Cancer, thrombosis and low-molecular-weight heparins
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CHAPTER 2

Cancer and venous thromboembolism

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Abstract

Venous thromboembolism occurs commonly in patients with cancer. The pathogenetic mechanisms of thrombosis involve a complex interaction between tumour cells, the haemostatic system, and characteristics of the patient. Among risk factors for thromboembolism the most important are long-term immobilisation, especially in hospital, surgery, and chemotherapy with or without adjuvant hormone therapy. Although prophylaxis and treatment of thromboembolism in patients with cancer draw on the agents that are commonly used in those without cancer, there are many special features of patients with cancer that make use of these drugs more challenging. Low-molecular weight heparins are the cornerstone of prophylaxis and treatment of venous thromboembolism in patients with cancer. These drugs have the potential to increase survival, at least in patients with more favourable outlook.

Introduction

Thromboembolism is a well-recognised complication of malignant disease. Clinical manifestations vary from venous thromboembolism to disseminated intravascular coagulation and arterial embolism. Disseminated intravascular coagulation is most commonly observed in patients with haematological malignant disorders and those with widespread metastatic cancer, whereas arterial embolism is most commonly observed in patients undergoing chemotherapy and in those with non-bacterial thrombotic endocarditis. This review focuses on the relation between cancer and venous thromboembolism.

Pathogenesis of thrombosis in cancer

Cancer growth is associated with the development of a hypercoaguable state. Patients with malignant disorders but no thrombosis commonly present with abnormalities in laboratory coagulation tests, which suggest a continuous process of fibrin formation and removal at different rates in these patients (1). Fibrin and other clot components have roles not only in thrombogenesis but also in tumour adhesion, spread, and metastasis (2). Many histopathological studies have shown the presence of fibrin or platelet plugs in and around many types of tumours (3) which suggests local activation of blood coagulation and an involvement of clotting mechanisms in the growth of malignant tissues.

Prothrombotic mechanisms

The activation of blood coagulation in patients with cancer is complex and multifactorial (4). General prothrombotic mechanisms are related to the host response to cancer and include the acute-phase reaction, paraprotein production, inflammation, necrosis, and hemodynamic disorders. Procoagulant effects are also exerted by anticancer chemotherapy and radiotherapy. However, a prominent part is played by tumour-specific clot-promoting mechanisms resulting from the prothrombotic properties expressed by tumour cells themselves. These properties are unique to the malignant state. Malignant cells can activate blood coagulation in several ways: by producing procoagulant, fibrinolytic, and proaggregating activities; by releasing pro-inflammatory and proangiogenic cytokines; and by interacting directly with host vascular and blood cells, such as endothelial cells, leucocytes, and platelets, by means of adhesion molecules.

Procoagulant, fibrinolytic, and proaggregating activities

Tumour cells produce procoagulant factors, among which the most studied are tissue factor and cancer procoagulant (5). Tissue factor, the primary activator of healthy blood coagulation, forms a complex with factor VII to activate factors X and IX by proteolysis. In healthy vascular cells, expression of tissue factor is tightly controlled; the factor is normally not expressed but is induced by inflammatory stimuli such as the cytokines interleukin 1 and tumour necrosis factor
(TNF) as well as bacterial lipopolysaccharides. In malignant cells, however, tissue factor is constitutively expressed. By contrast, cancer procoagulant is a cysteine proteinase that directly activates factor X independently of factor VII; it has been found in tumour cells and in tissues of the amnion and chorion but not in normal differentiated cells. Tissue factor and cancer procoagulant have been identified in several human and animal tumour tissues (6). The finding that severe coagulopathy in acute promyelocytic leukaemia resolves in parallel with the loss of blast-cell procoagulant activities from the patient’s bone marrow strongly supports the role of tumour procoagulants in promoting clotting complications in malignant disorders (7). Tumour cells can express all proteins that regulate the fibrinolytic system, including the urokinase-type and tissue-type plasminogen activators, plasminogen-activator inhibitors 1 and 2, and plasminogen-activator receptor (8). The increase in plasma concentrations of plasminogen-activator inhibitors and impairment in plasma fibrinolytic activity in patients with solid tumours indicate another tumour-associated prothrombotic mechanism. Tumour cells induce platelet activation and aggregation by direct cell–cell contact or by releasing soluble factors, such as ADP, thrombin, and other proteases (9). Circulating activated platelets expose on their surface the activation-dependent antigens P-selectin and CD 63. On aggregation they release their granule contents. Activation of platelets increases their capacity to interact by specific adhesive mechanisms with endothelial cells, leucocytes, and tumour cells.

