Epidemiology, risk and outcomes of venous thromboembolism in cancer

A. Falanga; L. Russo
Division of Immunohematology and Transfusion Medicine, Dept. Oncology-Hematology, Ospedali Riuniti, Bergamo, Italy

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Venous thrombosis, hypercoagulability, cancer, thromboprophylaxis

Summary
Cancer is associated with a fourfold increased risk of venous thromboembolism (VTE). The risk of VTE varies according to the type of malignancy (e.g., pancreatic cancer, brain cancer, lymphoma) and its disease stage and individual factors (e.g., sex, age, previous VTE history, immobilization, obesity). Preventing cancer-associated VTE is important because it represents a significant cause of morbidity and mortality. In order to identify cancer patients at particularly high risk, who need thromboprophylaxis, risk prediction models have become available and are under validation. These models include clinical risk factors, but also begin to incorporate biological markers. The major American and European scientific societies have issued their recommendations to guide the management of VTE in patients with cancer. In this review the principal aspects of epidemiology, risk factors and outcome of cancer-associated VTE are summarized.

Schlüsselwörter
Venöse Thrombose, Hyperkoagulabilität, Krebs, Thromboseprophylaxe

Zusammenfassung

Correspondence to:
Anna Falanga, MD
Division of Immunohematology and Transfusion Medicine, Department of Oncology-Hematology
Ospedali Riuniti di Bergamo
Largo Barozzi 1, 24128 Bergamo, Italy
Tel. +39/035/26 65 40, Fax +39/035/26 61 51
E-mail: annafalanga@yahoo.com

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Patients with cancer have an increased risk of venous thromboembolism (VTE) compared with patients without cancer. VTE, including pulmonary embolism (PE) and deep-vein thrombosis (DVT), is a major cause of morbidity and mortality in these patients (1). The reciprocal pathophysiological link between cancer and thrombosis is well recognized, although poorly understood. The incidence of VTE in cancer populations has been estimated at approximately one in 200, fivefold higher than that of the general population (2), and active malignant disease has been shown to be an independent risk factor for VTE (3, 4).

Overall, 18–29% of all VTE events in the population have been shown to be associated with cancer (5, 6).

Epidemiological and population-based studies provide detailed information on the scale of the problem and the identification of VTE risk factors. In a registry of 5 451 patients hospitalized with objectively confirmed DVT, cancer was reported in 39% of patients, made up of 62% with active cancer and 38% with a history of cancer (7). The incidence of VTE among hospitalized cancer patients is increasing. Several large retrospective analyses of hospital discharge data have reported a significant 28–36% increase in VTE events in this population over the period 1995–2003 (p < .0001 for the trend) (1).

Many factors can increase the thrombotic risk in cancer patients (1, 3), including
• classical thrombotic risk factors such as immobility, age, surgery, and
• risk factors peculiar of cancer such as advanced disease stage, type of cancer, chemotherapy, use of antiangiogenic drugs or erythropoietic growth factors.

Recently, the principal American and European scientific societies have issued their recommendations to guide the management of VTE in cancer patients (8–12, 13, 14). In this review, we will examine the
• impact of VTE on patients with cancer,
• effects of VTE on clinical outcomes,
• importance of thromboprophylaxis in this population,
• relevant ongoing clinical trials examining the prevention of VTE, and
• new pharmacologic treatment options.
**Epidemiology**

Large, population-based studies have shown that the risk of VTE is increased between 4- and 7-fold in patients with malignancy (3, 15). Studies based on hospital discharge have reported overall VTE incidences of 0.6–7.8% in patients with cancer, more than double the incidence of VTE in patients without cancer (1, 16–19). Recently, a retrospective cohort study of nearly two million patient hospitalizations in the United States reported an overall VTE rate of 4.1% among 10,155,986 cancer patients (1). In a subgroup analysis of the MEDENOX study, active cancer or a history of cancer were associated with a trend toward an increased risk of VTE (4).

However, the incidence of VTE in patients with cancer is probably underestimated by retrospective, population-based studies that report only symptomatic or objectively confirmed VTE events. The increased risk of VTE associated with cancer reflects in an increased likelihood of treatment failure (20, 21). This is most clearly seen with the high rates of VTE recurrence in cancer patients. For example, in a retrospective analysis of 1,303 patients with symptomatic VTE receiving oral anticoagulant therapy, patients with cancer (n = 264) experienced increased rates of VTE recurrence; 27.1 events per 100 patient-years versus 9 events per 100 patient-years in patients without malignancy (p = .003) (20).

