HOW I TREAT VENOUS THROMBOEMBOLISM IN PATIENTS WITH CANCER

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ABSTRACT

Venous thromboembolism (VTE) is a frequent complication in cancer patients, and represents an important cause of morbidity and mortality. Especially in those patients who have a poor life expectancy, preventing death from pulmonary embolism is the mainstay of treatment. Critically ill patients should promptly be administered thrombolytic drugs. Except for selected patients requiring aggressive therapy, the initial VTE treatment should be conducted with either adjusted-dose unfractionated heparin or fixed-dose low-molecular-weight heparin (LMWH). LMWHs have the potential to greatly simplify the initial treatment of VTE, making the treatment of suitable patients feasible in an outpatient setting. During anticoagulant therapy, cancer patients have a two- to four-fold higher risk of recurrent VTE and major bleeding complications when compared to non-cancer patients. The long-term administration of LMWH should be considered as an alternative to anti-vitamin K drugs in patients with advanced disease and in those with conditions limiting the use of oral anticoagulants. Prolongation of anticoagulation should be considered for as long as the malignant disorder is active. The evidence of lowered cancer mortality in patients on LMWH has stimulated renewed interest in these agents as antineoplastic drugs, and raises the distinct possibility that cancer and thrombosis share common mechanisms.
Venous thromboembolism (VTE) is a frequent complication in cancer patients, and represents an important cause of morbidity and mortality. It has been estimated that 1 in every 7 hospitalized cancer patients who die, do so from pulmonary embolism (PE) (1). Of these patients, 60% have localized cancer or limited metastatic disease, which would have allowed for longer survival in the absence of a fatal PE. The incidence of VTE in cancer patients has been described to be approximately 15%, with reported incidence rates ranging from 3.8 to 30.7% (2). However, it is likely to be much higher, as VTE is often asymptomatic or minimally symptomatic, and, even when symptoms are present, they are often nonspecific or mistakenly attributed to the underlying malignancy.

According to the “Medicare Provider Analysis and Review Record”, a database that records the primary discharge diagnosis and an additional four discharge diagnoses in the U.S.A, the rate of initial or recurrent thromboembolism in patients with cancer exceeds by far that recorded in those without malignancy; VTE complicates with similar frequency cancers of virtually all body systems (3).

Patients with cancer have a highly increased risk of VTE in the first few months after diagnosis and in presence of distant metastases (4). Moreover, this risk is further enhanced in presence of inherited thrombophilic abnormalities (4). Most thrombotic episodes occur spontaneously, that is in the absence of triggering factors commonly accounting for thromboembolic complications in subjects without cancer (4,5). The most common situations that increase the thromboembolic risk in cancer patients include immobilization, surgery, chemotherapy with or without adjuvant hormone therapy, and the insertion of central venous catheters (6).
Since in cancer patients the occurrence of a thrombotic episode is associated with a rate of serious clinical outcomes (including bleeding and recurrent VTE) that exceeds by far that expected in patients free from malignancy, the treatment of VTE in cancer patients is resource intensive and costly (7). Given the aging population and the inevitable rising incidence of cancer in industrialized nations, VTE in patients with cancer will become an increasingly common health issue unless more effective agents and less costly management strategies are developed in the near future (7,8).

TREATMENT OF ESTABLISHED VTE

INITIAL TREATMENT

Therapy of VTE complications in cancer patients remains a difficult clinical challenge. Cancer patients often require invasive surgical procedures, have an increased risk of infection, and may have therapy-related platelets drop that increase their bleeding risk.

Patients with cancer who develop a VTE episode should be managed according to guidelines that are currently delivered for patients free from malignancy (9). Especially in those cancer patients who have a poor life expectancy, preventing death from PE is the mainstay of treatment. Most patients with advanced cancer, indeed, do not survive long enough to develop late post-thrombotic sequelae or chronic pulmonary hypertension.

Intracaval filter

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 vena caval filter. In making this decision, the choice of permanent devices should be encouraged. Although a few experts question the placement of vena caval filters to prevent PE in patients with advanced malignant disease (10), I disagree with this view, as I believe that prolonging life and/or improving its quality is an invaluable goal to be achieved without hesitation even in patients in poor condition. My view is supported by recent 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 in spite of a recent 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 (11).

