event was 18.4/1000/0.5 year, with a 4.6-fold increased risk compared with cancer patients who did not have a thrombotic event in the 6 months after cancer diagnosis. In this study, patients with leukaemia, brain cancer, or cancer of the bladder, ureter, or testes were at highest risk for recurrence. In the RIETE registry of 15 520 consecutive patients with VTE, cancer was present in 20% and was

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associated with a two-fold increase in the risk of fatal PE within 3 months (Laporte *et al*, 2008). Risk factors for the recurrence on multivariate analysis were age <65 years or <3 months from cancer diagnosis to VTE (Trujillo-Santos *et al*, 2008). Those presenting with PE were more likely to have a PE recurrence than those initially presenting with DVT.

The clinical picture is further complicated by the fact that patients with cancer are also at increased risk of bleeding during anticoagulant therapy. In the study conducted by Prandoni *et al* (2002), referred to above, the 12-month cumulative incidence of major bleeding was 12.4% in patients with cancer and 4.9% in patients without cancer – a hazard ratio of 2.2. Notably, both recurrence and bleeding were directly related to cancer severity, and could not be explained by over- or under-anticoagulation (Prandoni *et al*, 2002). Similarly, in the study by Elting *et al* (2004), the risk of major bleeding during anticoagulant therapy was 12% (Elting *et al*, 2004). In the RIETE Registry, cancer was independently associated with a 1.7-fold increased risk of major bleeding (Ruiz-Giménez *et al*, 2008). Risk factors for bleeding in cancer patients were immobility, metastases, recent bleeding, or creatinine clearance $<30\,\mathrm{ml\,min^{-1}}$ (Trujillo-Santos *et al*, 2008).

A number of evidence-based guidelines on the management of VTE in both cancer and non-cancer patients have recently been published (Lyman *et al*, 2007; Kearon *et al*, 2008; Torbicki *et al*, 2008; NCCN, 2009). Given the impact of VTE on short-term and long-term outcomes in patients with cancer – and a potential gap between current guidelines and national clinical practice – a group of health-care providers based in the United Kingdom gathered in London in 2009 to discuss recent data and guidelines on cancer-associated thrombosis and to evaluate how these recommendations can be translated into best practices for the United Kingdom. This article, which is the third of four articles covering key topics in cancer thrombosis, focuses on treatment and secondary prevention of VTE in the cancer patient. The paper is structured as a brief review of key data and guidelines on acute treatment and secondary prevention of VTE in patients with cancer, followed by an edited transcript of the discussion surrounding these data.

TREATMENT OF VTE IN CANCER PATIENTS

In general, the goals of VTE treatment can be summarised as follows: (1) preventing fatal PE; (2) reducing short-term morbidities associated with acute leg or lung thrombus; (3) preventing recurrent VTE; (4) preventing the long-term sequelae of VTE (e.g., post-thrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension).

Anticoagulant therapy is the mainstay of treatment for VTE. Traditionally, pharmacological treatment of VTE has two phases, with the transition between phases marked by a switch from a parenterally administered anticoagulant with a rapid mechanism of action (e.g., UFH, low-molecular-weight heparin (LMWH), or fondaparinux (a synthetic pentasaccharide with the same antithrombin-dependent inhibition of factor Xa as LMWH)) to an oral vitamin K antagonist (e.g., warfarin). As will be discussed, recent clinical trials of established agents and the advent of new pharmacological options may change this paradigm. In addition to anticoagulants, a number of additional options exist for acute VTE, including systemic thrombolytic therapy, catheter-directed thrombolysis, mechanical thrombectomy, and use of vena caval filters.

Initial treatment of VTE

The use of UFH in the initial treatment of VTE is well established. The first and only trial that compared anticoagulant therapy with no therapy was published in 1960 (Barritt and Jordan, 1960, see Kearon *et al*, 2008). The trial that enrolled patients with symptomatic PE (with or without symptomatic DVT), who were randomly allocated to 1.5 days of heparin and 14 days of vitamin K antagonist therapy or no treatment, showed that anticoagulation significantly reduced recurrent PE and mortality. The need for initial treatment with a rapid-acting anticoagulant such as heparin was confirmed in a trial by Brandjes *et al* (1992). In this study, patients were assigned to either combination therapy (intravenous loading dose of 5000 U heparin, followed by an infusion of $1250\,\mathrm{U\,h^{-1}}$ for a minimum of 7 days, in combination with vitamin K antagonist acenocoumarol) or to acenocoumarol alone (Brandjes *et al*, 1992). The study was ended early because of an excess of events in the acenocoumarol group (20%) compared with the combined-therapy group (6.7%). Asymptomatic extension of venous thrombus was seen in 39.6% of patients in the acenocoumarol group and in 8.2% of the combination group. Notably, the rate of major bleeding was comparable in the two groups (Brandjes *et al*, 1992).

Although UFH as an initial treatment for VTE is highly effective, it is associated with a number of important limitations, including a short half-life, wide interpatient and intrapatient variability due to pharmacokinetic shortcomings, the need for frequent monitoring, a risk for heparin-induced thrombocytopenia, and, with long-term therapy, osteoporosis (a detailed discussion of the advantages and shortcomings of heparin can be found elsewhere in this supplement). Low-molecular-weight heparins have more predictable pharmacokinetics and greater bioavailability, which permits body-weight-adjusted dosing without the need for laboratory monitoring for most patients. This makes therapy much simpler and allows for outpatient treatment of many patients, reducing hospitalization, and improving their quality of life.