**Tumour-cell-derived cytokines**

Tumour cells produce and release various cytokines, including TNF, interleukin 1, and vascular endothelial growth factor (VEGF), which can be involved in the development of thrombotic disorders in patients with cancer (10). The major targets of tumour-derived cytokines are the vascular endothelium and leucocytes. TNFa and interleukin 1 induce the expression of endothelial procoagulant activity (tissue factor) and simultaneously down regulate the expression of thrombomodulin, the endothelial surface high affinity receptor for thrombin, which complexes thrombin to activate the potent anticoagulant protein-C system. Together, up-regulation of tissue factor and down-regulation of thrombomodulin lead to a prothrombotic condition in the vascular wall. The same cytokines strongly stimulate the production of the fibrinolysis inhibitor plasminogen-activator inhibitor 1, thus impairing the endothelial antithrombotic response. Tumour-derived VEGF also induces expression of tissue factor by endothelial cells, which implies involvement of tissue factor in tumour neovascularisation (11). Finally, cytokines induce changes in expression of endothelial-cell adhesion molecule, increasing the capacity of the vessel wall to attract leucocytes and platelets and promoting localised clotting activation and fibrin formation. In a similar way to endothelial cells, monocytes are activated by tumour cells, their products, or both to express tissue factor on their surfaces (12). Tumour-associated macrophages obtained from experimental and human tumours express substantially more tissue factor than do control cells, and circulating monocytes from patients with various types of cancer show increased tissue-factor activity. Tumour cytokines also attract and activate polymorphonuclear leucocytes, which release reactive oxygen species and intracellular proteases that have several activities on endothelial cells and platelets, modifying the haemostatic balance towards a prothrombotic state (13).

**Cell–cell interactions**

The presence of cell-adhesion molecules on the surface of tumour cells allows the possibility of direct interaction with healthy cells. During haematogenous spread, this interaction occurs with endothelial cells, platelets, and leucocytes. The capacity of tumour cells to adhere to both resting and cytokine-stimulated endothelium is well known, and adhesion-molecule pathways specific to different tumour-cell types have been identified (2,4). Malignant cells attached to the vessel wall promote localised clotting activation and thrombus formation and promote the adhesion and arrest of leucocytes and platelets by releasing cytokines. Cancer cells also directly activate platelets, adhere and migrate through the vessel wall, and are assisted by polymorphonuclear leucocytes in their interaction with endothelial cells.
Prothrombotic mechanisms and tumour progression

Tumour-specific prothrombotic properties contribute to the process of tumour growth and dissemination. The formation of thrombin, the final effector enzyme of the clotting cascade, and production of fibrin, the final product of the activation of blood coagulation, are coagulation-dependent mechanisms of tumour progression. In addition, tumour prothrombotic properties can interfere with the malignant process by coagulation-independent mechanisms. Relevant in this setting is the emerging role of the non-coagulant activities of tissue factor (2), particularly its capacity to modulate VEGF expression by malignant cells and normal vascular cells. This property regulates tumour neovascularisation and provides an important link in patients with cancer between activation of coagulation, inflammation, thrombosis, and cancer growth and metastasis (14).

Epidemiology and risk factors for thromboembolism in patients with cancer

Since the initial observation by Trousseau in 1865, many studies have addressed the relation between cancer and venous thromboembolism. This disorder is a common complication in patients with cancer. In some cases it is the first manifestation of cancer, so offering opportunities for diagnosis and treatment (15). In patients with malignant disorders, venous thromboembolism is an important cause of morbidity and mortality. Of every seven patients with cancer who die in hospital, one dies of pulmonary embolism (16). Of these patients, 60% have localised cancer or limited metastatic disease, and they would have survived for longer in the absence of pulmonary embolism. According to the Medicare Provider Analysis and Review Record database that records the primary discharge diagnosis and an additional four discharge diagnoses in the USA, initial or recurrent thromboembolism in patients with cancer exceeds by far that recorded in those without malignant disorders; thromboembolism complicates the course of cancers of virtually all body systems with similar frequency (17). The true frequency of venous thromboembolism in patients with cancer is not known, because of the surprising lack of information in almost all studies dealing with the natural course of malignant diseases. Most thrombotic episodes occur spontaneously, in the absence of triggering factors commonly accounting for thromboembolic complications in people without cancer (18,19). Patients with cancer have a highly increased risk of venous thromboembolism in the first few months after diagnosis and in the presence of distant metastases (19). The risk is further increased in the presence of inherited thrombophilic abnormalities (19). The most common situations that increase the risk of venous thromboembolism in patients with cancer include immobilisation, surgery, chemotherapy with or without hormone therapy, and the insertion of central venous catheters (20).