Since it has been clearly documented that patients with vena caval filters who do not receive concomitant anticoagulation are at high risk for recurrent deep vein thrombosis (DVT) of the lower extremities (12), only patients who are actively bleeding or who are at extremely high risk of bleeding should receive a filter without anticoagulation coverage. Once active bleeding has stopped or risk of bleeding reduced, patients with vena caval filters should receive or resume anticoagulant therapy.

Thrombolytic treatment

Those patients who present with severe hypotension or other clinical manifestations suggestive of critical PE and who do not have contraindications to thrombolysis should promptly be administered drugs that have the potential to rapidly restore the patency of obstructed pulmonary arteries (13). Among the drugs that have been shown to achieve a rapid and substantial lysis of fresh pulmonary emboli are urokinase, streptokinase, and t-PA. I favor the last, as the administration of a loading dose of 10 mg followed by the intravenous infusion of 90 mg
produces in only two hours the result that can be obtained by 12 to 24 hours of infusion of urokinase or streptokinase (14,15). As compared to heparin alone, the administration of t-PA relieves patients’ symptoms and improves prognosis to a greater extent (16-18). During the administration of t-PA or soon after its discontinuation heparin treatment should be implemented (16,18). Failure to obtain rapid clinical improvement with the infusion of thrombolytic drugs should raise the suspicion that saddle PE, arising as a consequence of tumor embolization and growth in situ, has occurred, and prompt the execution of thromboendarterectomy (19).

Recent studies have raised a renewed interest on the use of thrombolytic drugs also in those PE patients who, in spite of a stable condition, exhibit a right ventricular dysfunction as shown by echocardiography (20,21). In a recent prospective controlled study, 256 patients with submassive PE and a contemporary right ventricular dysfunction were randomly assigned to receive heparin alone or combined with t-PA (18). Treatment with heparin alone was associated with almost three times the risk of death or treatment escalation that was associated with heparin plus t-PA, and the probability of 30-day event-free survival was significantly higher in the latter group. No fatal bleeding or cerebral bleeding occurred in patients receiving heparin in combination with alteplase. The results of this study have the potential to expand the use of thrombolysis in patients with acute PE, at least in those with right ventricular dysfunction. However, given the higher hemorrhagic potential of thrombolytic drugs, particularly undesirable in cancer patients, further studies are required before thrombolysis is routinely implemented in the treatment of selected non-critical patients with PE.

As far as the role of local or systemic thrombolytic agents for acute DVT in cancer patients is concerned, available evidence is against their use except for very selected patients with massive iliofemoral thrombosis.
at risk of limb gangrene, where rapid venous decompression and flow restoration may be desirable (9,22). In patients with contraindications to pharmacological thrombolysis, percutaneous mechanical thrombectomy can be considered (9,22).

**Anticoagulant therapy**

Except for selected patients requiring aggressive treatments, the large majority of cancer patients should be treated with either unfractionated (UFH) or low-molecular-weight heparin (LMWH) (9). Whenever possible, heparin should be administered as soon as there is a reasonable possibility that venous thrombosis exists.

- **Unfractionated heparin**

  Although in clinical practice UFH has virtually been replaced by LMWHs, I 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. Therefore, in an unstable, complicated, hospitalized patient treatment with UFH is preferable. Also the presence of renal insufficiency makes it attractive to use a short-acting drug that in addition can be timely monitored and possesses a specific antidote (protamine sulphate).

  The anticoagulant response to UFH varies among patients, and the efficacy of heparin for treatment of VTE depends on whether a minimal anticoagulant effect is achieved. Laboratory tests are, therefore, required to measure the anticoagulant effect of UFH. Among them, the most widely used is the activated partial thromboplastin time (APTT) (23). It has been demonstrated, however, that APTT reagents provided by different manufacturers, and even reagent lots from the same manufacturer, yield
considerable APTT variation in response to equal amounts of heparin (24). To compensate for such variable response of APTT reagents, it seems practical that the therapeutic range is established locally by using protamine titration heparin levels (0.2 to 0.4 U/ml) or anti-Xa level (0.35 to 0.67 U/ml) as the reference standard (23).