A number of clinical studies and meta-analyses have compared the efficacy and safety of body-weight-adjusted LMWH, administered subcutaneously without monitoring, with monitored, dose-adjusted intravenous heparin (Quinlan *et al*, 2004; van Dongen *et al*, 2004) and found it to be more effective, with reduced major bleeding during initial treatment and overall mortality at follow-up (van Dongen *et al*, 2004). Individual studies have not specifically assessed the effect of LMWH as initial treatment in patients with cancer. However, a meta-analysis of 14 trials that included cancer subgroup data showed that LMWH was equivalent to UFH for mortality (RR 0.89, 95% CI 0.61 – 1.27) and for clinically suspected DVT (RR 0.73, 95% CI 0.23 – 2.28) (Akl *et al*, 2008). In a *post hoc* analysis that included all studies that assessed DVT (irrespective of diagnostic strategy), LMWH was superior to UFH (RR 0.72, 95% CI 0.55 – 0.94). Rates of PE and minor or major bleeding were similar for the two strategies.

Data on the subcutaneously administered factor Xa inhibitor, fondaparinux, in the initial treatment of VTE associated with cancer are more limited. *Post hoc* analyses of the cancer patient subgroups of two randomised trials (Büller *et al*, 2003, 2004) in which fondaparinux was compared with UFH (for initial treatment of PE) or LMWH (for initial treatment of DVT) suggest broadly similar efficacy and safety (van Doormaal *et al*, 2009). However, these data require confirmation.

In summary, LMWHs, or possibly fondaparinux, are the agents of choice for the initial treatment of most episodes of VTE occurring in patients with cancer. An exception is in the setting of massive PE characterised by shock or hypotension in which UFH remains the preferred mode of anticoagulation, as newer agents have not been properly evaluated and an immediate anticoagulant effect is required.

MANAGEMENT OF MASSIVE PE

Massive PE constitutes a medical emergency, and specialised medical advice should be sought. Patients presenting with PE

should be clinically risk stratified into high-risk and non-high-risk groups. The former is characterised by systolic hypotension (BP < 90 mm Hg) (Torbicki *et al*, 2008) and carries a short-term mortality of >15% (Torbicki *et al*, 2008). Pooled data from randomised trials in non-cancer patients suggest a significant reduction in mortality and PE recurrence with systemically administered thrombolytic therapy in this subgroup (Wan *et al*, 2004). Intravenous heparin should be started immediately ($80\,U\,kg^{-1}$ as a bolus, followed by infusion at the rate of $18\,U\,kg^{-1}\,h^{-1}$ and adjusted to keep the activated partial thromboplastin time (aPTT) ratio between 1.5 and 2.5 times control) (Torbicki *et al*, 2008). Oxygen should be administered if the patient is hypoxic (Torbicki *et al*, 2008). A number of thrombolytic regimens are approved for PE. In practice, recombinant tissue plasminogen activator (rtPA) is commonly used at a dose of 100 mg over 2 h, or at $0.6\,mg\,kg^{-1}$ over 15 min (maximum dose 50 mg) if the patient is rapidly deteriorating (Torbicki *et al*, 2008). In patients in whom thrombolytic therapy is contraindicated (e.g., intracranial bleeding), alternative approaches, depending on local availability and expertise, are surgical pulmonary embolectomy and percutaneous catheter embolectomy and fragmentation (Torbicki *et al*, 2008).

Secondary prevention of VTE

Heparins are used in the initial treatment of VTE to provide anticoagulant support during the period of time required to achieve an appropriate international normalised ratio (INR), generally 2.0–3.0, with oral warfarin. In patients without cancer, warfarin is subsequently continued for a period of up to 6 months or longer. The need for anticoagulation beyond the initial period of heparinisation was demonstrated 30 years ago (Hull *et al*, 1979). Subsequently, a large, multicentre, randomised trial suggested that longer-duration warfarin (6 months) was superior to short-duration therapy (6 weeks). In this study, 902 patients were randomly assigned to receive either 6 weeks or 6 months of oral anticoagulant therapy with a target INR of 2.0–2.85 (Schulman *et al*, 1995). At 2 years, the rate of recurrence in the 6-week group was 18.1%, compared with 9.5% in the 6-month group (see Figure 1). There was no difference between the groups in mortality or in the rate of major haemorrhage (Schulman *et al*, 1995).

Although warfarin is effective in preventing VTE recurrence, its safe use in cancer patients is complex. Warfarin has more than 200 known drug, food, or botanical interactions that can result in irregular responses to treatment (Bick, 2006). In cancer patients, malnutrition, nausea, vomiting, and diarrhoea may make achieving and maintaining a therapeutic INR with an oral agent challenging. The need for therapeutic monitoring may also present a considerable challenge and/or an undue burden to the patient. Interruption of therapy is more likely in patients with cancer and, given the slow onset and offset of action of warfarin, this can lead to considerable gaps in anticoagulant coverage (Bick, 2006). In addition to these issues, some evidence suggests that patients with cancer who are receiving warfarin are not only at particular risk for recurrent thromboembolic events but also have an increased risk for bleeding (Prandoni *et al*, 2002).

