bjh review

Management of thrombosis in cancer: primary prevention and secondary prophylaxis

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Summary

Although traditional anticoagulant regimens are highly effective and safe in most patients with venous thromboembolism (VTE), the aggressive natural history of VTE and the high risk of serious bleeding in cancer patients can complicate the management of VTE. In addition, because few clinical trials have focused on the prevention and treatment of VTE in this unique patient population, many clinical questions regarding the care of cancer patients with VTE remain unanswered. Currently, low-molecular-weight heparins and oral vitamin K antagonists are the most commonly used agents for the primary and secondary prophylaxis of VTE in patients with or without cancer, but their use is associated with pharmacological and practical limitations. This review will provide an up-to-date summary of the clinical trials that have addressed the management of VTE in patients with cancer. A brief discussion of the potential application of novel anticoagulants in these clinical settings is also included.

Keywords: neoplasm, venous thromboembolism, prophylaxis, low-molecular-weight heparin, heparin.

Anticoagulants are the mainstay therapy for the prevention and treatment of acute venous thromboembolism (VTE). Although these agents are highly efficacious and have an acceptable safety profile in most patients, cancer patients have a higher risk of VTE, recurrent thrombosis and anticoagulant-related bleeding compared with patients without cancer. These complications probably reflect the heightened hypercoagulable state associated with malignant diseases and the multiple co-morbid conditions in cancer patients that may alter their response to anticoagulant therapy and their risk of bleeding. Of the commercially available anticoagulants, including unfractionated heparin (UFH) and its derivatives [e.g. low-molecular-weight heparins (LMWHs) and danaparoid], vitamin K antagonists such as coumarin derivatives, direct thrombin inhibitors (e.g. bivalirudin and argatroban), and inhibitors of activated factor X (fondaparinux), only the heparins and warfarin have been studied and used to any extent in patients with cancer. Given the pharmacological and logistical limitations of these agents, it is hoped that novel anticoagulants will offer clinical advantages over traditional therapy. This review will begin with a brief summary of the epidemiology of VTE in cancer and provide a more detailed discussion of the recent clinical studies addressing the primary prevention and long-term treatment of VTE.

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VTE in patients with cancer

Patients with cancer represent 15–20% of all patients with thrombosis. Furthermore, about 10% of patients presenting with unprovoked or idiopathic thrombosis are diagnosed with early or advanced malignancy within the next 1–2 years of the thrombotic event (Prandoni *et al*, 1992; Lee & Levine, 2003). Hence, approximately one quarter of all thrombosis cases are related to underlying malignancy. Given the ageing population and the rising incidence of cancer in industrialized nations, VTE in patients with cancer will become an increasingly common health care issue.

In addition to the traditional risk factors for thrombosis (Table I), patients with cancer may have multiple factors that are unique to this population and can predispose them to VTE. Specifically, the risk of thrombosis in cancer patients increases with the use of chemotherapy, hormonal therapy as well as indwelling central venous catheters (Heit *et al*, 2000) and is higher for those having surgery than in patients undergoing surgery for benign disease (Kakkar *et al*, 1970; Gallus, 1997). Recent studies have shown that cancer increases the risk of thrombosis by four to sixfold (Heit *et al*, 2000) and the probability of death in cancer patients with VTE is higher than that of patients with cancer alone or VTE alone (Levitan *et al*, 1999; Sorensen *et al*, 2000). According to a population-based study by Sorensen *et al* (2000), the 1-year survival rate in patients diagnosed with cancer at the time of their thromboembolic event is 12%, as compared with 36% in cancer patients who are free of thrombosis but otherwise are matched for sex, age at the time of cancer diagnosis, tumour type and the duration of cancer. The higher mortality rate in cancer patients with VTE may indicate that VTE is a marker of

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Table I. Risk factors and conditions predisposing to venous thromboembolism (VTE).

- Age >40 years
- Cancer with or without chemotherapy
- History of VTE
- Prolonged immobility (confinement to bed or lower limb paralysis)
- Surgery (especially lower limb orthopaedic, major pelvic or abdominal)
- Trauma (e.g. hip fracture, acute spinal injury)
- Obesity
- Smoking
- Major medical illnesses (e.g. acute myocardial infarction, ischaemic stroke, congestive heart failure, acute respiratory failure)
- Oestrogens (e.g. oral contraceptives, hormone replacement therapy)
- Pregnancy
- Puerperium
- Antiphospholipid antibody syndrome
- Inherited hypercoagulable states (e.g. antithrombin deficiency, protein C deficiency, protein S deficiency, factor V Leiden, prothrombin gene mutation)
- Haematological conditions (e.g. paroxysmal nocturnal haemoglobinuria, essential thrombocytosis, polycythemia vera)

aggressive malignancies or that these patients are dying prematurely from thrombotic complications, or both.