Likewise, a prospective follow-up study of 842 patients with confirmed DVT, 181 patients with cancer and 661 without cancer, reported an annual VTE recurrence rate of 20.7% in cancer patients compared with 6.8% in patients without malignancy (21). This study also found that cancer patients are more than twice as likely to suffer bleeding complications during VTE treatment. Furthermore, the risks of bleeding and of recurrence were correlated with the stage of the cancer (21). Another study showed that cancer patients presented a higher rate of major bleeding associated with anticoagulation therapy compared with patients without cancer (20).

Among cancer patients, those incurring in a VTE event present with a worse survival outcome compared to thrombosis-free subjects (1, 16, 22–23).

The risk of VTE in patients with cancer steadily accumulates with each additional patient-related thrombotic risk factor. Many VTE risk factors are common among cancer patients (3, 16, 21, 24), for example, advanced age, prolonged immobility, a prior history of VTE, and comorbid conditions such as acute infection, heart disease, and respiratory disease.

The incidence of VTE according to tumour type and stage

The incidence of VTE complications in patients with cancer varies according to the type of cancer and its extent (Fig. 1). The rate of VTE is consistently higher in patients with cancer of the pancreas, stomach, brain, kidney, uterus, lung or ovary (25). Among the haematological malignancies, lymphoma and myeloma disease were reported to have the highest rates of VTE (1). Registry surveys and large epidemiological studies based on hospital discharge data have confirmed earlier autopsy series that the cancer diagnoses most strongly associated with the development of VTE (16, 26) are tumours of the brain, pancreas, ovary, lung, uterus, leukemia.

The extent of malignant disease also affects the likelihood of developing VTE. Multiple studies have shown an increased risk of VTE in patients with advanced-stage cancer (25). An analysis of data from the California Cancer Registry between 1993 and 1995 highlighted metastatic disease as the strongest predictor of VTE complications (22). Similarly, Blom et al. reported that cancer patients with distant metastases had almost a twofold increased risk of VTE compared with those without metastases (26).

The effect of anticancer treatments on VTE incidence

Many standard anticancer treatment strategies have been shown to increase the risk of VTE complications, these include both surgical procedures and non surgical treatments. Another important risk factor is the presence of a central venous catheter (27).

Surgery is a well-known risk factor for development of VTE in patients without cancer. Cancer patients undergoing surgery are at increased risk (i.e. 3- to 5-fold) for postoperative thrombosis compared to surgical patients who do not have cancer, and this risk can persist for up to seven weeks after the procedure (28).
In cancer patients undergoing surgery without prophylaxis, the incidence of DVT, as shown by screening procedures, is 40–80% and that of proximal DVT 10–20%.

The observational surgical @RISTOS registry evaluated the incidence of clinically overt VTE in a wide spectrum of consecutive patients undergoing surgery for cancer. Data from this registry identified VTE as the most common cause of death 30 days after surgery in cancer patients (46%), followed by cancer progression (12%) (29). Non-surgical anticancer treatment strategies are also associated with a high incidence of VTE. Active treatments including chemotherapy, adjuvant chemotherapy, hormonal therapy, antiangiogenic agents, and combination regimens all have a prothrombotic effect in cancer patients.

Chemotherapy, either as primary or adjuvant therapy, significantly increases the risk of VTE complications in patients with cancer. Recently, a prospective study of nearly 4,500 patients receiving outpatient chemotherapy reported a 2.7-fold increase in arterial thrombosis, and a 47-fold increase in the mortality rate from VTE compared with the general population (30). Hormone therapy in combination with chemotherapy enhances the incidence of VTE in women with breast cancer. Studies have reported that women who received the selective estrogen receptor modulator tamoxifen had a 1.5- to 7.1-fold increase in the risk of developing symptomatic VTE, compared with placebo or no treatment (31).

Third generation oral aromatase inhibitors seem to be associated with a lower rate of VTE.

In particular, anastrozole, a third-generation aromatase inhibitor, may be associated with a lower risk of VTE complications than tamoxifen (32), and represents an alternative agent for adjuvant treatment in women with early breast cancer and a low risk of recurrent tumours (33).

