Cancer, thrombosis and low-molecular-weight heparins
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CHAPTER 5

Approach to venous thromboembolism in the cancer patient.

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Opinion statement

Venous thromboembolism (VTE) is frequently encountered in cancer patients, acts as an important cause of morbidity and mortality, and may be a predictor of worse prognosis. In cancer patient who have a poor life expectancy, preventing death from pulmonary embolism is the mainstay of treatment. Patients who present with severe hypotension or other clinical manifestations suggestive of critical pulmonary embolism and do not have contraindications to thrombolysis should promptly be administered thrombolytic drugs. Except for selected cases requiring aggressive therapy, treatment of VTE in patients with cancer should not differ from that of patients without malignancy; the initial treatment should be conducted with adjusted dose of unfractionated heparin (UH), fixed dose of low-molecular-weight heparins (LMWH), or fondaparinux. LMWHs and fondaparinux have the potential to greatly simplify the initial treatment of VTE, making the management of the pathology feasible in an outpatient setting for selected patients. Traditionally, in cancer as well as in non-cancer patients, UH or LMWH or fondaparinux are overlapped by oral anticoagulation, targeted to reach an International Normalized Ratio (INR) between 2.0 and 3.0, and then followed by oral anticoagulants. However, during oral anticoagulant therapy, cancer patients exhibit a two-to-fourfold higher risk of recurrent VTE and major bleeding complications when compared to non-cancer patients. Studies performed during the current decade have demonstrated that LMWHs offer several advantages in terms of efficacy in preventing VTE recurrences without increasing the bleeding risk. According to International Guidelines, the long-term administration of LMWH should be considered an alternative to anti-vitamin K drugs in patients with advanced disease and in those with conditions limiting the use of oral anticoagulants. The targeted policy is to administer LMWH at full therapeutic doses for the first month of treatment and then 75% of the initial dose for at least the following 5 months of therapy. Prolongation of anticoagulation should be considered for as long as the malignant disorder is active. In patients with acute deep venous thrombosis and contraindications to anticoagulation, vena cava filters should be considered. If anticoagulation is temporarily contraindicated, retrievable filters should be considered. Only patients who are actively bleeding or who are at extremely high risk for bleeding should receive a filter without anticoagulation coverage.

Introduction

Venous thromboembolism (VTE) is a serious and potentially fatal disorder in patients with malignant disease and is often associated with an important impact on clinical outcome and quality of life. Across all cancers, the risk of VTE is elevated sevenfold, but in certain malignancies such as lung cancer or hematologic malignancies, the risk for VTE may be even higher (1–3). Cancer patients have a highly increased risk of VTE in the first few months after diagnosis and when distant metastases are present; the risk is further enhanced in the case of concomitant inherited thrombophilia (3). Most thrombotic episodes occur in the absence of triggering risk factors commonly encountered in patients without cancer. Cancer patients often face an increased risk of venous thromboembolism due to many factors directly related to the baseline disease, such as disease location, stage, type of malignancy, and its treatment. In addition, they typically present with a number of situations that predispose individuals to thrombosis, such as older age, immobilization, and frequent hospitalization. Cancer patients undergoing surgery have up to twice the risk of deep vein thrombosis (DVT) and three times the risk of pulmonary embolism (PE) as non-cancer patients undergoing surgery (4). VTE is further increased by cancer therapies, with a significant rise when chemotherapy or hormonal therapy is administered (1, 4). Moreover, patients with cancer who develop VTE are at elevated risk for recurrent thrombotic events, even when anticoagulation is within the target therapeutic range (5, 6). The clinical picture is further complicated by the fact that these patients are also at increased risk of bleeding during anticoagulation (5, 6). Because the occurrence of a thrombotic event in these patients is associated with serious clinical outcomes that exceed by far those expected in
patients free from malignancy, a number of evidence-based guidelines have delineated anticoagulation regimens for the initial treatment of VTE, the secondary prophylaxis, and the options for long-term anticoagulation in this setting (7-9). The treatment of VTE in cancer patients is resource intensive and costly, and other than preventing recurrent VTE and long-term sequelae of the pathology, is also directed to minimize the risk of bleeding while on anticoagulation (1,10,14).