Immobilisation

One of the most important triggering factors for venous thromboembolism is long-term immobilisation, especially during a hospital stay. This pattern was clearly confirmed by Shenand Pollack, (16) who reported that up to 14% of patients with cancer admitted to hospital died of autopsy-confirmed pulmonary embolism, compared with 8% of those without cancer (16).

Surgery

In the absence of adequate prophylaxis, patients with active cancer face a very high risk of developing venous thromboembolism postoperatively. In the absence of thromboprophylaxis, the overall incidence of postoperative deep-vein thrombosis is about two times higher in patients with cancer than in patients without malignant disease (15). Many factors contribute to this high frequency, including advanced age, long and complicated surgical procedures, and late mobilisation with long postoperative course owing to the patient's poor condition. If
thromboprophylaxis is not extended beyond the hospital stay, patients with cancer remain at risk of developing late venous thromboembolism (21, 22).

Chemotherapy, radiotherapy, and adjuvant hormone therapy

Patients with cancer are also at high risk of developing both venous and arterial thrombosis when they receive chemotherapy (23). In patients with high-grade glioma undergoing chemotherapy, the frequency of thromboembolic complications was as high as 16% (24). In a retrospective study in patients who had been given chemotherapy, the rate of thromboembolic complications arising within the first (3) months was unexpectedly high, giving an annual rate of 11% (25). The most reliable estimate of thromboembolic complications in patients undergoing chemotherapy comes from those with breast cancer. The frequency of chemotherapy-induced thromboembolic complications in women with stage II breast cancer undergoing chemotherapy was on average 7% in available studies assessing this risk (23). Among patients with stage IV breast cancer the risk was even higher (26). Hormone therapy combined with chemotherapy further increases the risk of thromboembolic complications in women with breast cancer (27). Even when given alone, tamoxifen to prevent recurrence or for prevention of breast cancer in women at high risk, slightly increases the rate of venous thromboembolism (28,29). By comparison with tamoxifen, third-generation oral aromatase inhibitors, such as the irreversible steroid inactivator exemestane, have the potential to be associated with a lower rate of thromboembolic events (30). Although radiotherapy is widely believed to be a risk factor for venous thromboembolism in patients with cancer, no study has as yet adequately investigated its role.

Central venous catheters

Long-dwelling central venous catheters have greatly improved the management of patients with cancer. However, their use has been associated with the occurrence of deep-vein thrombosis in the arms, especially in patients undergoing chemotherapy (31). The true frequency of deep-vein thrombosis in patients with central venous lines is difficult to estimate, because published data are somewhat conflicting. In the absence of thromboprophylaxis, Bern and colleagues (32) found that the rate of deep-vein thrombosis, as shown by phlebography, was 37%. Monreal and co-workers (33) found an even higher rate. By contrast, in case series in which ultrasonography or other non-invasive methods were used to detect arm deep-vein thromboses, a much lower rate has been reported (31,34). Along with the lower sensitivity of objective non-invasive methods in comparison with phlebography, the availability of new textures and coating of catheters, and the introduction of new procedures to reduce their invasiveness is likely to account for discrepancies between older and more recent studies.

Thromboprophylaxis

Although many patients with active cancer develop thrombotic complications spontaneously, in the absence of other risk factors, there is probably little point in providing thromboprophylaxis to all patients with cancer who are not undergoing surgical or medical therapy. However, a history of thromboembolism puts patients with cancer at such a high risk of recurrence that the systematic use of mechanical or pharmacological prophylaxis should be considered even in the absence of the common risk factors for thrombosis. Prevention of venous thromboembolism in cancer is an important challenge, because patients experiencing a thrombotic episode have a poor outcome with greater probability of death.