Clinical trials that have been performed in the late ‘80s and early ‘90s suggest that the adequacy of the initial treatment is crucial in order to reduce the risk of late thromboembolic recurrences (25-27). In recent years, however, the relation between the APTT response and the risk for late events has been questioned. In a critical overview of the most adequate trials that employed an initial heparin dose of at least 30 000 U/24 hours, Anand et al. failed to show a relationship between the inadequacy of the initial treatment, as expressed by the APTT results within the first 48 hours, and the risk for late recurrent events (28). In contrast, Hull and al. found a strong correlation between failure to reach therapeutic APTT within 24 hours and risk for late recurrences (29,30). Ultimately, Anand et al. reevaluated the results coming from three large multicentre trials comparing UFH to low-molecular-weight heparin (LMWH) in the initial treatment of acute VTE (31). A subtherapeutic APTT during the first 24 to 48 hours of treatment was not associated with a large increase in the risk of recurrent VTE. Notably, in all three original trials the investigators had been encouraged to adjust UFH according to a nomogram (32-34). We can, therefore, speculate that the use of UFH according to an accepted nomogram for the treatment of acute VTE is likely to result in a favorable clinical outcome even in patients who fail to achieve a therapeutic APTT in a timely fashion (35).

The use of heparin nomograms assures that most patients will achieve the therapeutic range for the APTT (35). This is particularly important for cancer patients, as they have a propensity towards heparin
resistance, which most likely results from the nonspecific binding of heparin to mononuclear white cells, vascular endothelial cells, and acute phase proteins (2). Among the most commonly used nomograms are those proposed by Cruickshank et al (36), Hull et al (37), and Raschke et al (26).

Subcutaneous heparin treatment has been suggested as an alternative to standard heparin on the basis of the results of a meta-analysis of eight clinical trials that compared two routes of administration in the acute treatment of DVT (38). This meta-analysis showed that subcutaneous heparin is at least as effective and safe as standard heparin, provided that a proper laboratory monitoring is performed in order to achieve a full therapeutic effect. Recently, a weight-based nomogram for the subcutaneous injection of heparin has been suggested that allows the rapid achievement of correct anticoagulation in most patients presenting with acute DVT while avoiding prolonged periods of excessive anticoagulation (39). This modality of heparin administration, 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 more than 20% of cancer patients (40).

Of interest, the use of the APTT to predict the heparin level in patients requiring high doses of heparin has repeatedly been questioned (41,42). Levine et al. randomized a group of patients requiring unusually high doses of heparin to achieve a therapeutic APTT to have their heparin therapy monitored either by the level of factor Xa (targeted range, 0.35 to 0.67 U/ml) or by the APTT (targeted range, 60 to 85 seconds) (42). The patients whose factor Xa levels were monitored required a significantly lower amount of heparin compared with the patients in the APTT group. These patients were equally protected, and experienced a lower rate of
major bleeding. The determination of the anti-Xa assay has, therefore, the potential to substitute for the APTT in those cancer patients in whom a therapeutic APTT is not reached in spite of relatively high doses of UFH, thus preventing those bleeding complications that might originate from an unnecessary increase in heparin dosage (23).

- Low-molecular-weight heparin

In recent years, LMWH derivatives of commercial heparin have been prepared that have a mean molecular weight of 4000-5000 daltons. They 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 (23). 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 body weight, once or twice daily, without laboratory monitoring (9).

These compounds have the potential to greatly simplify the initial treatment of DVT, making the treatment of suitable patients feasible in an outpatient setting (43,44). Treatment on home basis appears feasible and safe, which is particularly attractive for cancer patients, in whom prevention or reduction of hospital stay has the potential to improve the quality of life (32,33,45,46). According to the results of a recent worldwide survey, LMWHs are by far the most commonly used drugs for the initial treatment of VTE in cancer patients (47).

On the basis of the results of the many comparative trials between UFH and LMWH for the initial treatment of patients with DVT that were conducted in the ‘90s, LMWHs appear to be at least as effective and safe as UFH both in patients with and in those without cancer (48,49). 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 (48,49).