Among patients with cancer, those with ovarian, brain and pancreatic cancers have the highest incidence for VTE, whereas those with head and neck, bladder, and breast cancer have the lowest risks (Baron *et al*, 1998; Sorensen *et al*, 1998; Levitan *et al*, 1999). Unfortunately, the true incidence of VTE associated with various tumour types remains unknown for the majority of cancers because the appropriate cohort studies have not been conducted. On the contrary, the most common tumour types found in patients with VTE are cancers of the lung, colon, breast and prostate. This reflects the high prevalence of these cancers in the general population. Recent reports of very high rates of thrombotic complications in patients receiving experimental therapy with inhibitors of vascular endothelial growth factor (Kuenen *et al*, 2002; Marx *et al*, 2002; Kabbinavar *et al*, 2003) and other anti-angiogenic agents, such as thalidomide (Zangari *et al*, 2001; Desai *et al*, 2002; Rajkumar *et al*, 2002), have re-emphasized the importance of cancer therapy in the pathogenesis of thrombosis in cancer patients.

The natural history of VTE is more aggressive and anticoagulant treatment failure is more frequent in cancer patients than in patients without cancer (Prins *et al*, 1997; Baron *et al*, 1998; Sorensen *et al*, 1998). Based on prospective cohort data collected from anticoagulant clinics and randomized clinical trials, the annual risk of recurrent VTE is 21–27% and that of major bleeding is 12–13% in cancer patients (Hutten *et al*, 2000; Prandoni *et al*, 2002). These estimates represent a two to threefold risk of having recurrent thrombosis and a two to sixfold risk of haemorrhagic complications compared with patients without cancer (Hutten *et al*, 2000; Palareti *et al*, 2000; Prandoni *et al*, 2002).

Primary prevention

Surgical setting

Anticoagulant prophylaxis is routinely recommended for patients undergoing major surgery because the risk of postoperative thrombosis is substantial. For patients having surgery for cancer, the risk of VTE may be as high as 50% without prophylaxis (Geerts *et al*, 2001). The most commonly used prophylactic regimens consist of a single preoperative injection of a heparin (UFH or a LMWH), followed by subcutaneous injections starting within 12–24 h after surgery. Typically, UFH is given two or three times daily while LMWH requires only once-a-day injections. This difference is important to consider in terms of patient comfort, nursing time and the likelihood of potential drug error. In patients who have a high risk of bleeding, prophylaxis with compression stockings is often used as alternative, but it is less effective than anticoagulant prophylaxis, especially in high-risk patients (Wells *et al*, 1994; Geerts *et al*, 2001). Pneumatic compression devices are effective but they are cumbersome and interfere with early mobilization (Clarke-Pearson *et al*, 1984; Geerts *et al*, 2001). Prophylaxis is continued usually for few days during the patients' stay in hospital.

Although many trials have evaluated the efficacy and safety of heparins for surgical prophylaxis, there are few studies in patients undergoing surgery for cancer. Based on a meta-analysis published by Mismetti *et al* (2001), once-daily LMWH appears to be as efficacious and safe as multi-dose UFH in patients with cancer who are having major surgery. The largest randomized, placebo-controlled trial that compared LMWH with UFH in patients undergoing elective, curative surgery for colorectal cancer was conducted by the ENOXACAN Study Group (1997). Enoxaparin 40 mg, injected once a day and UFH 5000 U, given three times a day, were started 2 h before surgery. With 631 patients evaluable for the primary endpoint of venographically detected deep vein thrombosis (DVT) and symptomatic VTE, no difference in efficacy was detected between the two groups (14·7% vs. 18·2%, respectively), at the end of the 10-d treatment period. Notably, most of the thrombotic events were distal thrombi involving calf veins. Major bleeding was reported in 3–4% in both patient groups and a difference in mortality was not observed. More recently, the Canadian colorectal DVT prophylaxis trial also failed to find a statistically significant difference between UFH and LMWH in efficacy and bleeding in the subgroup of 475 patients with cancer. Interestingly, there was a trend in the incidence of VTE favouring LMWH (16·9% vs. 13·9%, $P = 0{\cdot}052$) in this high-risk population (McLeod *et al*, 2001).

More recently, the ENOXACAN II trial was conducted to examine the efficacy and safety of extending prophylaxis with LMWH beyond hospitalization in cancer patients (Bergqvist *et al*, 2002a). In this multicentre, double-blind, placebo-controlled trial, 501 patients undergoing elective, curative