New therapeutic agents that inhibit angiogenesis are being developed as treatments for various solid tumours such as non-small-cell lung cancer, breast cancer, and colon cancer. Targeted antiangiogenic agents, such as bevacizumab, the monoclonal antibody to vascular endothelial growth factor, have shown efficacy in improving survival rates among patients with advanced disease (34–36). However, the addition of bevacizumab to chemotherapy regimens is associated with a high incidence of thrombotic events. A systematic review and metaanalysis, which included a total of 7,956 patients with a variety of advanced solid tumours from 15 randomized controlled trials, indicated that bevacizumab was associated with an increased risk of VTE, with a relative risk of 1.33 (37).

Similarly, new cancer treatment regimens involving thalidomide or lenalidomide are associated with an increased risk of VTE when used concomitantly with chemotherapy or corticosteroids in patients with multiple myeloma (38, 39).

The use of recombinant human erythropoietin (EPO) and other haematopoietic growth factors, such as granulocyte-macrophage colony-stimulating factor and granulocyte-colony stimulating factor, as supportive therapy in cancer patients appear to increase the risk of VTE. However, a study in 147 patients with non-metastatic cervical or vaginal cancer has shown that EPO increases the risk of thrombosis by 15-fold (40). The use of EPO and white cell growth factors has been shown to be independently and significantly associated with VTE risk among patients on chemotherapy (41). Transfusions were also found to be associated with an increased risk of in-hospital mortality (42).

Long-term central venous catheters (CVC) have considerably improved the management of cancer patients. However, they also represent a significant risk factor for VTE.

CVC are thought to promote thrombosis through a number of mechanisms such as trauma to vessel walls, either directly or through high drug concentrations at the CVC site (43).

A number of retrospective studies have indicated a high risk of CVC-related thrombosis in malignancy: It ranges from 12 to 66% of cancer patients, depending on the type of cancer and its treatment, as well as the type, position, and duration of catheterization involved (44). However, recent randomized controlled trials in cancer patients have reported lower rates of CVC-related thrombosis (venographic events: 3.1–4.0% symptomatic and 18.1% asymptomatic). In these studies the use of either warfarin, dalteparin, or enoxaparin did not reduce the incidence of catheter-related DVT (45–47).

As CVCs are inserted into the large veins of the neck, chest, or groin, CVC-associated thrombosis often results in upper-extremity DVT. However, the results of the recent randomized clinical trials do not support the use of routine antithrombotic prophylaxis in all patients bearing a CVC (48).

Pathophysiology and risk assessment

Patients with cancer might displays many types of haemostatic disorders (49), ranging from haemorrhages to thrombosis and DIC, depending on the type of cancer. It is recognized that cancer is not an unique disease but rather a group of related diseases that manifest themselves in many different ways depending on the organ and cell of origin. More than 300 types of cancer have been identified, each with its own distinct properties. Therefore, it should be no surprise that some cancers cause more aberrations in haemostasis than others.

However, clinically overt thromboembolism and DIC are only the tip of the iceberg of systemic clotting abnormalities observed in patients with cancer.

Much more common is the finding of haemostatic abnormalities recognized only as the result of laboratory testing, which defines the in vivo hypercoagulable state. These assays have been developed for the specific measure of markers of both clotting and fibrinolysis activation, and markers of activation of haemostatic cellular components, including platelets, leukocytes, and endothelial cells.

The hypercoagulable state

The main principle in patients with cancer is that the clotting system is systemically activated, clotting factors are consumed, and...
fibrinolysis is activated. Approximately half of the patients with cancer, and as many as 90% of those with metastases, exhibit abnormalities in one or more routine coagulation parameters (50–53). The development of novel laboratory tests with increased sensitivity has enabled the detection of subtle alterations in the haemostatic system. Levels of plasmatic markers of clotting activation tend to be universally elevated in patients with cancer (54) indicating the in vivo ongoing thrombin generation and fibrin formation (55), e.g.

- thrombin-antithrombin complex (TAT),
- prothrombin fragment F1+2 (F1+2),
- fibrinopeptide A (FPA),
- plasminogen activator inhibitor 1 (PAI-1),
- D-dimer.

