way of thinking of CB-derived HSC (non-) expansion which could, if confirmed, be quickly translated into practical and useful clinical applications.

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Thrombosis and cancer: clinical relevance of a dangerous liaison

Venous thromboembolism (deep vein thrombosis and pulmonary embolism) and cancer are linked by a *two-way clinical association*. Indeed, an idiopathic or unprovoked episode of venous thromboembolism (VTE) may be the first clinical manifestation of an occult cancer while patients with clinically overt cancer are prone to have a thromboembolic complication.[1] The pathophysiology of thrombosis in cancer patients is rather complex. Cancer cells can activate the clotting system directly, by generating thrombin, or indirectly, by stimulating endothelial cells and circulating mononuclear cells to synthesize and express a number of procoagulant factors, including the tissue factor. An activation of blood coagulation has been consistently demonstrated in patients with cancer, but the correlation between these laboratory findings and clinical outcomes has been only partially elucidated.

Idiopathic VTE and occult cancer

Patients presenting with an idiopathic or unprovoked VTE have an approximately 10% probability of developing a cancer in the two years after the index event.[2] Because of the concerns about this adverse outcome, extensive screening for underlying cancer has been advocated in patients presenting with idiopathic VTE. In a recently published randomized trial the clinical benefit of extensive screening for occult cancer was compared with the management of no screening in patients with idiopathic VTE. The sensitivity of the extensive screening was found to be approximately 90%.[3] During the 2-year follow-up period, a newly diagnosed cancer was found in 10 of the 102 patients randomized to no-screening and 1 of the 99 patients randomized to extensive screening. After a follow-up of 2 years from the index event, no significant difference in cancer-related mortality was observed between the two groups (2.0% in the screened group and 3.9% in the not-screened group). In a second recently published study, Monreal *et al.*[4] prospectively evaluated the clinical benefit of a limited screening for occult cancer (abdominal ultrasound and laboratory markers of malignancy) in patients with acute VTE. This limited diagnostic work-up showed a sensitivity of approximately 50%, leading the authors to conclude for the opportuneness of a more extensive diagnostic screening. Based on the currently available data, there is not sufficient evidence to recommend routinely either exten-

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sive or limited screening for occult cancer in patients presenting with idiopathic VTE.

In a study reported in this issue of the journal (see page 214), Schutgens *et al*. found a correlation between high D-dimer level, measured in the acute phase of deep vein thrombosis (DVT), and the diagnosis of previously unknown cancer. Cancer was found in 22 of 190 patients who presented with DVT and had not previously been known to have a cancer. In 8 of these patients cancer was found at presentation while in the remaining 14 it was found during the follow-up. The most interesting finding of this study is that these 14 patients had statistically significantly higher levels of D-dimer at presentation than those of the patients who did not develop cancer during the follow-up. On the basis of these results, the authors concluded that high D-dimer levels at presentation are indicators of an increased chance of occult cancer in patients presenting with idiopathic DVT. The concept behind this study, to identify a subgroup of VTE patients at high risk of developing cancer and to make it the target of extensive screening, is certainly interesting. This approach may allow a more limited group to be targeted than the general group of patients with idiopathic VTE with obvious advantages in terms of patient care and reduced heath expenditure. The results of the study are of potential interest but they need to be confirmed in prospective randomized management studies in which D-dimer levels are used to make clinical decisions. Particular attention should be given to validating the safety of withholding screening for occult cancer in patients with low D-dimer levels. While waiting for the results of these studies, D-dimer levels should not be used alone for this purpose but should be at least associated with a rigorous clinical judgment.

The burden of VTE in cancer patients

About 15% of patients with cancer develop a clinically overt VTE during their disease. On the other hand, approximately 20% of patients presenting with VTE have cancer. These patients are hospitalized more frequently than VTE patients without cancer, are sicker and more prone to develop treatment side-effects. Patients with cancer more frequently have extensive or bilateral DVT of the lower limbs and venous thrombosis in unusual sites. Although patients with cancer may develop a thromboembolic complication at any stage, the risk of VTE is particularly high in association with three clinical settings surgery for cancer, chemotherapy and use of a central vein catheter (CVC).