abdominal or pelvic surgery for cancer were randomized and 332 were evaluable for the primary outcome. All patients received enoxaparin 40 mg once daily for the first 6–10 d after surgery. The first dose of enoxaparin was given at 10–14 h before surgery. After the initial postoperative period on enoxaparin, patients were then randomized to continue with enoxaparin 40 mg once daily or placebo injections until mandatory bilateral venography was performed between 25 and 31 d after surgery. The primary outcome was DVT detected on bilateral venography and symptomatic VTE. All outcome events were validated by a central committee that was blinded to treatment assignments. Patients were well matched in baseline characteristics and other risk factors for VTE. During the treatment period, 12·0% (20 of 167) of the placebo patients compared with 4·8% (8 of 165) of the enoxaparin patients had a confirmed thrombotic event ($P = 0{\cdot}02$). Proximal DVT was identified in three patients in the placebo group and one in the enoxaparin group. Only one patient had confirmed pulmonary embolism (PE). Therefore, extended prophylaxis with enoxaparin significantly reduced the rate of VTE by 60% (95% confidence interval (CI), 10–82%). During the double-blinded period, major bleeding occurred in none of the patients in the placebo group and 0·4% in the enoxaparin group. The absolute risk reduction of VTE of 7% found in this trial means that 14 patients must be treated to avoid one case of venographic DVT, while one case of major bleeding occurs in every 250 patients treated. There were no deaths during the treatment period but six (3·6%) patients in the placebo group and three (1·8%) in the enoxaparin group died during 3 months of follow up. A recent abstract reported that there was also no observed difference in mortality at 1-year follow up (7·7% vs. 9·5% respectively) (Bergqvist *et al*, 2002b).

Another randomized trial, studying extended prophylaxis after cancer surgery, reported similar results (Rasmussen, 2002). In an open-label study, 117 cancer patients received dalteparin 5000 U once daily for the first 7 d after abdominal surgery for cancer and then were randomized to continue dalteparin at the same dose or no further treatment for the next 21 d. All patients used graduated compression stockings throughout the study period. Mandatory bilateral venography was performed on day 28 and all venograms were assessed by independent radiologists who were unaware of patient treatment. Preliminary results showed that prolonging prophylaxis with dalteparin significantly reduced the incidence of proximal DVT from 15·9% to none ($P < 0{\cdot}005$). The number of patients needed to treat in order to avoid one episode of proximal DVT was six.

Recently, the first randomized trial evaluating a selective inhibitor of activated factor X for thromboprophylaxis in general surgery was reported. Fondaparinux is approved for prophylaxis in orthopaedic surgery and has also been evaluated for the treatment of DVT and PE (Turpie *et al*, 2002; Buller *et al*, 2003, 2004). In the PEGASUS trial, a phase III, double-blind, double-dummy trial, 2927 patients undergoing high-risk abdominal surgery were randomized to receive once-daily injections of fondaparinux 2·5 mg or dalteparin 5000 U (Agnelli *et al*, 2003). Based on a composite outcome of DVT detected with bilateral venography performed on days 5–10 after surgery and symptomatic VTE up to day 10, a difference in the incidence of thrombosis was not observed (4·6% vs. 6·1%, respectively; $P = 0{\cdot}14$). Major bleeding was also comparable between the groups. Interestingly, a *post hoc* analysis of the subgroup of 1408 patients with cancer found that fondaparinux was associated with a statistically significant reduction in VTE compared with dalteparin (4·7% vs. 7·7%; $P = 0{\cdot}02$). Although prophylaxis studies in the orthopaedic population have suggested that fondaparinux is more efficacious than LMWH (Turpie *et al*, 2002), further studies are needed to investigate the subgroup results from PEGASUS, given the potential for bias in *post hoc* subgroup analyses.

Patients undergoing surgery for central nervous system malignancies have a very high risk of thrombosis. Craniotomy for brain tumours is associated with a risk of VTE of up to 60% in the immediate postoperative period and a risk of 23% at 1 year after diagnosis (Marras *et al*, 2000; Anderson *et al*, 2001). Two randomized trials have shown that LMWH prophylaxis started after neurosurgery can reduce the risk of VTE without increasing serious bleeding. About 80% of the patients in these trials were undergoing neurosurgery for a malignancy. In the trial by Nurmohamed *et al* (1996), patients were randomized to nadroparin or placebo starting at 18–24 h after surgery. Mandatory bilateral venography detected DVT in 31 of 166 patients (18·7%) assigned to nadroparin compared with 47 of 179 patients (26·3%) randomized to placebo ($P = 0{\cdot}047$). Major bleeding was reported in six and two patients respectively ($P = 0{\cdot}087$). Unexpectedly, mortality was significantly higher in the nadroparin group, but none of the deaths were judged to be related to study drug. In another placebo-controlled randomized trial, Agnelli *et al* (1998) demonstrated that giving enoxaparin 40 mg once daily starting within 24 h after surgery reduced the risk of VTE by 47% compared with placebo; 22 of 153 patients (17%) *versus* 42 of 154 patients (32%), respectively, had DVT confirmed on bilateral venography. In this trial, differences in bleeding and overall mortality were not observed. In both studies, all patients also wore graduated compression stockings. Combining the results from these trials with another placebo-controlled study in a meta-analysis, Iorio and Agnelli (2000) reported that prophylaxis with LMWH resulted in a 38% relative risk reduction of VTE ($P < 0{\cdot}001$) without an excessive increase in the bleeding risk. Based on the incidence of VTE and bleeding observed in these studies, one may expect to have one major non-fatal bleeding event in excess of every 11 cases of venous thromboembolic event prevented. Although these trials provide reliable evidence that LMWH prophylaxis is efficacious in this setting, neurosurgeons continue to favour using mechanical prophylaxis while patients are in hospital because of the concern about intracerebral haemorrhage (Carman *et al*, 2003). Routine prophylaxis beyond discharge is not recommended but an ongoing international, placebo-

controlled randomized trial is studying the use of LMWH for extended prophylaxis in patients with high-grade gliomas.