To test the hypothesis that LMWH treatment can be extended to cover the entire spectrum of patients presenting with acute VTE (thus including also patients with non-critical PE), two multicentre clinical trials have been performed in the second half of the ‘90s (34,50). In the first investigation (34), all consecutive patients with acute thromboembolism were enrolled in the study irrespective of the modality of clinical presentation, whereas in the second investigation (50), only patients with symptomatic PE were eligible for the study. Cancer patients formed approximately 20% of the study populations. In both studies, the investigated LMWH (reviparin and tinzaparin, respectively) proved to be at least as effective and safe as UFH. These results have recently been supported by those of a meta-analysis of all available comparative clinical trials addressing the treatment of PE (51). Interestingly enough, findings from recent cohort and randomized studies suggest that under some circumstances even non-critical patients with symptomatic PE may be treated at home with LMWHs, including a substantial proportion of patients with cancer (45,46,52).

In analogy with the use of UFH, 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 different from that observed during UFH administration (53).

- **Beyond heparins**

  New categories of drugs are emerging that have the potential to rapidly change the therapeutic scenario both in patients with and in those
without cancer. They include inhibitors of factor Xa and inhibitors of factor IIa.

Among the former is fondaparinux, which is the first of a new class of synthetic antithrombotic agents designed specifically for a single physiologic target in the coagulation cascade, and acts by indirectly inhibiting factor Xa. It selectively binds to antithrombin and induces a conformational change of its molecule that increases the anti-Xa activity of antithrombin by almost 300 times. Fondaparinux has a linear pharmacokinetic profile, allowing once-daily subcutaneous administration, and a predictable anticoagulant response. Consequently, routine coagulation monitoring is not necessary. This compound does not bind to platelet factor-4, which makes the development of immune thrombocytopenia extremely unlikely. These properties make fondaparinux an attractive therapeutic alternative to the treatment of VTE in patients with cancer, as it has the potential to further simplify treatment, making it easier to treat patients at home with a drug that does not require platelet monitoring at all (54).

In two large phase III multicentre clinical trials, involving the treatment of almost 4500 patients with clinically symptomatic DVT or PE (approximately 10% with cancer), the once daily subcutaneous administration of 7.5 mg of fondaparinux was found to be at least as effective and safe as UFH for the treatment of PE (55), and as effective and safe as enoxaparin for the treatment of DVT (56).

In contrast with drugs that inhibit thrombin indirectly (such as heparins), new categories of direct thrombin inhibitors have emerged in recent years, which show great potential. They include hirudin, bivalirudin, and active-site inhibitors (such as argatroban and melagatran). Agents that directly inhibit thrombin have several advantages over (LMW)heparins, including the inhibition of fibrin-bound thrombin, a dose
response that is more predictable because there is no binding to plasma proteins, and a lack of potential to produce immune thrombocytopenia. Among these preparations, ximelagatran (an oral prodrug that is converted to melagatran and does not require laboratory monitoring) show promise for treatment of VTE. Ximelagatran can be employed as the sole treatment in patients with VTE, which is especially desirable in patients with cancer.

The double-blind, phase III THRIVE treatment study randomized 2491 patients with acute DVT with or without clinically symptomatic PE, including approximately 15% with cancer, to receive either oral ximelagatran (36 mg twice daily) alone for 6 months or conventional doses of enoxaparin followed by warfarin (57). In this trial, ximelagatran was found to be as effective and safe as conventional treatment. It should be noted, however, that in approximately 9% of patients receiving ximelagatran an increase of liver enzymes (more than three times the upper limit of the normal value) was observed, which was transient in the large majority of patients. For the time being, an FDA panel has rejected the manufacturer’s application for approval of ximelagatran because of concerns regarding safety. Further developments are expected in the near future.

Finally, major improvements in antithrombotic treatment can be expected as the new oral classes of direct anti-Xa and thrombin inhibitors have completed their development phase.