Surgical interventions

According to widely accepted guidelines, low-molecular-weight heparin (LMWH) in low doses, low-dose unfractionated heparin, or physical measures should be used in patients with cancer who face long-term immobilisation or low-risk surgical procedures (35). Patients with cancer
undergoing extensive surgery are at extremely high risk of postoperative venous thromboembolism. Accordingly, more intensive prophylactic regimens are needed, such as doses of LMWH about twice as high as suggested for low risk procedures, adjusted-dose heparin, or oral anticoagulants (35). Once-daily injections of LMWH are at least as effective and safe as several injections of unfractionated heparin for prevention of postoperative venous thromboembolism in patients with cancer (36–38). In this setting, fondaparinux (a short-acting pentasaccharide) shows promise. In a trial to address the value of fondaparinux (2,5 mg once daily) for prevention of postoperative venous thromboembolism in patients undergoing major abdominal surgery, fondaparinux was more effective than enoxaparin in the subgroup of patients with cancer without increasing the risk of haemorrhage (39). Recent trials (22,40) have suggested that use of LMWH until 4 weeks after surgical intervention provides an additional thromboprophylactic effect without increasing the risk of haemorrhage. In patients who have had bleeding episodes or who are at high risk of bleeding, physical measures such as graduated compression stockings or external pneumatic compression should be used instead of pharmacological prophylaxis (41). According to the results of two randomised trials (42,43) in patients with cancer undergoing elective neurosurgery, the combination of LMWH (starting within 24 h of surgery) and graduated compression stockings is more effective than, and as safe as, elastic stockings alone for prevention of postoperative venous thromboembolism.

Chemotherapy and radiotherapy

In the only available study,(44) fixed low-dose warfarin (1 mg/day) for 6 weeks, followed by doses that maintained the international normalised ratio (INR) at 1.3–1.9 was effective and safe for prevention of chemotherapy-induced thromboembolism in women with metastatic breast cancer. Whether this strategy or approaches that involve LMWH are effective and safe in other oncological settings remains to be shown. No adequate study has yet assessed the preventive value of antithrombotic strategies in patients undergoing radiotherapy.

Central venous catheters

Two randomised controlled studies (32,45) documented the benefit of fixed low-dose warfarin (1 mg once daily) in decreasing the frequency of arm venous thrombosis related to indwelling central venous catheters. Subcutaneous dalteparin (2500 IU once daily for 90 days) was also highly beneficial for prevention of arm thrombosis in patients with cancer who had venous access devices (33). However, three other clinical trials found no benefit from 1 mg warfarin daily (46,47) or 40 mg enoxaparin once daily (48) compared with no prophylaxis. Thus, neither low-dose warfarin nor prophylactic LMWH can be recommended as routine prophylaxis for patients with cancer who have indwelling central venous lines (35).

Treatment of venous thromboembolism

Initial treatment

Those patients who present with clinically unstable life threatening PE and who do not have contraindications to thrombolysis (such as ongoing or recent bleeding and brain metastasis) should promptly be administered drugs that have the potential to rapidly restore the patency of obstructed pulmonary arteries (49-51). Among the drugs that have been shown to achieve a rapid and substantial lysis of fresh pulmonary emboli are urokinase, streptokinase and tissue-type plasminogen activator (t-PA). The use of the last should be encouraged, because the administration of a loading dose of 10 mg followed by the intravenous infusion of 90 mg produces in only 2 h the result that can be obtained by 12 - 24 h of infusion of urokinase or streptokinase (52,53). As compared to heparin alone, the administration of t-PA relieves patients' symptoms and improves prognosis to a greater extent (54-56). During the administration of t-PA or soon after its discontinuation heparin treatment should be implemented
As far as the role of thrombolytic agents for acute deep-vein thrombosis (DVT) in cancer patients is concerned, available evidence is against their use except for very selected patients with massive ilio-femoral thrombosis who are at risk of limb gangrene and for whom a rapid venous decompression and flow restoration may be desirable (49-51). In patients with contraindications to catheter-directed thrombolysis, surgical thrombectomy can be considered (49-51).