Studies have also compared the use of LMWH with UFH in the neurosurgical setting (Goldhaber *et al*, 2002; Macdonald *et al*, 2003). In a randomized, double-blind trial, 150 patients undergoing craniotomy for malignant brain tumours were randomized to either enoxaparin 40 mg once daily or UFH 5000 U twice daily, starting on the first postoperative day (Goldhaber *et al*, 2002). All patients also received intermittent pneumatic compression devices as well as graduated compression stockings. The primary endpoint was in-hospital DVT detected on routine duplex venous ultrasonography performed before discharge. Symptomatic DVT did not develop in any patient but asymptomatic DVT was diagnosed in 14 of 150 (9·3%) patients. Nine of 75 patients in the enoxaparin group *versus* five of 75 in the UFH group had evidence of DVT; of these, two patients in each group had proximal DVT. Three patients had postoperative bleeding complications: one patient in the enoxaparin group had a confirmed haemorrhagic stroke and one patient in each group had an asymptomatic decrease in haematocrit without any overt bleeding. The investigators concluded that their multimodality approach to VTE prophylaxis achieved excellent efficacy and safety, although the study was underpowered to detect a difference between enoxaparin and UFH. In a similarly-designed, open-labelled pilot study, Macdonald *et al* (2003) concluded that twice-daily UFH 5000 U and once-daily dalteparin 2500 U appeared to be safe and were associated with a low incidence of VTE when these agents were used in combination with intermittent pneumatic compression devices.

Prophylaxis in women undergoing surgery for gynaecological malignancies has been studied in small cohort studies and randomized trials (Clarke-Pearson *et al*, 1983; Fricker *et al*, 1988; Clarke-Pearson *et al*, 1990; von Tempelhoff *et al*, 1997; Heilmann *et al*, 1998; Baykal *et al*, 2001; Maxwell *et al*, 2001). A Cochrane database meta-analysis of the various pharmacological agents available for prophylaxis found that UFH and LMWH are both effective in preventing DVT compared with placebo, even in women with gynaecological malignancies (odds ratio 0·30, 95% CI 0·10–0·89) and that these agents appear to be equally effective (Oates-Whitehead *et al*, 2003). However, there is no evidence as yet to suggest that heparin, warfarin or aspirin reduce the incidence of PE. Furthermore, in open-labelled, controlled studies, Clarke-Pearson *et al* have reported that UFH given three times daily (Clarke-Pearson *et al*, 1990), but not twice daily (Clarke-Pearson *et al*, 1983), is effective in reducing DVT in this surgical population. They also reported recently that intermittent pneumatic compression prophylaxis is likely to fail in women having surgery for gynaecological malignancies (Clarke-Pearson *et al*, 2003).

Very few studies have evaluated thromboprophylaxis in other surgical oncology settings, including thoracic (Cade *et al*, 1983; Azorin *et al*, 1997), urologic (Bigg & Catalona, 1992; Sawczuk *et al*, 2002) and orthopaedic surgery (Lin *et al*, 1998). Based on limited published data, it appears that prophylaxis with either UFH or LMWH is effective and relatively safe, but properly conducted studies are needed to address the issue in each surgical setting separately.

Medical setting

Compared with the thromboprophylaxis in the surgical oncology setting, prophylaxis in cancer patients on chemotherapy has received even less research attention. To date, only one randomized control trial has evaluated primary prophylaxis with warfarin in patients receiving outpatient chemotherapy (Levine *et al*, 1994). In this placebo-controlled study, women with stage IV breast cancer were randomized to receive low-dose warfarin or placebo for the duration of their multiagent chemotherapy. Warfarin was given at 1 mg daily for the first 6 weeks and then the dose was adjusted to maintain the international normalized ratio (INR) at 1·3–1·9. Seven of 159 patients receiving placebo compared with one of 152 taking warfarin-developed symptomatic, objectively confirmed thromboembolic events. The relative risk reduction of 85% associated with warfarin use was statistically significant ($P = 0{\cdot}03$). No difference in any or major bleeding was found, with a total of five patients in the placebo group and eight patients in the warfarin group having had any bleeding.