**Treatment**

Treatment of established venous thromboembolism and the therapeutic management of thromboembolic complications in cancer patients remains a difficult clinical challenge. In fact, the frequent presence of co-morbid conditions and their specific treatment at the same time the thrombotic episode is managed often interfere with anticoagulation and make it quite difficult to reach and maintain an adequate therapeutic range of oral anticoagulants. Moreover, cancer patients may experience a chemotherapy-related platelet drop that increases the bleeding risk. Nevertheless, patients with cancer who develop a VTE episode should be managed according to the guidelines that are currently available for patients free from malignancy (7). Besides that, low-molecular-weight heparins (LMWHs) should be considered the treatment of choice for at least the first 3–6 months of long-term treatment (7-9).

Anticoagulation therapy is also the mainstay treatment for newly diagnosed VTE for cancer patients. It relieves the acute symptoms of venous congestion, reduces the likelihood of embolism, and prevents the extension of established thrombi in the initial treatment of the pathology. However, based on the accepted concept that the risk of recurrent thrombosis is increased in the presence of any ongoing risk factor, in order to prevent recurrent VTE over the long term, continuous anticoagulant therapy is recommended for the whole period in which cancer is active, provided that no important contraindications are present. Hence, the treatment of VTE is usually considered as having two phases—initial and long term—that are aimed at different therapeutic goals. These goals can be summarized as preventing fatal pulmonary embolism (PE), reducing short-term morbidity, preventing recurrent episodes of VTE, and preventing the long-term sequelae such as post-thrombotic syndrome and chronic pulmonary hypertension (1, 7–10).

**Initial treatment**

**Thrombolytic treatment for pulmonary embolism**

Patients who present with severe hypotension or other clinical manifestations suggesting massive 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. Drugs that have been shown to achieve this goal areurokinase, streptokinase, and tissue-type plasminogen activator (t-PA) (7,10,14). We favour the last, because the administration of a loading dose of 10 mg followed by intravenous infusion of 90 mg in only 2 h or 100 mg t-PA over 2 h without a loading dose (approved by the US Food and Drug Administration) achieves the results obtained with 12 or 24 h of infusion of urokinase or streptokinase (11). During the administration of t-PA or soon after its discontinuation, heparin treatment should be implemented. The failure to obtain a rapid clinical improvement raises the suspicion of a saddle embolism and prompts evaluation for thrombo-endarterectomy. Some studies have raised the interest of applying thrombolytic therapy in PE patients with stable conditions, but with a right ventricular dysfunction highlighted at echocardiography. However, given the hemorrhagic risk of thrombolytic therapy, which would be devastating in cancer
patients, further confirmations are needed before thrombolysis could be implemented in non-critical PE patients (7–11).