These abnormalities can further worsen with the start of antitumour therapies (56). For example, a study by Falanga et al. demonstrated that in patients with non-Hodgkin lymphoma and multiple myeloma, the plasma levels of haemostatic parameters, elevated at baseline, significantly increased after receiving high dose cyclophosphamide, followed by G-CSF, for hematopoietic stem cell mobilization and autologous transplantation (57).

### Haemostatic markers and VTE risk

Until recently, only few prospective studies have evaluated the utility of serial measurements of haemostatic markers for predicting VTE (as confirmed by objective test) in cancer patients. In one of these studies conducted in patients undergoing surgery for abdominal cancer, Falanga et al. found that presurgical TAT complex levels were significant predictors of postoperative DVT (58).

Current research is focusing on a number of biomarkers that may be helpful in identifying cancer patients who are at higher risk of developing thrombosis who might benefit from primary thromboprophylaxis. Emerging markers are represented by platelet count, leukocyte count, D-dimer, tissue factor (TF), P-selectin, and plasma microparticles.

In a study by Khorana and colleagues the pre-chemotherapy platelet count higher than 350,000 platelet/microliter have shown to be predictive of subsequent thrombosis during chemotherapy (41). The inclusion of D-dimers and soluble P-selectin in a validated risk assessment model increased the capability to predict VTE (59, 60). Targeted thromboprophylaxis utilizing model-based and/or biomarker-based approaches may provide an optimal risk/benefit ratio. In this context, emerges the important role of circulating, submicrometric membrane fragments that circulate in the blood bearing on their surface TF and procoagulant phospholipids.

Due to these properties, in the preceding years, plasma microparticles are being investigated in connection with cancer progression and thrombosis development. A recent study by Toth and colleagues showed that the concentration of microparticles derived from platelets is elevated in patients with breast cancer, compared to patients with benign breast lesions (61).

Another study performed in patients with essential thrombocythaemia, a myeloproliferative neoplasm characterized by high risk of thrombosis, demonstrated the presence of increased levels of circulating microparticles of platelet and endothelial cell origin, which was more prominent in those patients with more risk factors for thrombosis (62). MP levels are currently developed by ongoing clinical trials as a criterion to enroll high risk patients (63).

### Risk stratification

The interaction and relative effects of the risk factors associated with VTE in cancer patients is highly complex, making the pre-
The pathogenesis of the hypercoagulable state

The pathogenesis of blood coagulation activation in patients with cancer is complex and multifactorial. Among other factors, a prominent role is played by tumour cell-specific clot promoting properties, which may contribute to the process of tumour growth and dissemination (67). The principal mechanisms (Fig. 2) include the

- expression of TF by tumour cells,
- production of MP and inflammatory cytokines by tumour and/or host cells,
- direct adhesion of tumour-cells to platelets, leukocytes, and endothelial cells.

In addition to their primary role in haemostasis and blood coagulation, proteins and cellular components of the haemostatic system may play several roles in tumour neoangiogenesis and metastasis formation. In particular, TF supports tumour growth and metastasis by coagulation-independent mechanisms, involving VEGF up-regulation and PAR-2 activation (68). Altogether, the coagulation system activation, with generation of thrombin and fibrin, and the activation of platelets, leukocytes, and endothelial cells, play a crucial role in the progression of cancer.

Recent extensive experimental evidence shows that platelets support tumour metastasis (69). Moreover, platelets exert a protective role in the maintenance of tumour vascular integrity and may represent a target for the specific destabilization of tumour vessels (70). Finally, MP shed by tumour cells and platelets, which carry proangiogenic factors, are new important players in maintaining tumour growth and proliferation.

Recently, molecular studies of experimental models of human cancer (i.e. hepato-ma, brain tumours and colon cancer) demonstrate that oncogene and repressor gene-mediated neoplastic transformation (e.g. activation of MET, loss of PTEN, induction of K-ras and loss of p53) activate clotting as an integral feature of neoplastic transformation (67). Furthermore, a mutation of EGFR gene renders cancer cells hypersensitive to the action of coagulation proteins, such as TF; as a result, a micro-environment promoting tumour growth is generated (71). These data confirm that a reciprocal cancer-thrombosis connection exists, by which cancer cells support clot formation, and clotting proteins support cancer growth and dissemination.