Despite the results of this study, the use of low-dose warfarin is not routinely or frequently used in patients receiving chemotherapy or other medical treatments for cancer for a number of reasons. First, low-dose warfarin is poorly tolerated in some patients and the use of low-dose warfarin with INR monitoring is a laborious task that is unattractive to both patients and physicians. Secondly, the relatively low risk of VTE of 4% in the control patients, in this study, raises the question of whether routine prophylaxis is warranted, especially as the risk of bleeding was also around 4%. Thirdly, there has been no other study conducted to confirm these findings. Lastly, the results from Levine *et al* (1994), especially regarding bleeding, cannot be extrapolated to patients with other tumour types or those receiving different chemotherapeutic regimens.

Clinical trials have not been performed to evaluate primary prophylaxis specifically in hospitalized medical oncology patients. Several large, randomized trials studying prophylaxis using LMWH or fondaparinux have included small numbers of cancer patients but the results of the cancer subgroups have not been reported (Samama *et al*, 1999; Cohen *et al*, 2003; Leizorovicz *et al*, 2004). Based on current information from other clinical settings, it is likely that standard anticoagulant prophylaxis would reduce the risk of VTE in cancer patients hospitalized for medical reasons, but the associated risk of anticoagulant-related bleeding is a serious concern. Many of these patients are very ill and often have thrombocytopenia. Well-designed trials are needed in this population to examine the efficacy and safety of thromboprophylaxis.

Treatment of VTE

Initial therapy

The standard regimen for the treatment of acute VTE consists of initial therapy with UFH or LMWH followed by long-term therapy with a coumarin derivative for secondary prophylaxis. To date, multiple randomized trials and meta-analyses of these trials have confirmed that, for initial therapy, LMWHs are at least as efficacious as UFH in reducing recurrent thrombosis and are likely to be associated with a lower risk of major bleeding (Koopman *et al*, 1996; Levine *et al*, 1996; The Columbus Investigators, 1997; Gould *et al*, 1999; Dolovich *et al*, 2000; Merli *et al*, 2001; van Dongen *et al*, 2004). Furthermore, LMWHs can be given in an outpatient setting without the need for laboratory monitoring and has a lower risk of heparin-induced thrombocytopenia (Harrison *et al*, 1998; Wells *et al*, 1998). In many developed countries, outpatient LMWH has become the standard of care for the initial treatment in patients with DVT or haemodynamically stable PE.

The relative efficacy and safety of LMWHs and UFH have not been formally investigated in patients with cancer. Cancer patients were included in randomized trials but they represented only 10–15% of the total population. Furthermore, many cancer patients with VTE would not have been included in these trials because of the poor performance status. Based on the published data extracted from trials that reported on the outcomes of the subgroup of cancer patients, it appears that LMWHs and UFH have similar efficacy in patients with and without cancer (Table II). Unfortunately, there have been no published data on the bleeding risk of therapeutic doses of LMWH compared with UFH in cancer patients. But clearly, outpatient LMWH therapy reduces hospitalization and cohort studies have shown that cancer patients can be treated safely at home with LMWH (Harrison *et al*, 1998; Wells *et al*, 1998; O'Shaughnessy *et al*, 2000; Ageno *et al*, 2002).

For several LMWHs, both once-daily *versus* twice-daily injections are available or approved for use but there is a paucity of data that have directly compared the two regimens.

Table II. The efficacy of low-molecular-weight heparins (LMWHs) and unfractionated heparin (UFH) for initial therapy of venous thromboembolism (VTE) in patients with and without cancer.

		3-Month incidence of recurrent VTE		
	Patients (*n*)	LMWH (%)	UFH (%)	*P*-value
Cancer	546	9·2	9·2	NS
No cancer	2275	4·0	4·2	NS

Combined results from four randomized trials (Koopman *et al*, 1996; Levine *et al*, 1996; The Columbus Investigators, 1997; Merli *et al*, 2001) showing the 3-month rates of recurrent VTE separately for patients with and without cancer.

In one study, intravenous UFH was compared with subcutaneous enoxaparin at 1·0 mg/kg of body weight given twice daily or 1·5 mg/kg injected once daily for the initial treatment of DVT (Merli *et al*, 2001). No difference in symptomatic recurrent VTE or bleeding was detected among the three treatment groups for all patients. However, among the subgroups of patients with cancer, patients receiving once-daily enoxaparin had a twofold risk of recurrent VTE compared with patients on twice-daily injections (12·2% vs. 6·4%). This difference was not statistically significant. Twice-daily administration of the LMWH reviparin also appeared to be more efficacious than once-daily injections in a randomized trial conducted by Breddin *et al* (2001). Results of patients with cancer were not reported separately in this study. Given the hypercoagulable status of cancer patients, it is possible that twice-daily administration of LMWH is required in order to provide a more steady state of anticoagulation, but this hypothesis has not been tested. Of note, patients in the once-daily enoxaparin group (Merli *et al*, 2001) received only 75% of the total daily doses received by those in the twice-daily group, so that the observed difference in recurrent VTE in that study could have been related to dose rather than frequency of injections.