As a result of the shortcomings of warfarin in cancer patients, the possible benefits of LMWH for prevention of recurrent VTE have been evaluated in a number of randomised trials. The largest of these was the CLOT trial in which, after initial standard LMWH treatment, oral anticoagulation and LMWH (dalteparin) were compared for prevention of recurrent VTE in 672 patients with cancer (Lee *et al*, 2003). The recurrence rate over 6 months was 9% in the LMWH group compared with 17% in the oral anticoagulant group, a 52% ($P = 0.002$) reduction in favour of LMWH (Figure 2). There were no significant differences in major bleeding or death between the two groups (Lee *et al*, 2003). In this trial, dalteparin was administered at a full-treatment dose for the first month, followed by a 75% treatment dose for the remaining 5 months (Lee *et al*, 2003). This regimen is now licensed in the United Kingdom for treatment of VTE in patients with cancer, and a number of systematic reviews and meta-analyses comparing LMWH with oral anticoagulation in the long-term treatment of VTE in patients with cancer have been published (Akl *et al*, 2008; Noble *et al*, 2008; Louzada *et al*, 2009). They show that, compared with oral anticoagulants, LMWH reduces the risk of recurrence by about 50%, with no difference between treatment modalities in major bleeding or mortality.

The use of anticoagulation in the thrombocytopenic patient remains challenging. Different options can be considered. For example, the label for dalteparin recommends a reduction in daily dose of 2500 IU if the platelet count falls to $50-100 \times 10^9$/l, until it recovers to $\geqslant 100 \times 10^9$/l, and discontinuation if the platelet count falls to $< 50 \times 10^9$/l. In a prospective cohort study, 203 patients with metastatic cancer and VTE received LMWH at treatment dose for 1 week (Monreal *et al*, 2006). The dose was then reduced to 10 000 IU daily, irrespective of weight, for 3 months. The dose was further reduced to 5000 IU daily at platelet counts $< 50 \times 10^9$/l and to 2500 at counts $< 10 \times 10^9$/l. Recurrent VTE developed in 9% of patients (fatal in two patients). Five percent had a major bleed (fatal in six patients) (Monreal *et al*, 2006). Although unsupported by specific data, others have recommended a 50% dose reduction of LMWH if the platelet count is $< 50 \times 10^9$/l and discontinuation if the platelet count is $< 20 \times 10^9$/l (Falanga and Rickles, 2007).

Consideration should be given to insertion of a vena caval filter if anticoagulation is contraindicated because of thrombocytopenia or active bleeding, but again firm data are lacking. Thus, the optimal approach to management of VTE in this setting is

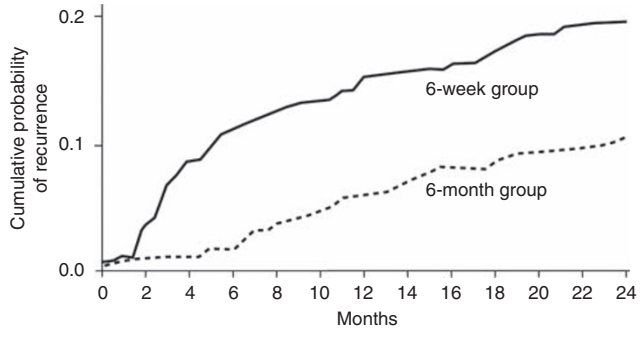

Figure 1 Cumulative probability of recurrent VTE after a first episode, according to duration of anticoagulation with a vitamin K antagonist (Schulman *et al*, 1995). Copyright © [1995] Massacusetts Medical Society. All rights reserved.

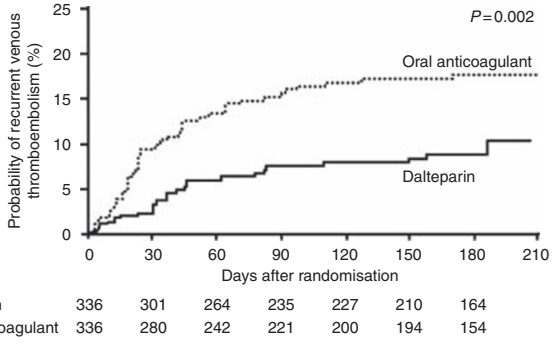

Figure 2 Probability of symptomatic recurrence of VTE among patients with cancer, according to whether they received secondary prophylaxis with dalteparin or oral anticoagulant therapy for acute VTE. Reproduced with permission from Lee *et al* (2003).

uncertain. In individual circumstances in which there is a clear wish not to interrupt LMWH therapy, it may be reasonable to continue at a slightly reduced dose with platelet support to maintain the count $>50 \times 10^9$/l and to reduce to a prophylactic dose, discontinue LMWH, or consider insertion of a vena caval filter if this is not possible.