Anticoagulant therapy

Except for selected cases that require aggressive therapy with thrombolytic agents (i.e., in the case of massive PE or phlegmasia cerulea dolens, upper extremity DVT in patients with central venous catheter that must be kept patent), most cancer patients should receive the subcutaneous administration of therapeutic dosages (adjusted to body weight) of aLMWH administered daily or twice daily. Alternatively, full-dose intravenous unfractionated heparin (i.e., heparin dosages that are able to prolong and maintain activated partial thromboplastin time between 1.5 and 3.0 times the control value) may be administered. LMWH or unfractionated heparin (UH) should be given for a minimum of 5 days, overlapped by oral anticoagulants and then followed by only oral anticoagulants when an INR between 2.0 and 3.0 has been firmly reached. LMWHs have higher bioavailability, and because of their reduced plasma protein binding have a more predictable pharmacokinetic profile and a longer half-life. For all of the LMWHs evaluated in phase III randomized trials on VTE patients, of whom 10%–15% were cancer patients, the 3-month incidence of recurrent VTE was approximately 4% and the risk of major bleedings during the first week of therapy was less than 2%. It has been demonstrated that they are at least as effective and safe as UH in the initial treatment of VTE (12,13). Nevertheless, there are only limited data from randomized trials and cohort studies that show heparin and LMWH are equally effective in preventing symptomatic recurrent VTE in cancer patients with VTE (14). A recent systematic review of the literature has shown that the use of LMWH over UH in the initial treatment of VTE in cancer patients was associated with a significantly reduced mortality rates in cancer patients (relative risk 0.71; 95%CI, 0.52–0.98) (15). Besides that, LMWHs make therapy much simpler and allow for outpatient treatment, which is particularly attractive for most cancer patients, in whom a reduction of hospital stay has the potential to improve the quality of life (1, 2,7,10,14,16). Moreover, recent studies have demonstrated that outpatient management is feasible for selected patients with DVT and low-risk PE and is associated with similar outcomes as in hospital treatment (17,18). Although in clinical practice UH has virtually been replaced by LMWH, some indications for UH still remain, especially in some subgroups of cancer patients. The short half-life of intravenous UH indeed allows for rapid reversal of anticoagulation in patients who begin to bleed or require an invasive procedure. Therefore, in patients at high risk for bleeding, treatment with UH may be preferable. Also, the presence of renal insufficiency makes it attractive to administer a short-acting drug that can be timely monitored and has a specific antidote (protamine sulphate). In fact, UH is hepatically cleared whereas LMWH is renally excreted. New categories of drugs have emerged that can rapidly change the futurescenario in patients with and without cancer. These include inhibitors of factors Xa and IIa. Fondaparinux, a synthetic antithrombotic agent that acts indirectly inhibiting factor Xa, has the potential to further simplify treatment, making it easier to treat patients at home with a drug that does not require platelet monitoring, which is mandatory with UH/LMWH for the risk of heparin-induced thrombocytopenia. During the current decade, two large trials on these molecules have been performed and found that the once-daily administration of 7.5 mg of fondaparinux was at least as effective and safe as enoxaparin for the treatment of DVT and as effective and safe as UH for the treatment of PE in a cohort of patients that also included patients with cancer (19, 20 Class I). Data on the subcutaneous administration of fondaparinux in the initial treatment of VTE associated with cancer are limited, but they suggest similar efficacy and safety as in patients without cancer (21). Other emerging anti-Xa compounds that can be administered orally infixed doses are rivaroxaban and apixaban. Some phase III trials of these agents for management of VTE are ongoing and also include patients with cancer (10,14,22). New, oral direct-thrombin inhibitors may soon be encountered in clinical practice. Among these preparations, dabigatran at the dose of 150 mg three times daily was found to be as effective and safe as warfarin for treatment of acute venous
thromboembolism in patients who underwent an initial treatment of 8–10 days of LMWH. This trial enrolled a subgroup of patients with cancer (23, Class I).

**Inferior vena cava filters**

For various reasons, patients with cancer and acute proximal DVT may exhibit a permanent contraindication to anticoagulant treatment more frequently than among patients free from malignancy. In these patients, the only option is the insertion of an inferior vena cava (IVC) filter to prevent pulmonary embolism. Moreover, it has been clearly demonstrated that patients with vena cava filters who do not receive concomitant anticoagulation are at high risk for recurrent DVT: only patients who are actively bleeding or who are at extremely high risk for bleeding should receive a filter without anticoagulation coverage (7–10,24). The only available open-label randomized trial on permanent IVC filters in patients with VTE suggested that IVC filter insertion was associated with a reduced risk of PE, balanced ban increased risk of DVT and no overall effect on mortality (25). In those cases in which anticoagulation is temporarily contraindicated, retrievable filters should be considered. Such filters should optimally be retrieved within a timeline variable by specific IVC filter devices (8,10,14).