Anticoagulant therapy

Except for selected patients requiring aggressive treatments, the large majority of cancer patients should be treated with therapeutic doses of low-molecular-weight heparin (LMWH), unfractionated heparin or fondaparinux (UFH) (49-51). Except for patients with severe renal failure, in whom UFH still represents the treatment of choice, in all other patients the VTE episode should be managed with LMWHs, as they represent the standard of long-term treatment (49-51). In the absence of contraindications, LMWHs should be administered as soon as there is a high probability that venous thrombosis exists, even before the diagnostic algorithm is completed. LMWHs present a number of potential advantages over UFH, including a longer plasma half-life, an improved subcutaneous bioavailability and less variability in response to fixed doses (49). As a result of these pharmacokinetic properties, a stable and sustained anticoagulant effect is achieved when these drugs are administered subcutaneously in doses adjusted to bodyweight, once or twice daily, without laboratory monitoring (49). These compounds have the potential to greatly simplify the initial treatment of DVT and of selected low-risk patients with PE (9), making the treatment of suitable patients feasible in an outpatient setting (58-60). Treatment on home basis appears feasible and safe, which is particularly attractive for cancer patients, in whom prevention or reduction of hospital stay haste potential to improve the quality of life (61-62). According to the results of worldwide surveys, LMWHs are by far the most commonly used drugs for the initial treatment of VTE in cancer patients (63, 64).

Based on the results of many comparative trials between UFH and LMWH for the initial treatment of patients with DVT that were conducted in the 1990s, LMWHs appear to be at least as effective and safe as UFH both in patients with and in those without cancer (65, 66). It should be noted, however, that in these clinical trials cancer patients represented only 10 - 15% of the total population, as the majority of them were excluded because of their poor performance status. Of interest, the use of LMWH was associated with a significantly lower mortality, which was essentially dependent on the reduction of cancer-related mortality (65, 66). It should not be forgotten that patients undergoing LMWH treatment require close monitoring of platelet count, as the risk of heparin-induced thrombocytopenia in medical patients treated with LMWH may not be negligible (67). Although in clinical practice UFH has virtually been replaced by LMWHs, we think that several indications still remain for UFH, especially in cancer patients. The short half-life of intravenous UFH indeed allows for rapid reversal of anticoagulation in patients who begin to bleed or will require an invasive procedure. Also, the presence of severe renal insufficiency (i.e., creatinine clearance lower than 30 ml/min) makes it attractive to use as a short-acting drug that in addition can be timely monitored and possesses a specific antidote (the protamine sulfate). UFH is generally administered intravenously, whereas the use of nomograms assures that most patients will achieve the therapeutic range for the activated partial thromboplastin time (APTT), the most commonly recommended test for its monitoring (68). Subcutaneous heparin treatment has been suggested as an alternative to intravenous standard heparin, provided that the APTT is performed in order to achieve a full therapeutic effect (69). This modality of heparin administration, which is particularly desirable in those cancer patients who have difficult vein access, has been shown to be as effective and safe as LMWH for treatment of patients with acute VTE, including > 20% of cancer patients (70). In addition, fixed-dose unmonitored UFH is a reasonable option for out-of-hospital management in patients with severe renal impairment (71). Fondaparinux is the first drug of a new class of synthetic antithrombotic agents designed specifically for a single physiological target in the coagulation cascade and acts by indirect inhibition of factor Xa. This compound does not bind to platelet factor-4, which makes the development of immunethrombocytopenia extremely unlikely. In two large Phase III multicenter
clinical trials, involving the treatment of almost 4500 patients with clinically symptomatic DVT or PE (~10% with cancer), the once-daily subcutaneous administration of 7.5 mg of fondaparinux (5 mg in individuals weighing < 50 kg, 10 mg in those weighing > 100 kg) overlapped with and followed by vitamin K antagonists (VKA) was found to be at least as effective and safe as UFH or LMWH for the treatment of DVT or PE (72,73). However, when the analysis is confined to the only cancer patients randomized to the Matisse DVT study, recurrent VTE was found to be significantly more frequent in patients who had received an initial treatment with fondaparinux than in those allocated to the enoxaparin arm (74). In any case, fondaparinux is rarely employed for the initial treatment of VTE in cancer patients, because unlike LMWHs it is not (yet) registered for the long-term treatment of thromboembolic disorders nor can it be followed by VKAs, whose efficacy is definitely lower than that of LMWHs (75).

**Alternative options: intracaval filters**

On average, patients with cancer present with major-often permanent-contraindications to anticoagulant treatment much more frequently than patients free from malignancy. In these patients, the only therapeutic option is the insertion of a (either retrievable or permanent) vena caval filter (49-51), which should be done without hesitation, as it has the potential to prevent (recurrent) PE events in patients with acute VTE. Indeed, prolonging life and/or improving its quality are invaluable goals to be achieved even in patients with poor condition. Our view is supported by findings from a Spanish registry. In a large number of patients with acute VTE who were managed without the insertion of a vena caval filter after a recent episode of major bleeding, the incidence of fatal bleeding and that of fatal PE in patients with cancer was 10 times as high as that observed in those without malignancy (76). As soon as the bleeding resolves, anticoagulation should be resumed; accordingly, the filter should be removed (77).