Duration of anticoagulant therapy

The optimal duration of anticoagulant therapy for prevention of recurrent VTE in patients with cancer has not been specifically studied. Guidelines recommend that it should continue as long as the patient has active cancer (Lyman *et al*, 2007). In practice, this means indefinite treatments in patients with metastases or in those receiving anticancer therapy. However, each patient should be assessed individually in terms of the risk/benefit ratio of continuing *vs* stopping anticoagulants, life expectancy, quality of life, and patient preference. The CLOT trial data referred to earlier in favour of LMWH over oral anticoagulation did not extend beyond 6 months. It seems likely that the benefit of LMWH would extend beyond this period if continuing anticoagulation is required, but consideration may be given to oral anticoagulant therapy in individual instances.

Prevention of PTS

Post-thrombotic syndrome is a common cause of morbidity following DVT. It occurs in 20–50% of patients overall after symptomatic DVT. Typical features include chronic pain, swelling, heaviness, oedema, and skin changes in the affected limb (Kahn, 2006) and can be difficult to distinguish clinically from recurrent DVT. Use of graduated compression stockings providing an ankle pressure of 40 mm Hg for 2 years has been compared with no mechanical support and shown to reduce the incidence of total and severe PTS by approximately 50% (Brandjes *et al*, 1997).

Vena caval filters

There is only one open-label randomised trial of IVC filters in patients (mostly without cancer) presenting with VTE (PREPIC, 2005). In this trial, the filters were permanent and all patients received standard anticoagulant therapy. Long-term follow-up suggested that filter insertion was associated with a reduced risk of PE, counter-balanced by an increased risk of DVT, and no overall effect on mortality (PREPIC, 2005). Guidelines on the use of vena caval filters were published by the British Committee for Standards in Haematology (Baglin *et al*, 2006). The consensus was that there were no strong evidence-based indications for filters but their use should be considered in cases in which anticoagulation is contraindicated, or has to be interrupted within the first month of treatment to allow surgery, or in which there is occurrence of PE despite adequate anticoagulation. In those cases in which anticoagulation is contraindicated, it should be resumed as soon as the contraindication is no longer present, and retrievable filters should be considered in this setting. Such filters should be retrieved within 3 months of insertion where appropriate, or else left in permanently.

Treatment of central venous catheter-related thromboembolism

No randomised, controlled trials have been reported that evaluate the effects of particular therapeutic strategies on the outcomes of central venous catheter (CVC)-related thrombosis. Indeed, both the natural history and management of CVC-related thrombosis have been studied surprisingly little. In the RIETE Registry of 104 patients with cancer and CVC-related thrombosis, 10% of patients presented with symptomatic PE and 4% developed recurrent PE at 3-month follow-up, including one fatal event (Monreal *et al*, 2006). In routine practice, the catheter is commonly removed and the patient is anticoagulated with LMWH in the standard way for VTE in patients with cancer (i.e., with LMWH) for at least 3 months. Whether it is necessary to remove the catheter is unclear. Current recommendations from the National Comprehensive Cancer Network (NCCN) are to remove the catheter if it is not required and anticoagulate for at least 3 months. If the catheter is required and there is no contraindication to anticoagulation, it may be reasonable to leave the catheter in place and anticoagulate for at least 3 months after it is eventually removed. If symptoms worsen while the catheter remains in place or if anticoagulation is contraindicated, the catheter should be removed (NCCN, 2009).

Therapeutic anticoagulation failure

Therapeutic anticoagulation failure, defined as an extension of DVT, or new DVT, or PE while on therapeutic levels of recommended anticoagulation therapy, is relatively common in patients with cancer (Prandoni *et al*, 2002). The recurrence rate in the LMWH arm of the CLOT trial was 9%, much higher than would be seen in a non-cancer population of patients with VTE. Management in this setting has not been systematically studied, and the measures taken in practice depend in part on the individual circumstances in which the recurrence took place. Among patients receiving vitamin K antagonist therapy, INR should be assessed and adjusted, if necessary, to a higher INR range after acute therapy with UFH or LMWH (Streiff, 2006). Alternatively, and particularly among patients who experience recurrence despite therapeutic levels of a vitamin K antagonist, long-term LMWH represents a reasonable option. Vena caval filters represent another option in patients with therapeutic anticoagulation failure, particularly in those with VTE who have contraindications to anticoagulant therapy (NCCN, 2009). However, the hypercoagulable state associated with cancer affects all vasculature; thus, regional approaches to preventing recurrent VTE, such as vena caval filters, may not provide adequate protection in these patients (Streiff, 2006). In fact, placement of an IVC filter may be associated with an increased risk for recurrent thromboembolic disease (NCCN, 2009).

When a recurrent thrombotic event occurs in a patient receiving heparin (UFH or LMWH), a diagnosis of heparin-induced thrombocytopenia should be considered. Expert advice should be sought, if necessary, for confirmation of diagnosis and provision of non-heparin anticoagulants. More commonly, recurrence represents therapeutic failure. Compliance issues should be considered along with escalation of the dose of LMWH or converting from a once-daily to a twice-daily regimen (NCCN, 2009). For patients receiving a 75–80% maintenance dose of LMWH, this would mean increasing to a treatment dose. For those receiving a treatment dose at the time of recurrence, the dose could be increased by 20–25%. This approach was reported in a recent retrospective cohort study of 70 cancer patients with recurrent VTE despite anticoagulation (67% while on LMWH, 33% while receiving a vitamin K antagonist) (Carrier *et al*, 2009). Six (8.6%) patients had a second recurrence with this approach. The dose was further escalated by 20–25% in three patients who had a further VTE event at 120% of a therapeutic dose. None of them had a thrombotic recurrence; however, bleeding was seen in 3 out of 70 patients.