Long-term therapy

Coumarin derivatives are the mainstay of long-term anticoagulant treatment for preventing recurrent VTE (Hyers *et al*, 2001). These vitamin K antagonists are started within the first 24 h of diagnosis and are continued for a minimum of 3 months. Because of the differences in anticoagulant response between patients and within patients over time, dose adjustments are needed based on the INR. For the majority of patients with VTE, the target therapeutic range is 2·0–3·0 (Hirsh *et al*, 2001). Unpredictable anticoagulant response can result from drug interactions, changes in vitamin K status, liver dysfunction, gastrointestinal disturbances such as vomiting and diarrhoea, and consumption of alcohol. Furthermore, because vitamin K antagonists have a delayed onset of action and prolonged clearance of the anticoagulant effect, it is difficult to manage in patients who require frequent interruption of their anticoagulant therapy. Thus, for cancer patients who require periodic invasive procedures (e.g. therapeutic paracentesis) or experience frequent episodes of chemotherapy-induced thrombocytopenia, treatment with warfarin is very problematic. Switching to or bridging with heparins may be indicated in these circumstances to provide more thorough and flexible coverage when invasive procedures are necessary (Dunn & Turpie, 2003; Kearon & Hirsh, 2003; Scafer *et al*, 2003).

Although standard oral anticoagulant therapy is highly effective in most patients, warfarin is associated with frequent recurrent VTE in the oncology population. Treatment failures may be related to subtherapeutic anticoagulation but recurrent VTE also occurs commonly while the INR is maintained

within the therapeutic range. In a prospective cohort study of 181 cancer and 661 non-cancer patients on oral anticoagulant therapy, the 12-month cumulative incidence of recurrent VTE was 20·7% in cancer patients *versus* 6·8% in patients without cancer (Prandoni *et al*, 2002). These estimates are consistent with other studies. In particular, Hutten *et al* (2000) reported that the incidence of recurrence is increased in cancer patients relative to patients without cancer irrespective of the INR achieved (Table III). For example, for INRs within the therapeutic range, the recurrence incidence is 18·9/100 patient-years in cancer patients vs. 7·2/100 patient-years in patients without cancer. Overall, based on the available literature, the risk of recurrent VTE is two to threefold higher in cancer patients (Lee & Levine, 2003).

Cancer patients on oral anticoagulant therapy also have a high risk for major bleeding. In the study by Prandoni *et al* (2002), the 12-month cumulative incidence for major bleeding was 12·4% vs. 4·9% for patients with and without cancer respectively. These estimates are also consistent with those from the study by Hutten *et al* (2000), in which the incidence of major bleeding in these patient groups were 13·3/100 patient-years and 2·1/100 patient-years respectively. In contrast to the INR-related increase in bleeding observed in patients without cancer, the incidence of bleeding in patients with malignancy did not follow a similar pattern. Indeed, the highest incidence of bleeding was found in the group with subtherapeutic INRs (Table IV).

Once outpatient LMWH therapy was established as effective and safe for initial treatment, studies followed to compare the efficacy and safety of long-term LMWH with oral anticoagulant therapy for secondary prophylaxis. The majority of these studies are small and included primarily patients without cancer (Pini *et al*, 1994; Das *et al*, 1996; Hamann, 1998; Gonzalez-Fajardo *et al*, 1999; Lopaciuk *et al*, 1999; Veiga *et al*, 2000; Lopez-Beret *et al*, 2001; Hull *et al*, 2002). Two meta-analyses of these studies have found a statistically non-significant reduction of approximately 30% in the risk of recurrent VTE favouring LMWH (van der Heijden *et al*, 2001; Iorio *et al*, 2003), while one of these reviews found a significant reduction of 62% in the risk of bleeding with LMWH (van der Heijden *et al*, 2001).

To date, two published clinical trials have examined the use of long-term LMWH as an alternative to warfarin therapy in cancer patients with acute VTE (Meyer *et al*, 2002; Lee *et al*, 2003). The CANTHANOX trial compared 3 months of standard warfarin therapy with enoxaparin therapy in cancer patients with proximal DVT, PE or both (Meyer *et al*, 2002). All patients were treated initially for at least 4 d with therapeutic doses of enoxaparin at 1·5 mg/kg once daily and were randomized to either continue with enoxaparin at the same dose or warfarin therapy. After 147 patients were randomized, the study was terminated prematurely because of poor recruitment. A total of 75 patients in the warfarin group and 71 patients in the enoxaparin group were evaluable for the primary endpoint of treatment failure, defined as symptomatic, recurrent VTE and/or major bleeding within the 3-month treatment period. About 52% of the study patients had metastatic malignancy at randomization and these patients were equally distributed between the treatment groups. By 3 months, 15 patients had recurrent VTE or major bleeding in the warfarin group compared with seven patients assigned to enoxaparin. The difference was not statistically significant ($P = 0{\cdot}09$). The majority of the outcome events were major bleeding, reported in 12 and five patients respectively. Of these, six patients in the warfarin group died of bleeding. At 6-month follow up, 38·7% of the warfarin patients and 31·0% of the enoxaparin patients had died. Based on these results, the investigators concluded that warfarin is associated with a high bleeding risk in cancer patients with VTE and that prolonged treatment with LMWH may be as effective and safer than oral anticoagulant therapy.