Prophylaxis of VTE

The prevention of VTE in cancer patients is of vital importance in light of the difficulties associated with the treatment of VTE in these patients, as they are also prone to greater recurrence rates and a higher incidence of bleeding complications (20, 21).
It has been shown that cancer patients undergoing surgery benefit from effective pharmacological prophylaxis (72), and that extended-duration thromboprophylaxis with LMWH may be beneficial to patients undergoing major abdominal or pelvic surgery (73). This is reflected in guidelines: All patients undergoing major cancer surgery should receive heparin-based prophylaxis for a minimum of 7–10 days, with supportive mechanical prophylaxis in those patients at highest risk (74).

Clinical trials have evaluated enoxaparin thromboprophylaxis in cancer patients undergoing surgery. In the ENOXACAN randomized trial, enoxaparin was compared directly with unfractionated heparin (UFH) for its ability to prevent DVT in 631 patients undergoing elective cancer surgery. Overall, 16.5% of patients developed thromboembolic complications, with no statistically significant difference noted between the two groups. In the ENOXACAN II study, patients undergoing surgery for abdominal malignancy received one week enoxaparin, and were then randomized to enoxaparin or placebo for another 21 days (73). Bilateral venography was performed at the end of treatment. There was a statistically significant reduction in DVT from 12% with placebo to 4.8% with extended prophylaxis. These results have been confirmed by the data from a trial by Rasmussen et al. in which patients undergoing general surgery received regular postoperative prophylaxis or extended prophylaxis with LMWH dalteparin (75).

In surgical patients, current guidelines recommend prophylactic anticoagulation for cancer patients, unless contraindicated because of their haemorrhagic risk. However, prolonged post-discharge thromboprophylaxis still remains controversial.

In cancer patients there are two main clinical situations in which VTE prophylaxis should be considered:

- The patient is bedridden for prolonged periods of time.
- The ambulatory patient is receiving chemotherapy or radiation.

Thromboprophylaxis has been shown to decrease DVT specifically in high-risk hospitalized patients. In the last decades, the use of prophylaxis with LMWH has been extensively explored. The first important study was the MEDENOX study (76). A post-hoc analysis of this study demonstrated a 50% risk reduction of objectively confirmed VTE (symptomatic and asymptomatic) in cancer patients receiving LMWH enoxaparin compared with placebo (77). Similarly, dalteparin at a dose of 5000 IU once daily was shown in the PREVENT trial to reduce the risk of VTE in acutely ill medical patients, with a low overall incidence of major bleeding.

Several randomized controlled trials of thromboprophylaxis in ambulatory cancer patients have been reported. The most recent trials, conducted in patients with advanced pancreatic cancer who receive systemic chemotherapy, have shown positive results with LMWH prophylaxis. In particular, the CONKO-004 trial found a 87% risk reduction of VTE using LMWH enoxaparin at 1 mg/kg body weight once daily for three months compared with no prophylaxis (9.9% vs 1.3%; p < 0.01) (78, 79), while the FRAGEM study reported a 61% risk reduction using the CLOT study therapeutic regimen of LMWH dalteparin (31% vs 12%; p = 0.02) (80). Results from these trials are in contrast with other studies evaluating LMWH given at prophylactic doses in ambulatory cancer patients. In particular, TOPIC-1 and TOPIC-2 trials, conducted to evaluate the effect of LMWH certoparin prophylaxis in patients with advanced breast cancer or non-small cell lung cancer, did not show statistically significant improvement of VTE rate with the use of LMWH compared to placebo (81). Similarly, in the PRODIGE study, patients with malignant glioma received prophylaxis with LMWH dalteparin: VTE rate was lower in the LMWH group (9%) compared to placebo (14.9%), however, this did not reach the statistical significance (82).

Recently, LMWH nadroparin was found to reduce the incidence of thromboembolic events in ambulatory cancer patients receiving chemotherapy for metastatic or locally advanced disease[83]. In particular, the results showed that 15/769 (2%) patients treated with nadroparin had a thromboembolic events versus 15/381 (3.9%) patients treated with placebo. VTE accounted for 22 events, with rates of 1.4% under nadroparin group and 2.9% under placebo group, respectively.