In conclusion, management of VTE in patients with cancer remains a challenge. Recent data support the use of LMWH both as the initial treatment for VTE and as the preferred option for secondary prevention. It should continue for a minimum of 6 months and longer if the cancer remains active. Both recurrent thrombosis and bleeding remain common problems, and further studies are required to optimise management. The advent of new anticoagulants, many of them oral, will hopefully provide

significant advances in therapy, although the challenge of providing anticoagulation without increasing the risk of bleeding is likely to remain.

DISCUSSION

Annie M Young: Should we be switching people that are on warfarin to low-molecular-weight heparin? Specifically, how should we manage patients who have had pulmonary emboli, are on warfarin, and have had treatment for cancer?

Peter K Maccallum: There are 2 issues. One is probably education of clinicians. We used to get a lot of patients who would come in under the relevant medical team and then be referred to the anticoagulant clinic on warfarin. In my experience, a small proportion of patients are prepared to stay on warfarin, but the majority who are offered LMWH switch.

Annie M Young: I do not think outpatients are permitted a choice.

Ajay K Kakkar: There are 2 reasons for that. First, dalteparin was not available in the UK until recently for this indication. The second issue is the point you raised. There will be a very large number of people who, beyond 6 months, will be on warfarin, because the general consensus view is that cancer patients with VTE should receive anticoagulant therapy to prevent recurrent thrombosis. Therefore, even in centres that use LMWH for the first 6 months of therapy, they put them on warfarin because they do not want to promote self-injection. There is a study ongoing to evaluate whether 12 months of anticoagulation with LMWH is more effective and as safe as 6 months of treatment. Another complicating factor is the recent availability – or imminent availability – of newer agents. The studies for these agents will include a small number of cancer patients, and it might be assumed that these agents should also be used in patients with cancer-associated thrombosis.

Faculty: Many haematologists are not aware of the issues surrounding anticoagulation for the secondary prevention of VTE, and they tend to keep people on warfarin. There are also many haematologists who keep patients on LMWH, but reduce the dose by 75% at 6 months.

Peter K Maccallum: In the absence of evidence, one can have a discussion with the patient to make a decision. There are some patients who are, by the end of the 6 months, unwilling to continue daily injections.

Faculty: Another problem is the drug-drug interactions seen with warfarin, particularly in the cancer patient who is undergoing treatment. In many ways, LMWH is easier to use.

Faculty: Qualitative data also suggest that warfarin has a negative effect on quality of life in patients with cancer, in part because these patients require frequent venopuncture for monitoring, but also because of the uncertainty and lack of freedom imposed by the monitoring regimen.

Ajay K Kakkar: Dosing presents a major issue with some LMWHs. How do you assess the appropriate de-escalated dose to ensure that the safety profile of the regimen is maintained? LMWH is dosed close to the margin for an increased rate of bleeding, so it is important to be very regimen sensitive when using these agents.

John Pasi: Separately, recurrent thrombosis occurring in fully anticoagulated cancer patients is a major issue.

Faculty: I agree. Most of the calls I get from the oncology unit are about patients who have had a recurrent event while on anticoagulation. At the moment, there are no good answers, and one has to make a common sense judgment regarding the treatment of these patients. Another key issue is anticoagulation in thrombocytopenic patients.

Faculty: Can we discuss duration of therapy? Many believe that patients with advanced disease should stay on indefinite anticoagulation. I want to challenge that, particularly in the typical breast or prostate cancer patient who has a median survival of 3–5 years.

Peter K Maccallum: The current recommendations suggest that indefinite coagulation should be considered.

Faculty: But if a patient is in remission, is it safe to stop? I do not know of any physicians who keep cancer patients on anticoagulation for 3–5 years after their first clot.

Annie M Young: It does happen in clinical practice.

Faculty: I would suggest that even patients with stable disease are at higher risk of VTE than patients without cancer.

Peter K Maccallum: There is an opportunity to include this in the consensus statement. If you look at global guidelines, the view is generally that antithrombotic therapy should be continued while there is active cancer or active anticancer therapy. However, there is always a question with breast cancer – what should physicians do with patients who are on tamoxifen for 5 years? I think this is a very difficult question, because warfarin is associated with a major risk for bleeding. In my opinion, warfarin at a full anticoagulant dose in such good-prognosis patients is problematic.

Faculty: Again, there is some role for discussion with patients. In the clinic, we often ask patients whether bleeding or having another VTE is their biggest worry. For many of them, thrombosis is a significant issue.

Ajay K Kakkar: This discussion clearly reflects the real problem of where we are in terms of treatment. We have solid data to guide treatment for the first 6 months, but no real guidance thereafter.