**LONG-TERM ANTICOAGULATION**

**The choice of the drug**

Traditionally, in cancer as well as in non-cancer patients (LMW)heparin has been overlapped by oral anticoagulation targeted to reach an International Normalized Ratio (INR) between 2.0 and 3.0 (9). It
should be noted, however, that there are many unique issues in cancer patients that often make treatment more difficult. Chemotherapy, hormonal agents, invasive procedures and the presence of long-term venous catheters not only increase the risk of thrombosis but also create complex clinical situations that make anticoagulation particularly problematic (6,8). For example, temporary cessation of anticoagulant therapy may be needed to accommodate chemotherapy-induced thrombocytopenia and invasive procedures, while poor nutrition, infection, concomitant medication, and impaired liver function can cause unpredictable changes in the dose-response of oral anticoagulants.

In addition, cancer patients are often resistant to oral anticoagulant therapy while at the same time exhibiting a higher hemorrhagic risk. The best evidence of a higher risk of recurrence and clinically relevant hemorrhages while patients are receiving anticoagulation comes from a retrospective analysis of data from two large randomized clinical trials (58) and two prospective cohort studies (59,60).

Hutten et al. extracted the rates of recurrent VTE and major bleedings in more than 1,300 patients receiving at least three months of oral anticoagulant therapy for an acute episode of DVT (58). The overall incidence of recurrent thrombosis in patients with cancer was 27.1 per 100 patient-years, versus 9.0 per 100 patient-years in those without cancer. The risk of major bleeding was 13.3 per 100 patient-years and 2.1 per 100 patients-years, respectively.

Palareti et al. compared the outcome of anticoagulation courses in 95 cancer patients and 733 patients without malignancy (59). Based on 744 patient-years of treatment and follow-up, there was a trend towards 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 have recently completed a prospective cohort study in 842 consecutive patients with DVT who were administered conventional anticoagulation, of whom 181 were carriers of cancer (60). 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 to 5.4). The risk correlated with the extent of cancer. At the time of recurrence, the level of anticoagulation was within or above the therapeutic range in a higher proportion of patients with cancer than in patients without cancer. 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 to 4.1). Also the hemorrhagic risk correlated with the extent of cancer. At the time of bleeding, the level of anticoagulation was above the therapeutic range in similar proportions of patients with and without cancer. Of interest, most episodes of recurrent events and major bleeding were spontaneously, i.e., developed in the absence of triggering risk factors.

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. Among findings that have been described in association with an increased risk of recurrent VTE in cancer patients are development of new metastases, multiple episodes of neutropenia, and previous VTE (61). This risk correlates with the extent of cancer (60). Accordingly, more aggressive initial or long-term treatment has the potential to reduce the risk of recurrent thrombosis. However, a complicating factor in improving anticoagulant therapy in
cancer patients is the occurrence of excess bleeding in combination with excess recurrent VTE complications. Although some improvements can be expected from optimizing laboratory monitoring of anticoagulant therapy, most bleeding and thrombotic complications occur in patients with anticoagulant parameters within the therapeutic range. Therefore, a change in anticoagulant intensity is a case of Hobson’s choice where it is likely to achieve less thrombotic complications for the price of more bleeding or less bleeding for more thrombotic complications. Possibilities for improvement using the current paradigms of anticoagulation seem, therefore, limited and new treatment strategies should be developed.

According to the results of recent randomized clinical trials and prospective cohort studies, LMWHs in full doses for the first month followed by a dose ranging from 50 to 75% of the initial regimen has the potential to provide a more effective antithrombotic regimen in cancer patients with venous thrombosis than the conventional treatment, and is not associated with an increased hemorrhagic risk (62,63), even in patients with disseminated cancer such as those with liver or brain metastases (64). In addition, LMWHs provide an anticoagulation that is easier to administer, more convenient and flexible, and not influenced by nutrition problems or liver impairment (6,8). 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 (9). However, as the cost of the long-term prophylaxis of recurrent VTE with LMWH exceeds by far that of oral anticoagulants (65), and increases the risk of osteoporosis (66), I think that the use of LMWHs for this indication should not be generalized. Since the rate of recurrent VTE and bleeding complications exceeds that of non-cancer patients only in those with advanced disease (36), I still recommend warfarin prophylaxis in patients with less advanced disease.
According to the results of a recent worldwide survey, vitamin K antagonists are still the most commonly used drugs for long-term prevention of recurrent VTE in cancer patients (47).