In a similar patient population, the randomized comparison of low-molecular-weight heparin *versus* oral anticoagulant therapy for the prevention of recurrent VTE in patients with cancer (CLOT) trial evaluated the use of long-term dalteparin (Lee *et al*, 2003). In this multicentre, randomized, open-labelled study, 676 cancer patients with proximal DVT, PE or both were randomized to usual treatment with dalteparin initially followed by 6 months of oral anticoagulant therapy or dalteparin alone for 6 months. In the dalteparin group, patients received therapeutic doses at 200 U/kg once daily for the first month and then 75–80% of the full dose for the next 5 months. Patients were followed for the primary outcome of symptomatic, recurrent VTE and secondary outcomes of bleeding and survival. Over the 6-month treatment period, a total of 80 patients had a confirmed, symptomatic recurrent thromboembolic event; 27 of 338 in

Table III. The incidence of recurrent venous thromboembolism in relation to the international normalized ratio (INR).

	No. of events (per 100 patient-years)		
INR range	Cancer	No cancer	Total
≤2·0	54·0	15·9	23·7
2·1 to 3·0	18·9	7·2	9·2
>3·0	18·4	6·4	8·7

Modified from: Hutten *et al* (2000).

Table IV. The incidence of major bleeding in relation to the international normalized ratio (INR).

	No. of events (per 100 patient-years)		
INR range	Cancer	No cancer	Total
≤2·0	30·6	0·0	3·1
2·1 to 3·0	11·2	0·8	2·6
>3·0	0·0	6·3	5·1

Modified from: Hutten *et al* (2000).

the dalteparin group and 53 of 338 in the oral anticoagulant group. The cumulative risk of recurrent VTE at 6 months was reduced from 17% in the oral anticoagulant group to 9% in the dalteparin group, resulting in a statistically significant risk reduction of 52% ($P = 0{\cdot}002$). In the oral anticoagulant group, the INR was therapeutic or higher for 70% of the total treatment time and 25 of the 53 recurrences occurred while the INR was 2·0 or above. Accordingly, one episode of recurrent VTE is prevented for every 13 patients treated with dalteparin. Overall, there were no differences in major or any bleeding between the groups; major bleeding was reported in 6% in the dalteparin arm and 4% in the oral anticoagulant arm. By 6 months, 39% of the patients had died in each group; 90% because of progressive cancer. At 1 year, over 60% of the patients were dead. These figures are not surprising given that 67% of the patients had metastatic cancer at the time of study enrolment. The mean duration of treatment time in both groups was approximately 120 d.

Two unpublished studies have also evaluated LMWH for long-term use in cancer patients and the results have been presented in abstract form. A subgroup analysis of the long-term Innohep® treatment evaluation study reported improved efficacy with tinzaparin over warfarin in the 167 patients with cancer (Hull *et al*, 2003). Tinzaparin reduced the rate of recurrent VTE by half, but this was not statistically significant because of the small number of patients. Moreover, a difference in recurrent VTE was not found for the two treatment groups overall (3% in both groups) (Hull *et al*, 2002). Similarly, in the ONCENOX study, enoxaparin was compared with warfarin in cancer patients with VTE. Again, no differences in efficacy or bleeding were observed because the study was prematurely terminated after 101 patients were randomized (Deitcher *et al*, 2003).

In summary, there is strong evidence that long-term LMWH is efficacious and safe for preventing recurrent VTE in cancer patients. Bleeding does not appear to be increased compared with warfarin therapy but this remains a major concern in cancer patients receiving long-term anticoagulant therapy because of their co-morbid conditions. Daily injections appeared to be well tolerated but the main practical limitation of using LMWH for the long term is drug cost. A cost-effective analysis has suggested that LMWH might be a cost-effective drug for secondary prophylaxis of VTE, especially in patients at high risk of recurrence and where the drug cost is lower (Marchetti *et al*, 2001).

Recurrent VTE

Although recurrent VTE is relatively frequent in cancer patients while on oral anticoagulant therapy, treatment in this setting has not been investigated in clinical trials. Traditionally, four options are available after initial re-treatment with UFH or LMWH: continue with oral anticoagulant therapy aiming for a higher target INR; switch to activated partial thromboplastin time-adjusted, twice-daily injections of UFH; use once daily, weight-adjusted LMWH; or insert an inferior vena caval filter. None of these alternatives have been compared or rigorously evaluated. A recent randomized trial showed that vena caval filters reduce the short-term risk of PE, but more patients in the filter group developed recurrent DVT and postphlebitic syndrome during follow-up (Decousus *et al*, 1998). It is possible that filters are associated with even higher risks of recurrent DVT in cancer patients as a result of their heightened hypercoagulable state. Therefore, the use of filters should be limited to situations where anticoagulant therapy cannot be used because of serious, active bleeding.