Based on the well-established VTE risk and emerging evidence showing the benefits of prophylaxis, a number of experts’ guidelines and consensus statements have been published on the use of VTE prophylaxis for cancer patients. The recommendations of the various guidelines in the different clinical settings are summarized in Table 2 (8–14). There is a broad agreement among the scientific panels on the importance of thromboprophylaxis in hospitalized patients with cancer, including prolonged prophylaxis in high-risk surgical patients. Prophylaxis is not routinely recommended for ambulatory patients with cancer (with exceptions) or for central ve-

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<td><strong>Thromboprophylaxis</strong></td>
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<td>patients undergoing surgery</td>
<td>prophylaxis with low-dose UFH or LMWH for at least 7–10 days</td>
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<td>extended prophylaxis up to four weeks after discharge in patients with high risk features</td>
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<td>hospitalized patients</td>
<td>VTE prophylaxis with antiocoagulants</td>
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<td>ambulatory patients receiving chemotherapy</td>
<td>only patients with multiple myeloma receiving thalidomide or lenalidomide prophylaxis with LMWH or adjusted dose warfarin</td>
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**Table 2** Primary prophylaxis in the cancer patient: recommendations
ous catheters. All the panels agree that LMWH are preferred for the long-term treatment of VTE in cancer.

**Treatment of VTE**

The therapy of thromboembolic complications in cancer patients remains a difficult clinical challenge. Patients with cancer who develop a VTE episode should be managed according to guidelines that are currently delivered for patients free from malignancy. Except for selected patients requiring aggressive treatments, the large majority of cancer patients should be treated with therapeutic doses of unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH), followed by LMWH as the preferred agent for long-term monotherapy (84–85). This replaces the traditional regimens for the treatment of acute VTE using initial therapy with UFH, LMWH or fondaparinux followed by long-term therapy with a vitamin K antagonist (VKA).

Novel oral anticoagulants have emerged that can rapidly change the therapeutic scenario in patients with without cancer. These oral anticoagulants that achieve rapid inhibition of activated factor X or thrombin may offer an easier solution than LMWH but studies focusing on treatment of cancer-associated thrombosis with these agents are lacking. To date, some of these new agents have shown comparable efficacy and safety compared with traditional anticoagulants in randomized trials that included primarily patients without cancer (86–87).

**Initial treatment**

Several randomized trials and different metaanalysis have confirmed that for initial therapy LMWH is at least as efficacious as UFH in reducing recurrent thrombosis and is associated with a lower risk of major bleeding (88). Data for the cancer patient subgroup are much more limited but suggest a reduction in the 3-month mortality with LMWH use (88, 89). Fondaparinux also has similar efficacy and safety as the heparins for the initial treatment of VTE in the general population (90, 91). However, a recently published post-hoc, subgroup analysis of the 477 cancer patients in the MATISSE DVT and PE trials suggests that fondaparinux may be less effective than LMWH but more effective than UFH (92).

Bleeding associated with these parenteral agents for initial therapy in cancer patients has not been reported (93). Unfortunately, formal clinical trials comparing UFH, LMWH and fondaparinux are unlikely to be conducted to define their relative risks and benefits in the oncology population.

**Long-term treatment**

Several randomized trials have compared the effects of LMWHs with warfarin and other VKAs for long-term therapy in patients with cancer (94–97). In particular, in the CLOT study, 676 patients with active cancer and acute VTE were randomized to receive usual treatment with dalteparin (200 IU/kg body weight daily for 5 to 7 days) followed by VKA therapy or dalteparin alone for six months. Dalteparin was associated with a 52% reduction in recurrent VTE compared with VKA (dalteparin 9% versus VKA 17%, p = 0.002) (95). Overall, there were no differences in bleeding and mortality between the groups.

The other trials differ in design from the CLOT study mainly in the duration of treatment (3 months) and the type and dose of LMWH used. Although none of these other trials demonstrated statistically significant differences between the LMWH and warfarin, there were strong trends favouring LMWH in all the studies. Based on published evidence, international guidelines recommended LMWH as the first-line, evidence-based choice for long-term therapy of VTE in patients with active cancer (84, 85).

**Novel anticoagulants**

Novel anticoagulants, including dabigatran, rivaroxaban and apixaban, have limited data in patients with cancer. These are effective anticoagulants with no requirement for laboratory monitoring and have minimal drug interactions. They are administered orally once or twice a day, making them very attractive options for long term use.