CONSENSUS STATEMENT

Following the development of VTE, cancer patients remain at elevated risk for recurrent thrombotic events. Treatment is further complicated by the increased risk of bleeding while on anticoagulants.

Acute management of VTE to prevent a fatal pulmonary embolus, as well as reduction in both short-term and long-term

Table 1 Regimens and contraindications for LMWH in the United Kingdom

Agent	Brand name	Regimen for secondary prevention	Key contraindications/cautions in patients with cancer
Dalteparin sodium	Fragmin	For extended treatment: ● 200 IU kg^{-1} (max 18 000 IU) s.c. once daily × 1 month ● Then 150 IU kg^{-1} (max 18 000 IU) s.c. once daily × 5 months (Fragmin PI, 2009)	● Patients with cancer undergoing regional anaesthesia (Fragmin PI, 2009) ● Dose reduction may be warranted in patients with cancer who experience thrombocytopenia or have renal insufficiency (Fragmin PI, 2009)
Enoxaparin sodium	Clexane	● 1.5 mg kg^{-1} once daily for extended prophylaxis (Meyer *et al*, 2002)	● Use with caution in patients with renal or hepatic impairment and in low-weight patients (Clexane PI, 2009)
Tinzaparin	Innohep	● 175 U kg^{-1} once daily (Hull *et al*, 1979)	● Use with caution in patients with renal impairment

Note that some regimens are based on studies conducted in non-cancer patients.

sequelae of thrombosis, relies on the use of a rapid-acting, parenterally administered anticoagulant such as UFH, LMWH, or fondaparinux (see Table 1). In non-cancer patients, an oral vitamin K antagonist (e.g., warfarin) may be initiated and continued for at least 6 months, with indefinite treatment considered in patients at increased risk of recurrence. In contrast, in patients with VTE and cancer, LMWH is now the preferred approach because of better protection against recurrent thrombosis without increasing the risk of bleeding. It has additional advantages in this population in that it is more flexible in terms of interruption for invasive procedures or thrombocytopenia and avoids the need for close INR monitoring that is essential with warfarin and is particularly challenging in cancer patients. The result is that blood tests and hospital visits can be minimised, thereby improving the quality of life. Warfarin may still be used in cases in which there is a clear patient preference to avoid injections. If the cancer is in remission and there are no additional risk factors for recurrence, anticoagulant therapy can generally be stopped at 6 months. If the cancer remains active or there are ongoing risk factors, consideration should be given to continuing anticoagulation beyond 6 months, after discussing with the patient. Randomised trials have not been conducted beyond this stage in these patients. Low-molecular-weight heparin is likely the option of choice in cases in which the decision is taken to continue anticoagulation, but warfarin is an alternative approach in cases in which this would be preferred by the patient.

Massive pulmonary embolus, catheter-related thrombosis, and recurrent VTE despite anticoagulation are clinical scenarios for which evidence on management in the setting of malignancy is limited. However, guidance on treatment, based on the limited evidence, extrapolation from a non-malignant setting, and clinical expertise are provided. Management recommendations are based on the NCCN Clinical Practice Guidelines in Oncology: Venous Thromboembolic Disease (NCCN).

Conflict of interest

R Coleman has received lecture fees from Pfizer and grant support from Boehringer Ingelheim. P MacCallum has received consulting fees from Pfizer and Boehringer Ingelheim.

REFERENCES

Akl EA, Terrenato I, Barba M, Sperati F, Sempos EV, Muti P, Cook DJ, Schünemann HJ (2008) Low-molecular-weight heparin *vs* unfractionated heparin for perioperative thromboprophylaxis in patients with cancer: a systematic review and meta-analysis. *Arch Intern Med* **168:** 1261 – 1269

Baglin TP, Brush J, Streiff M (2006) Guidelines on use of vena cava filters. *Br J Haemotol* **134:** 590 – 595

Barritt DW, Jordan SC (1960) Anticoagulant drugs in the treatment of pulmonary embolism. A controlled trial.. *Lancet* **1:** 1309 – 1312

Bick RL (2006) Cancer-associated thrombosis: focus on extended therapy with dalteparin. *J Support Oncol* **4:** 115 – 120

Blom JW, Vanderschoot JP, Oostindiër MJ, Osanto S, van der Meer FJ, Rosendaal FR (2006) Incidence of venous thrombosis in a large cohort of 66 329 cancer patients: results of a record linkage study. *J Thromb Haemost* **4:** 529 – 535

Brandjes DP, Büller HR, Heijboer H, Huisman MV, de Rijk M, Jagt H, ten Cate JW (1997) Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. *Lancet* **349:** 759 – 762

Brandjes DP, Heijboer H, Büller HR, de Rijk M, Jagt H, ten Cate J (1992) Acenocoumarol and heparin compared with acenocoumarol alone in the initial treatment of proximal-vein thrombosis. *N Engl J Med* **327:** 1485 – 1489

Büller HR, Davidson BL, Decousus H, Gallus A, Gent M, Piovella F, Prins MH, Raskob G, Segers AE, Cariou R, Leeuwenkamp O, Lensing AW (2004) Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. *Ann Intern Med* **140:** 867 – 873