As new categories of drugs are emerging that have the potential to replace conventional treatment for the secondary prevention of VTE (67), major improvements are soon expected for long-term treatment of cancer patients with venous thrombosis.

The optimal duration

According to the results of recent prospective cohort and population-based studies (68-70), 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. Among the factors associated with an increased risk of recurrent VTE after anticoagulation withdrawal in cancer patients are residual vein thrombosis, as determined by compression ultrasound on the day of drug suspension, and abnormal D-dimer values, measured on the day of drug suspension and one month later (71). In view of the persistently high risk of recurrent thrombotic events, prolongation of anticoagulation should be considered for as long as the malignant disorder is active provided that it is not contraindicated. For most patients, this translates into life-long anticoagulation. Anyway, also in candidates to long-term anticoagulation, this decision should be frequently reassessed during patients’ follow-up.

TREATMENT OF RECURRENT VTE

The anticoagulation strategy in the treatment of patients with recurrent venous thromboembolism during oral anticoagulation is not rigidly standardized (6,8). A patient who develops recurrent VTE while the
INR is sub-therapeutic can be retreated with unfractionated or LMWH for a few days, and then oral anticoagulant therapy can be continued with the INR kept between 2.0 and 3.0. For those who experience warfarin failure and develop a recurrent episode while the INR is therapeutic, the long-term management is less clear. Three options are acceptable after initial re-treatment with unfractionated or LMWH: continue with oral anticoagulant therapy aiming for a higher target INR of 3.0 to 3.5, switch to adjusted-dose twice daily subcutaneous standard heparin to maintain a therapeutic APTT, or use once daily weight-based LMWH. I favor the last. Of interest, Luk and associates conducted a retrospective study to evaluate the efficacy of therapeutic doses of dalteparin for the treatment of recurrent VTE that occurred while patients were on warfarin therapy (72). Of the 32 patients who were identified, and had long-term dalteparin treatment, 20 had cancer. Subsequent recurrent thrombotic events during follow-up occurred in only 3 patients, including one with cancer. If a patient was already receiving once daily weight-based dose LMWH, further treatment requires the long-term administration of full-dose LMWH. For patients with a high risk of pulmonary embolism, or who are hemodynamically unstable, an inferior vena caval filter can be inserted in addition to any one of the above options.

**IMPACT OF ANTITHROMBOTIC DRUGS ON CANCER EVOLUTION AND DEVELOPMENT**

Anticoagulant treatment of cancer patients, particularly those with lung cancer, has been reported to improve survival (73). Since then, studies conducted in animal tumor models have demonstrated that both UFH and LMWH interfere with various processes involved in tumor growth and metastasis (74). 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 (6,74).

Numerous studies have been performed in recent years that have addressed the value of LMWH in comparison with UFH in the treatment of VTE, and an updated meta-analysis of the most adequate reports was published in 2000 (49). In eight of the nine studies reporting on the long-term follow-up of enrolled patients, the analysis of total mortality exhibited a surprising trend in favor of LMWH. In the five studies, that provided subgroups analysis, this effect was entirely attributable to differences in the subgroup of patients with cancer.

The evidence of lowered cancer mortality in patients on LMWH has stimulated renewed interest in these agents as antineoplastic drugs. Four randomized studies have recently 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 (75-78). Two of these studies showed a favorable impact of the tested heparin on patients’ survival, this result being particularly evident in those with better prognosis (75,78). In the other two studies, a post-hoc analysis showed a better survival in subgroups of patients with less advanced disease (76,77). These results are encouraging, but further studies on wider samples of patients are needed before LMWH can be implemented in the routine treatment of patients with cancer.

Of interest, in a recent trial addressing the value of different durations of warfarin for prevention of recurrent thromboembolism in patients with the first episode of VTE, the development of late malignancies was recorded much more frequently in patients allocated to six weeks than in those allocated to six months of anticoagulation (79). These results raise the distinct possibility that cancer and thrombosis
share common mechanisms. A recent investigation, conducted on a mouse model, has provided the first direct genetic evidence for the link between oncogene activation and thrombosis, and suggests a potential role for antithrombotic drugs for prevention and treatment of invasive cancer (80).

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