**Long-term anticoagulation**

While on VKA treatment, cancer patients with venous thrombosis have a risk of recurrent VTE and major bleeding that is higher than that reported in patients free from malignancies. The best evidence comes from a retrospective analysis of data from two large randomized clinical trials and two prospective cohort studies (78-80). Hutten et al. extracted the rates of recurrent VTE and major bleedings in more than 1300 patients receiving at least 3 months of oral anticoagulant therapy for an acute episode of DVT (78). The overall incidence of recurrent thrombosis in patients with cancer was 27.1/100 patient-years, versus 9.0/100 patient-years in those without cancer. The risk of major bleeding was 13.3/100 patient-years and 2.1/100 patients-years, respectively. Palarett et al. compared the outcome of anticoagulation courses in 95 cancer patients and 733 patients without malignancy (79). Based on 744 patient-years of treatment and follow up, there was a trend toward a higher rate of thrombotic complications in cancer patients (6.8 vs 2.5%; relative risk = 2.5). The rate of major bleeding was significantly higher in cancer patients (5.4%) than in those without malignancy (0.9%; relative risk = 6.0). We conducted a prospective cohort study in 842 consecutive patients with DVT who were administered conventional anticoagulation, of whom 181 had cancer (80). The 12-month cumulative incidence of recurrent thromboembolism in cancer patients was 20.7 versus 6.8% in patients without cancer, for an age-adjusted hazard ratio of 3.2 (95% CI: 1.9 - 5.4). The 12-month cumulative incidence of major bleeding was 12.4% in patients with cancer and 4.9% in patients without cancer, for an age-adjusted hazard ratio of 2.2 (95% CI: 1.2 - 4.1). In summary, cancer patients have a three- to four-fold higher risk of recurrent VTE during anticoagulant therapy than cancer-free patients, very likely as a consequence of the release of cancer procoagulants that are not inhibited by conventional anticoagulation. This risk correlates with the extent and the type of cancer (80). Recently, a stratification score has been developed and validated that has the potential to help clinicians predict the VTE recurrence risk and thus tailor treatment, improving clinical outcomes while minimizing costs (81). According to the results of three randomized clinical trials, LMWHs in full doses for the first month followed by a dose ranging from 50 to
100% of the initial regimen have the potential to provide a more effective antithrombotic regimen in cancer patients with venous thrombosis than the conventional treatment and are not associated with an increased hemorrhagic risk (75,82,83), even in patients with disseminated cancer such as those with liver or brain metastases (84). In addition, LMWHs provide an anticoagulation that is easier to administer, more convenient and flexible and not influenced by nutrition problems or liver impairment (1). Thus, the long-term administration of LMWH should now be considered the treatment of choice in patients with metastatic disease and in those with conditions limiting the use of oral anticoagulants (49-51). On average, after discontinuation of antithrombotic treatment cancer patients with venous thrombosis present a risk for recurrences that is almost twice as high as that observed in patients free from malignancies (85-87). However, the risk of recurrence after stopping anticoagulation depends on the setting. For example, a patient who develops VTE after surgery for cancer has a low risk of recurrence if the cancer was completely resected. Like wise, a patient who develops VTE while receiving neo-adjuvant chemotherapy for potential micrometastatic cancer has a considerably lower risk of recurrence if anticoagulation is stopped after the chemotherapy is completed than a patient with metastatic disease who continues to receive combination chemotherapy. In principle, prolongation of anticoagulation should be considered for as long as the malignant disorder is active provided that it is not contraindicated. This decision should be frequently reassessed during patients’ follow up.

**Treatment of challenging situations**

The treatment of challenging situations has recently been addressed by the Subcommittee of the International Society of Thrombosis and Haemostasis (77).