Büller HR, Davidson BL, Decousus H, Gallus A, Gent M, Piovella F, Prins MH, Raskob G, van den Berg-Segers AE, Cariou R, Leeuwenkamp O, Lensing AW (2003) Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. *N Engl J Med* **349:** 1695 – 1702

Carrier M, Le Gal G, Cho R, Tierney S, Rodger M, Lee AY (2009) Dose escalation of low molecular weight heparin to manage recurrent venous thromboembolic events despite systemic anticoagulation in cancer patients. *J Thromb Haemost* **7:** 760 – 765

Clexane [prescribing information]. *Guildford*. Sanofi-Aventis: Surrey, UK, 2009

Elting LS, Escalante CP, Cooksley C, Avritscher EB, Kurtin D, Hamblin L, Khosla SG, Rivera E (2004) Outcomes and cost of deep venous thrombosis among patients with cancer. *Arch Intern Med* **164:** 1653 – 1661

Falanga A, Rickles FR (2007) Management of thrombohemorrhagic syndromes (THS) in hematologic malignancies. *Hematology Am Soc Hematol Educ Program* 165 – 171, doi:2007/1/165 [pii] 10.1182/asheducation-2007.1.165

Fragmin [prescribing information], Pharmacia Limited: Sandwich, Kent, UK, 2009

Hull R, Delmore T, Genton E, Hirsh J, Gent M, Sackett D, McLoughlin D, Armstrong P (1979) Warfarin sodium versus low-dose heparin in the long-term treatment of venous thrombosis. *N Engl J Med* **301:** 855 – 858

Kahn SR (2006) The post-thrombotic syndrome: progress and pitfalls. *Br J Haematol* **134:** 357 – 365

Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ (2008) Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edn). *Chest* **133:** 454S – 545S

Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH (2007) Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. *J Thromb Haemost* **5:** 632 – 634

Laporte S, Mismetti P, Décousus H, Uresandi F, Otero R, Lobo JL, Monreal M (2008) Clinical predictors for fatal pulmonary embolism in 15 520 patients with venous thromboembolism: findings from the Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE) Registry. *Circulation* **117:** 1711 – 1716

Lee AY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, Rickles FR, Julian JA, Haley S, Kovacs MJ, Gent M (2003) Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med* **349:** 146 – 153

Levitan N, Dowlati A, Remick SC, Tahsildar HI, Sivinski LD, Beyth R, Rimm AA (1999) Rates of initial and recurrent thromboembolic disease among patients with malignancy versus those without malignancy: risk analysis using Medicare claims data. *Medicine (Baltimore)* **78:** 285 – 291

Louzada ML, Majeed H, Wells PS (2009) Efficacy of low- molecular- weight-heparin versus vitamin K antagonists for long term treatment of cancer-associated venous thromboembolism in adults: a systematic review of randomized controlled trials. *Thromb Res* **123:** 837 – 844

Lyman GH, Khorana AA, Falanga A, Clarke-Pearson D, Flowers C, Jahanzeb M, Kakkar A, Kuderer NM, Levine MN, Liebman H, Mendelson D, Raskob G, Somerfield MR, Thodiyil P, Trent D, Francis CW (2007) American Society of Clinical Oncology guideline: recommendations for venous thromboembolism prophylaxis and treatment in patients with cancer. *J Clin Oncol* **25:** 5490 – 5505

Meyer G, Marjanovic Z, Valcke J, Lorcerie B, Gruel Y, Solal-Celigny P, Le Maignan C, Extra JM, Cottu P, Farge D (2002) Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study. *Arch Intern Med* **162:** 1729 – 1735

Monreal M, Falgá C, Valdés M, Suarez C, Gabriel F, Tolosa C, Montes J (2006) Fatal pulmonary embolism and fatal bleeding in cancer patients with venous thromboembolism: findings from the RIETE registry. *J Thromb Haemost* **4:** 1950 – 1956

NCCN Clinical Practice Guidelines in Oncology: Venous Thromboembolic Disease (V.1.2009) National Comprehensive Cancer Network Web site. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed 28 August 2009

Noble SI, Shelley MD, Coles B, Williams SM, Wilcock A, Johnson MJ (2008) Management of venous thromboembolism in patients with advanced cancer: a systematic review and meta-analysis. *Lancet Oncol* **9:** 577 – 584

Prandoni P, Lensing AW, Piccioli A, Bernardi E, Simioni P, Girolami B, Marchiori A, Sabbion P, Prins MH, Noventa F, Girolami A (2002) Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. *Blood* **100:** 3484 – 3488

PREPIC Study Group (2005) Eight-year follow-up of patients with permanent vena cava filters in the prevention of pulmonary embolism: the PREPIC (Prevention du Risque d'Embolie Pulmonaire par Interruption Cave) randomized study. *Circulation* **112:** 416 – 422

Quinlan DJ, McQuillan A, Eikelboom JW (2004) Low-molecular-weight heparin compared with intravenous unfractionated heparin for treatment of pulmonary embolism: a meta-analysis of randomized, controlled trials. *Ann Intern Med* **140:** 175 – 183

Ruiz-Giménez N, Suárez C, González R, Nieto JA, Todolí JA, Samperiz AL, Monreal M (2008) Predictive variables for major bleeding events in patients presenting with documented acute venous thromboembolism. Findings from the RIETE Registry. *Thromb Haemost* **100:** 26 – 31