**Long-term treatment of venous thromboembolism**

**Vitamin K antagonists**

Vitamin K antagonists (e.g., warfarin) remain an acceptable option for secondary prophylaxis, even in cancer patients with VTE. The suggested protocol is to administer oral anticoagulants to maintain an INR between 2.0 and 3.0. In fact, once the INR has reached the therapeutic target and after overlap of a minimum of 5 days, UH or LMWH can be stopped and warfarin is continued for the remainder of the treatment period. This period requires, especially in cancer patients, frequent monitoring of the INR in order to maintain a therapeutic anticoagulant effect. However, there are many issues unique to cancer patients that make this treatment more difficult. Chemotherapy, invasive procedures, impaired nutrition, and need for multiple concomitant medications that may interfere with oral anticoagulants generate difficulties with maintaining therapeutic INR and make this approach problematic, often leading to considerable gaps in anticoagulant coverage. In fact, unpredictable changes in the dose response of vitamin K antagonists due to drug interactions, in addition to gastrointestinal problems, liver impairment, and interruption of therapy for invasive procedures, may result in erratic INR levels and non-therapeutic anticoagulation in cancer patients. This may lead to frequent visits to the hospital or clinic for laboratory monitoring, adding further discomfort to the patients or family members who provide transportation or other support (7–10,14). Furthermore, it has been demonstrated that cancer patients with established DVT are more likely to develop recurrent thromboembolic complications and major bleeding while on oral anticoagulant therapy, even when the therapeutic anticoagulant target has been maintained (5,6). In a study carried out at our institution, it has been highlighted that the cumulative incidence of recurrent VTE in cancer patients was 20.7% compared with 6.8% in non-cancer patients, furan age-adjusted hazard ratio of 3.2. These risks correlate with the extent of cancer. The 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. The hemorrhagic risk also correlates with the extent of disease (5, Class II). This high risk of anticoagulant-related bleeding in cancer patients has also been demonstrated in a study by Hutten et al (6, Class II) that reported an incidence of major bleeding as high as 13.3 per 100 patients-years in cancer patients on oral anticoagulant therapy, compared with 2.1 per 100 patient-years in patients without cancer. Hence, possibilities for improvement using the current paradigm of anticoagulation for cancer patients with VTE seem limited and new treatment strategies have been developed.
Low-molecular-weight heparins

The long-term administration of LMWH has been compared to warfarin among cancer patients with venous thromboembolism in several clinical trials. The Secondary Prevention Trial of Venous Thrombosis with Enoxaparin (CANTHANOX) compared 3 months of standard warfarin therapy with enoxaparin in cancer patients with DVT, PE, or both (26). A total of 75 patients in the warfarin group and 71 patients in the enoxaparin group were evaluable for the cumulative endpoint of recurrent symptomatic VTE and/or major bleedings during the 3-month treatment period. Fifteen patients had recurrent VTE and/or major bleedings in the warfarin group, compared with seven in the enoxaparin group. The majority of the events were major bleedings, reported in 12 and five patients, respectively. Based on the results of this study, the investigators concluded that warfarin was associated with a higher bleeding risk in cancer patients with VTE and that prolonged treatment with LMWH may be as effective as warfarin therapy with an improved safety profile. In the oral anticoagulant therapy for long-term anticoagulation in cancer patients with venous thromboembolism, the CLOT trial, cancer patients with VTE were randomized to receive either the LMWH dalteparin full doses for the first month and then 75% of the initial dosage for an additional 5 months, or oral anticoagulation with warfarin. Over a 6-month period, there was a 50% reduction of recurrent VTE in patients treated with LMWH with no differences in bleeding risk (27). The Randomized Trial of the Effect of Low-Molecular-Weight Heparin Versus Warfarin Sodium on the Mortality in the Long-Term Treatment of Proximal Deep Vein Thrombosis (LITE) study evaluated tinzaparin for long-term use. It has reported improved efficacy with tinzaparin over warfarin in 167 patients with cancer; tinzaparin reduced the rate of recurrent VTE by half and no difference in bleeding events was observed (28). In addition to improved efficacy in cancer patients, LMWHs provide an anticoagulation regimen that is easier to administer, flexible, and not influenced by nutritional problems or liver impairment. Because LMWHs have been recognized as more efficacious than warfarin to reduce symptomatic recurrent VTE in cancer patients with DVT or PE, new treatment recommendations and international guidelines have stated that LMWH should now be considered the treatment of choice in patients with active malignant disease, for at least the first 3–6 months of long-term treatment (7-9). The suggested policy is to administer LMWH at full therapeutic dose for the first month of treatment followed by 75% of the initial dose for the following 5 months of long-term therapy (1,7–10,16,29). According to the most recent international guidelines, prolongation of anticoagulation should be considered for as long as cancer is active (7-9). For several LMWHs, both once daily and twice daily injections are available and approved for the treatment of VTE. A study by Merli et al (30) has demonstrated no differences in symptomatic recurrent VTE or bleeding when UH was compared with subcutaneous enoxaparin at 1.0 mg/kg of body weight administered twice daily or 1.5 mg/kg injected once daily for the initial treatment of VTE. In this study, the subgroup of patients with cancer receiving once daily enoxaparin experienced a higher risk of recurrences when compared with patients on twice-daily injections (12.2% vs 6.4%), although the difference was not statistically significant (30). Breddin et al (31) have shown that twice daily injections of reviparin reduce thrombus burden better than once daily administration in a randomized trial among cancer and non-cancer patients with DVT (31). For long-term treatment of VTE in the cancer patient, only the once-daily regimens have been studied in randomized clinical trials, likely because they seem more acceptable and carry less discomfort for the patient. There could be a role for twice-daily LMWH injections in treating recurrent episodes of VTE (21,29–31). LMWH should be used with caution in patients with significant renal insufficiency (creatinine clearance G30 mL/min), either in the initial treatment or during secondary prophylaxis. Among these patients we quite often prefer to administer UH for the initial treatment of VTE, overlapped for at least 5 days and until vitamin K antagonists have reached an INR between 2.0 and 3.0 for 2 consecutive days. Then we continue with vitamin K antagonists (INR between 2.0 and 3.0) during the whole secondary prophylaxis, since vitamin K antagonists are hepatically cleared whereas LMWHs are renally excreted.
Duration of anticoagulation