**Management of recurrent VTE despite anticoagulation**

Recurrent VTE despite appropriate anticoagulation is common among cancer patients (88,89). Cancer patients with symptomatic recurrent VTE despite therapeutic anticoagulation with VKA should be switched to therapeutic weight adjusted doses of LMWH. Cancer patients with symptomatic recurrent VTE despite anticoagulation with LMWH should continue with LMWH at a higher dose, starting at an increase of ~ 25% of the current dose or increasing it back up to the therapeutic weight-adjusted dose if they have been receiving on-therapeutic dosing. All cancer patients with recurrent VTE despite anticoagulation should be reassessed 5-7 days after a dose escalation of their anticoagulant therapy. Patients with symptomatic improvement should continue the same dose of LMWH and resume their usual follow up. In patients without symptomatic improvement, the peak anti-Xa level can be used to estimate the dose of further escalation (77).

**Management of cancer-associated VTE in patients with thrombocytopenia**

Thrombosis is commonly diagnosed in patients with malignancy and thrombocytopenia. Full therapeutic doses of anticoagulation without platelet transfusion should be given in patients with platelet count ≥ 50 10⁹/l. In patients with platelet count < 50 10⁹/l, the recommended strategy diverges in patients with acute (< 1 month) from those with subacute (1-3 months) or chronic (> 3 months) VTE. In the former group, full therapeutic doses of anticoagulation with platelet transfusion should be given to maintain a platelet count ≥ 50 10⁹/l. If platelet transfusion is not possible or contraindicated, the insertion of a retrievable filter is suggested, as well as its removal when platelet count recovers and anticoagulation can be resumed. In the remaining groups, subtherapeutic or prophylactic doses of LMWH should be used in patients with platelet count of 25 - 50 10⁹/l, whereas anticoagulation should be discontinued in patients with platelet count< 25 10⁹/l (77).
Management of cancer-associated VTE patients who are bleeding

A careful and thorough assessment of each bleeding episode, including identification of the source, its severity or impact, and reversibility should be done, as well as the usual supportive care with transfusion and surgical intervention to correct the bleeding source, whenever indicated and possible. Withholding anticoagulation in patients having a major or life-threatening bleeding episode is mandatory. Insertion of a caval filter is suggested for patients with acute or subacute VTE who are having a major or life-threatening bleeding episode, whereas it is discouraged in patients with chronic VTE. Once the bleeding resolves, anticoagulation should be initiated or resumed, and the retrievable caval filter (if inserted) should be removed (77).

Potential of the novel direct oral anticoagulants

As new categories of drugs have emerged that have the potential to replace conventional treatment for the initial and long-term treatment of VTE, major improvements are expected for the management of cancer patients with venous thrombosis. They include direct inhibitors of factor Xa (such as rivaroxaban, apixaban and edoxaban) and direct inhibitors of factor IIa (such as dabigatran etexilate). They possess several advantages over conventional drugs, including the inhibition of fibrin-bound Xa or thrombin, respectively, a dose-response that is more predictable because there is no binding to plasma proteins, and a lack of potential to produce immune thrombocytopenia. As a consequence of their pharmacokinetic and pharmacodynamic properties, they can be administered orally, in fixed doses, without laboratory monitoring. Based on available information coming from well-designed and conducted Phase III randomized clinical trials, they possess a more favourable benefit-to-risk profile than the old compounds, make it possible to implement the treatment from the beginning and cover the whole spectrum of clinical presentations, including severe PE (90-95). However, for the time being their use in patients with cancer requires caution. Indeed, only a small minority of patients with cancer (consistently around 5%) were included in the abovementioned studies. More importantly, in these studies the comparator was warfarin, and not a LMWH, which represents the standard of treatment in cancer patients with thrombosis (49). Severe liver and renal dysfunctions, which contraindicate the use of all new oral compounds, are quite common in patients with cancer. There is uncertainty about the proper management of patients requiring emergency procedures and in those with thrombocytopenia. Finally, for the time being these drugs still lack proper antidotes. The novel anticoagulants should be investigated more carefully before routine usage in cancer patients. There are lessons to be learned from the studies conducted long time ago with fondaparinux, a parenteral potent inhibitor of factor Xa. Indeed, when the analysis of the Matisse DVT study, addressing the treatment of patients with DVT, was confined to the only subgroup of cancer patients, recurrent VTE was found to be significantly more frequent in patients who had received an initial treatment with fondaparinux than in those allocated to enoxaparin (74).