Schulman S, Rhedin AS, Lindmarker P, Carlsson A, Lärfars G, Nicol P, Loogna E, Svensson E, Ljungberg B, Walter H (1995) A comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism. Duration of Anticoagulation Trial Study Group. *N Engl J Med* **332:** 1661 – 1665

Streiff MB (2006) Long-term therapy of venous thromboembolism in cancer patients. *J Natl Compr Cancer Netw* **4:** 903 – 910

Torbicki A, Perrier A, Konstantinides S, Agnelli G, Galiè N, Pruszczyk P, Bengel F, Brady AJ, Ferreira D, Janssens U, Klepetko W, Mayer E, Remy-Jardin M, Bassand JP, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Zamorano JL, Andreotti F, Ascherman M, Athanassopoulos G, De Sutter J, Fitzmaurice D, Forster T, Heras M, Jondeau G, Kjeldsen K, Knuuti J, Lang I, Lenzen M, Lopez-Sendon J, Nihoyannopoulos P, Perez Isla L, Schwehr U, Torraca L, Vachiery JL (2008) Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology. Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). *Eur Heart J* **29:** 2276 – 2315

Trujillo-Santos J, Nieto JA, Tiberio G, Piccioli A, Di Micco P, Prandoni P, Monreal M (2008) Predicting recurrences or major bleeding in cancer patients with venous thromboembolism. Findings from the RIETE Registry. *Thromb Haemost* **100:** 435 – 439

van Dongen CJ, van den Belt AG, Prins MH, Lensing AW (2004) Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism. *Cochrane Database Syst Rev* Art. No. CD001100, doi:10.1002/14651858.CD001100.pub2

van Doormaal FF, Raskob GE, Davidson BL, Decousus H, Gallus A, Lensing AW, Piovella F, Prins MH, Büller HR (2009) Treatment of venous thromboembolism in patients with cancer: subgroup analysis of the Matisse clinical trials. *Thromb Haemost* **101:** 762 – 769

Wan S, Quinlan DJ, Agnelli G, Eikelboom JW (2004) Thrombolysis compared with heparin for the initial treatment of pulmonary embolism: a meta-analysis of the randomized controlled trials. *Circulation* **110:** 744 – 749

CLINICAL SCENARIOS

Treatment of limb VTE

- Acute management
  - Commence LMWH in preference to UFH
    - — Dalteparin 200 U kg^{-1} once daily s.c.
    - — Tinzaparin 175 U kg^{-1} once daily s.c.
    - — Enoxaparin 1.5 mg kg^{-1} once daily s.c. (alternatively, enoxaparin 1 mg kg^{-1} every 12 h s.c.)
  - Fondaparinux may be considered
    - — Fondaparinux 5 mg (<50 kg); 7.5 mg (50 – 100 kg); 10 mg (>100 kg) daily s.c.
- Maintenance treatment
  - Continue LMWH at 75 – 80% treatment dose
  - Alternatively, administer warfarin at a dose to achieve an INR of 2 – 3 if not on myelosuppressive chemotherapy or complex supportive/concomitant medications
  - Continue for at least 6 months. Indefinite treatment recommended if active metastatic disease is observed or there is continued exposure to potentially thrombogenic anticancer therapy
- Anticoagulation contraindicated
  - Recent central nervous system bleed
  - Active major bleed (>2 U in 24 h)
  - Platelets $< 50 \times 10^9$/l
  - Severe platelet dysfunction
  - Known bleeding tendency, e.g., haemophilia
  - Elevated PT or aPTT above therapeutic target level
  - Severely limited life expectancy or no palliative benefit
  - Patient refusal

Pulmonary embolus

- Assess severity, including ECHO or CT angiography if necessary for right heart enlargement. Consider as high risk for death (15%) if systolic BP <90 mm Hg
- High-risk massive embolus
  - Oxygen
  - Commence heparin 80 U kg^{-1} and infuse at 18 U kg^{-1} h^{-1} to maintain aPTT between 2.0 and 2.5 (p 16)
  - Commence thrombolyis with rtPA 100 mg over 2 h or up to 50 mg over 15 min if rapidly deteriorating
- Uncomplicated
  - Treat as for VTE

CVC-related thrombosis

- Preservation of catheter access not essential
  - Remove line and anticoagulate for 3 months
- Preservation of catheter access clinically important
  - Anticoagulate with line *in situ* and for at least 3 months after removal. Removal of line and reinsertion at a later date may be necessary if symptoms worsen (e.g., recurrent emboli or increasing arm swelling)

Vena caval filter placement

- Contraindications to anticoagulation (p 32)
- Failure of anticoagulation
- Non-compliance
- Documented multiple PE and chronic pulmonary hypertension

Therapeutic anticoagulant failure

- During vitamin K antagonist therapy
  - Check compliance
  - Increase target INR to 3 – 4
  - Change to LMWH
  - Consider vena caval filter
- During LMWH therapy
  - Check compliance
  - Increase 75 to 80% maintenance dose to full-treatment dose
  - Consider increase from treatment dose by 20 – 25%
  - Convert once-daily to twice-daily administration
  - Consider vena caval filter