Luk *et al* (2001) conducted a retrospective study to evaluate the efficacy of dalteparin for the treatment of recurrent VTE that occurred while patients are on warfarin therapy. Using the databases of thrombosis clinics at three tertiary facilities, the investigators identified 32 patients who were treated with long-term dalteparin 200 U/kg, once daily. Twenty (62·5%) of these patients had cancer. During follow up, 3 of 32 (9%) patients experienced a subsequent recurrent thrombotic event and one of them had cancer; all responded to treatment with higher doses of dalteparin.

Duration of therapy

Duration of anticoagulant therapy has not been addressed in cancer patients. Based on the accepted concept that the risk of recurrent thrombosis is increased in the presence of any ongoing risk factor, it is generally recommended that patients with metastases continue with 'indefinite' therapy because metastatic malignancy is a persistent risk factor. In those without metastases, anticoagulant treatment is recommended for as long as the cancer is 'active' and while the patient is receiving antitumour therapy. In general, it is advisable to re-evaluate frequently the risk-benefit ratio of ongoing anticoagulant therapy in individual patients, taking into consideration the overall clinical status of the patient, including the quality of life and life expectancy.

Future directions

The recent advances in the management of VTE in cancer patients are exciting. The results of the ENOXACAN II and Rasmussen trials provide reliable evidence that extended prophylaxis with LMWH following major surgery for cancer reduces the risk of VTE without significantly increasing the risk of bleeding. However, because both studies used venographically detected thrombosis as the primary endpoint, it remains unknown whether the reduction of these events is clinically relevant. The reduction of proximal DVT in the Rasmussen study does suggest that extended prophylaxis would probably reduce symptomatic thromboembolic events, but it is still premature to recommend extended prophylaxis routinely in cancer patients after surgery without further studies (Khushal *et al*, 2002). However, given that extended prophylaxis may reduce symptomatic thrombosis following

hip replacement surgery (Eikelboom *et al*, 2001; O'Donnell *et al*, 2003), selected patients undergoing cancer surgery will probably benefit from extended prophylaxis with LMWH. Furthermore, with the current trend to reduce the length of stay in hospital, it may become necessary for patients to continue 'usual' prophylaxis upon hospital discharge.

The CLOT trial presents compelling evidence that LMWHs should become the standard of care for initial and long-term treatment of VTE in cancer patients. The major obstacle in changing clinical practice is the cost of the drug. However, this expense may be offset by health care savings from a reduction in the need for investigations and hospitalizations associated with recurrent VTE. The study by Luk *et al* (2001) also demonstrates that LMWH is effective in treating cancer patients with recurrent VTE. Although this study provides a low level of evidence for the use of LMWH in this setting, long-term LMWH is the most practical strategy.

To date, the studies evaluating new anticoagulants have included few or no patients with cancer. Given the differences in the natural history and response to therapy between patients with and without cancer, research is needed to study the efficacy and safety of these agents specifically in the various oncology settings. The PEGASUS trial (Agnelli *et al*, 2003) provides preliminary but weak evidence that fondaparinux may be more effective than LMWH for prophylaxis in the surgical oncology setting, but further studies are needed to verify this observation. The long-acting formulation of fondaparinux and idraparinux is currently being tested in phase III trials (Koopman & Buller, 2003). This drug is given by once-weekly injections but has no specific antidote. These features may be disadvantageous for patients with cancer because of their risk of bleeding and the need for rapid reversibility of anticoagulant effects. New oral agents are potentially the most attractive alternatives to traditional agents because of the route of administration and the elimination of laboratory monitoring. However, these drugs, including ximelagatran, a pro-drug of the direct thrombin inhibitor melagatran, are still in various developmental phases and have not been evaluated carefully in patients with cancer (Gustafsson, 2003). Although they are convenient, their efficacy and safety profiles will be critical in determining how they compare with traditional anticoagulants. In particular, prolonged ximelagatran use has been associated with marked elevations of alanine transaminase in up to 13% of patients (Gustafsson, 2003; Wallentin *et al*, 2003). This is problematical in cancer patients in whom liver enzymes and function are already abnormal, secondary to their disease or treatment.

Although there are still many unanswered clinical questions in thrombotic management in oncology patients, the introduction of LMWHs has improved and simplified both prophylaxis and treatment regimens. More studies are required in this population to look at antithrombotic therapy, especially on issues regarding primary prophylaxis, duration of therapy, bleeding, quality of life, cost-effectiveness and the influence of anticoagulants on cancer survival. Whether novel anticoagulants will offer better risk-benefit and quality of life profiles than LMWHs awaits further study.

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