In a recently reported phase III, double-blind RECOVER trial, dabigatran was compared with warfarin in patients with acute VTE. Only 5% of patients included in this trial had VTE in association with cancer. However, the efficacy and safety of dabigatran in this subgroup were similar to those in patients without cancer (86). One small phase II randomized feasibility trial has studied the use of apixaban in patients with advanced or metastatic cancer (98). Patients were randomized to one of three doses of apixaban or placebo during the first 12 weeks of first or second line chemotherapy. With approximately 30 patients per group, the study found a very low bleeding rate in those treated with apixaban and a time- and dose-effect on F1+2 and other markers of coagulation.

Considering the high risk of recurrent thrombosis and bleeding in patients with cancer, it is important that further research is done to understand the antithrombotic impact of these new agents in cancer patients before accepting it for treatment of cancer-associated thrombosis.

**Treatment of recurrent thrombosis**

Cancer patients are at high risk for recurrent VTE. In a prospective cohort study, 20.7% of cancer patients developed recurrent VTE compared with 6.8% of patients without cancer. In a recently presented prospective observation study, Louzada et al. identified a series of characteristics associated with a higher risk of recurrent VTE and based upon this analysis have developed a scoring system to identify patients at higher and lower risk of recurrent VTE. Women and patients with lung cancer or previous episodes of VTE were at higher risk for recurrent thromboembolism, while patients with breast cancer and stage I disease were at lower risk (99).

Interestingly, LMWH was not associated with a lower risk of recurrent VTE than VKA therapy. Using a scoring system incorporating risk factors for recurrence, they...
found that patients with less than one point had a 4.5% risk of recurrent VTE while patients with one or more points had a risk of 19.7%. If validated in prospective studies, this scoring system or a variation of it may prove useful in identifying cancer patients who are a lower risk for recurrent VTE and may not benefit from indefinite therapy.

Although randomized controlled trial data are lacking to guide optimal management in oncology patients with recurrent thrombosis, observational data and increasing clinical experience support the use of LMWH in this setting. In patients who developed a recurrence while on warfarin therapy, the recommended practice is to switch these patients to LMWH because it is more efficacious than warfarin. Raising the intensity of warfarin therapy is not recommended because of the potential for increasing bleeding without a benefit in reducing recurrent VTE. Patients with cancer have a high risk of bleeding as well as a high risk of recurrent thrombosis despite achieving therapeutic and even higher INRs (20, 100).

For patients who developed a recurrence while on LMWH, dose escalation of LMWH is often effective. In a small cohort study of oncology patients with recurrent thrombosis while on LMWH or warfarin, escalating the dose of LMWH by 20 to 25% or switching to LMWH, respectively, was effective in preventing further thrombotic episodes (100). During three months of follow-up, 6 patients out of 70 (8.6%) developed another recurrence while one patient had a major bleeding event and two had minor bleedings. The success of escalated doses of LMWH suggests that the standard weight-adjusted dose regimens are insufficient in some patients with cancer. This is not surprising given the heightened prothrombotic state of these patients.

Conclusions, outlook

Patients with cancer are at high risk of developing VTE, and the risk of VTE varies according to the type of malignancy and its disease stage.

The pathogenesis of cancer-associated VTE is multifactorial and includes demographic, cancer-associated, and treatment-related risk factors. Hospitalization, surgical, and non surgical cancer treatments (i.e. chemotherapy, hormonal or immunosuppressive agents in conjunction with chemotherapy), or the presence of a CVC increases the risk of VTE patients.

Effective VTE prophylaxis for cancer patients at significant risk of thrombosis reduces the burden of VTE and improves outcomes. All current guidelines recommend that all patients hospitalized for cancer should be considered for VTE prophylaxis in the absence of contraindications to anticoagulant therapy.

The current development of VTE predictive models, using the increasing knowledge of the clinical and biological markers of thrombosis in cancer, is important for identifying high-risk patients and reducing associated morbidity and mortality.

Areas that warrant further research include the
- benefit of prophylaxis in the ambulatory setting,
- risk/benefit ratio of prophylaxis for hospitalized patients with cancer,
- understanding of incidental VTE, and
- impact of anticoagulation on survival.

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