Management of incidentally detected isolated VTE

Asymptomatic PE is a common finding in medical oncology due to the routine use of modern computed tomography (CT) scanners for cancer staging. Although the clinical relevance of these incidental findings is unknown, based on the results of a few investigations conducted in recent years, they are likely to impact on both the incidence of recurrent VTE and on the overall prognosis to the same degree as the symptomatic findings (96-102). Accordingly, the most recent international guidelines recommend the same initial and long-term anticoagulation as for comparable patients with symptomatic PE (49). However, there is still uncertainty about the optimal management of patients with the incidental detection of isolated (i.e., not associated with DVT) sub-segmental PE. Indeed, whether the outcome of these patients is comparable to that of patients with symptomatic involvement of sub-segmental arterial vessels (103) is unknown, as is the accuracy of detecting on CT scans that were not specifically ordered to diagnose PE.
Higher risk of false positive diagnosis compared to patients with suspected PE cannot be excluded. In a series of 70 patients diagnosed with subsegmental PE, this diagnosis was confirmed in only 51% by a reviewing radiologist (104). PE may not be acute but chronic. In a series of 65 cases of untreated subsegmental PE reported so far, none of these patients developed recurrent VTE (105). Finally, there is uncertainty about the outcome of patients with incidental PE who receive anticoagulants. In a cohort study of 51 patients with incidental PE, 5 (9.8%) patients developed major bleeding of which 2 cases were fatal (100). Thus, a careful evaluation should be individually done rather than giving full-dose anticoagulation to all cancer patients with the occasional detection of isolated subsegmental PE. An exception can be made for patients with the involvement of multiple sub-segmental vessels, as these patients are unlikely to differ from those with the involvement of more proximal arteries. While patients with incidentally detected proximal DVT should be managed not differently from those with clinical symptoms, in patients with incidentally detected below-knee DVT, as well as in those with incidental thrombosis in other sites, such as portal, splenic or mesenteric veins, there is no evidence favouring anticoagulation (49).

Treatment of catheter-related thrombosis

Central venous catheters are extensively used in patients with cancer to secure delivery of chemotherapy and to facilitate phlebotomy. Unfortunately, considerable morbidity can result from early complications or late sequelae, ranging from arterial puncture, pneumothorax and bloodstream infections to catheter-related thrombosis. Contemporary studies have shown that the incidence of symptomatic catheter-related thrombosis is ~5%, whereas the incidence of the asymptomatic one is higher, at 14 -- 18% (106). The significance and mechanisms of catheter design, material, insertion location and technique, position of the catheter tip and other risk factors in contributing to the development of catheter-related thrombosis are not well understood. Efforts to reduce thrombotic complications, involving flushing the catheter with heparinized solutions, the use of heparin-bonded catheters and systemic anticoagulant prophylaxis, have been largely ineffective (106). As published data and clinical experience suggest that catheter-related thrombosis is associated with a low risk of thrombosis recurrence and post-thrombotic syndrome (107), conservative treatment is recommended. A sensible approach is to remove the catheter only if central venous access is no longer required, the device is non-functional or defective or line-related sepsis is suspected or documented. Unless contraindicated, therapeutic anticoagulation should be given using either LMWH alone or LMWH followed by warfarin therapy. A short period of anticoagulation (3 - 5 days of LMWH) may even salvage some thrombosed catheters and obviate the need to remove and replace the line. Anticoagulation is recommended for a minimum of 3 months and while the catheter remains in place (49).

Impact of antithrombotic drugs on cancer evolution

Anticoagulant treatment of cancer patients, particularly those with lung cancer, has been reported to improve survival (108). Since then, studies conducted in animal tumour models have demonstrated that both UFH and LMWH interfere with various processes involved in tumour growth and metastasis (109). These processes might include fibrin formation, binding of heparin to angiogenic growth factors such as basic fibroblast growth factor and vascular endothelial growth factor, modulation of tissue factor and other mechanisms (109). The evidence of lowered cancer mortality in patients on LMWH in comparison with those treated with UFH (65,66) has stimulated renewed interest in these agents as antineoplastic drugs. Five randomized studies have compared the long-term survival of cancer patients receiving conventional treatment with that of patients receiving a supplementary dose of LMWH in therapeutic or prophylactic doses (110-114). Two of these studies showed a favourable impact of the tested heparin on patients' survival, this result being particularly evident in those with better prognosis (112,113). In the other two studies, post-hoc analysis showed a better survival in subgroups of patients with less
advanced disease (110,111). The fifth virtually excluded any appreciable advantages (114). Although a meta-analysis gave some support to this hypothesis (115), current evidence that LMWH reduces mortality is weak.
References