The risk of a recurrent VTE episode is higher in the presence of an ongoing risk factor. Prospective cohort and population-based studies have shown that after discontinuation of warfarin, patients with active cancer and venous thrombosis have a risk of recurrence almost twice as high as that in patients without malignant disorders (32). In a study carried out at the authors’ institution aiming at evaluating the clinical course of patients during 8 years after their first episode of DVT in a cohort of patients of whom a subgroup had cancer, it was demonstrated that the cumulative incidence of VTE recurrences was as high as 30% after 8 years of follow-up. The presence of cancer greatly increased the risk of recurrences, having a hazard ratio of 1.72 (95% CI, 1.3–2.25), which was even higher than that of patients with Thrombophilia (33). In view of the persistently high risk of recurrent VTE events, secondary prophylaxis should be considered for as long as cancer is active, provided that no contraindication occurs. A periodic evaluation of the risk-benefit ratio of continuing anticoagulant therapy is recommended. The decision should consider patient preference, anticancer treatments, co-morbid conditions, and life expectancy together with quality of life (1,7).

Recurrent episodes

Cancer patients are more likely to develop recurrent thromboembolism during anticoagulation than patients without malignancy. The anticoagulation strategy for recurrent venous thromboembolism during oral anticoagulation is not rigidly set out. If the patient develops a recurrent VTE while the INR is sub-therapeutic its suggested to re-treat the patient with UH or LMWH for few days followed by continuation of oral anticoagulation with a strictly monitored INR that must be kept between 2.0 and 3.0. For those patients who experience warfarin failure and develop a recurrent episode while on therapeutic range of anticoagulation, long-term management is less clear. Three options seem acceptable after an initial re-treatment with UH or LMWH:

1) continuing with oral anticoagulant therapy with an INR between 3.0 and 3.5,
2) switching to adjusted doses of subcutaneous UH to maintain activated partial thromboplastin time (aPTT) ratio in the therapeutic range,
3) or use once-daily weight-adjusted LMWH. For patients with a high risk of pulmonary embolism or who are hemodynamically unstable, a filter can be inserted in the inferior venacava in addition to any of the above-mentioned options.

The management of patients who develop a recurrent episode while on LMWH has not been investigated. Experts have empirically recommended increasing the dose of LMWH, administering it in the fashion of twice-daily injections, or treating patients with aPTT adjusted UH (7–10, 29). In a Study by Carrier et al (34), dose escalation of LMWH was tested to manage recurrent VTE occurring despite standard anticoagulation in cancer patients. This study has shown that dose escalation of LMWH can be effective for treating cases that are resistant to standard weight-adjusted doses of LMWH or a vitamin K antagonist (34).
References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance


This article reports on fondaparinux for the initial treatment of VTE among patients with cancer