Post-operative VTE

For a similar type of operation, post-operative VTE occurs 3-5-time more frequently in cancer patients than in non-cancer patients.[5] In cancer patients undergoing surgery without prophylaxis, the incidence of DVT is 40-80% and that of proximal DVT 10-20%, as shown by screening procedures. Most of the patients with positive screening are asymptomatic. In a large multicenter study the incidence of fatal pulmonary embolism was 1.6% in cancer patients and 0.5% in those without cancer (p=0.05).[6] A recent prospective study focused on the incidence of clinically overt VTE in patients undergoing surgery for cancer and found an incidence of 2.1% at the 30th post-operative day despite the fact that most of the patients were receiving pharmacological prophylaxis. About 40% of VTE events occurred later than three weeks after the surgery. The 30-day mortality was 1.72% and approximately half of the deaths were due to pulmonary embolism.[7] Extensive abdominal or pelvic surgery, age older than 60 years, obesity, previous VTE episodes and prolonged immobility place patients with cancer at particularly high risk of post-operative VTE. Once-daily low molecular weight heparin (LMWH) is as safe and effective as multiple daily injections of unfractionated heparin (UFH) in reducing the incidence of post-operative VTE. The benefit of extended prophylaxis for VTE after cancer surgery was demonstrated by the ENOXACAN II study.[8] This study reported a statistically significant reduction from 12% to 4.8% in the rate of DVT associated with extended prophylaxis (4 weeks) as compared with shorter prophylaxis (1st post-operative week). Despite pharmacological prophylaxis, the incidence of VTE in patients undergoing surgery for cancer remains high. This problem prompted the evaluation of several new antithrombotic agents in a clinical setting.[9,10]

Chemotherapy

While receiving chemotherapy and/or hormone therapy, cancer patients have an increased risk of developing VTE. Data on radiotherapy are less clear. The risk of VTE associated with chemotherapy is dependent on many contributing factors including cancer stage, age, co-morbidities, bed rest, and the type and intensity of the therapeutic regimens. Most of the data on the incidence of chemotherapy-associated VTE derive from studies in women with breast cancer. In these patients, the risk of VTE ranges from 4% to 15% and is even higher in patients with metastatic cancer. The incidence of VTE in patients with a variety of cancers, including cancer of the colon, lung, breast and genitourinary tract, was recently reported to be approximately 10% per year.[11]

Warfarin 1 mg a day has been reported to be safe and effective in reducing VTE complications in patients with stage IV breast cancer.[12] However, the available evidence to recommend routine antithrombotic prophylaxis in whatever type of cancer is modest. More data about this matter will be available after the completion of several ongoing studies designed to assess the clinical benefit of antithrombotic prophylaxis to prevent chemotherapy-associated VTE.

Central vein catheters (CVC)

Currently, many cancer patients have a long-term CVC inserted for chemotherapy. CVC offers the cancer patients advantages that are potentially outweighed by complications such as CVC-related DVT and infections. The incidence of asymptomatic CVC-related DVT is estimated to be about 20%, while the rate of clinically overt DVT of upper limbs ranges between 2 and 4%. Some features of the catheter may influence the occurrence of VTE complications.[13]

The role of antithrombotic prophylaxis in the prevention of CVC-related thrombosis is controversial. Although some open label studies[14,15] demonstrated that both LMWH and warfarin had benefit in preventing CVC-related complications, more recent randomized, placebo controlled trials,[16,17] in which either symptomatic or venography-detected thrombosis was measured, did not confirm this benefit. Recently, a multicenter, randomized, double-blind, placebo-controlled study assessed the efficacy and safety of enoxaparin, given for 6 weeks, in the prevention of VTE in 385 cancer patients with CVC. In this study, a 22% not statistically significant risk reduc-

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tion in the rate of CVC-related VTE was detected in patients receiving enoxaparin compared to in those receiving placebo.[18] Based on the available data, the use of prophylaxis for catheter-induced thrombosis remains controversial and more studies are required.

Clinical course of VTE in cancer patients

When VTE is objectively confirmed, anticoagulant therapy is required. According to the current guidelines, treatment is started with adjusted-dose UFH or fixed dose LMWH for 5 to 7 days and continued with oral anticoagulation. Recurrence of VTE is more common in cancer patients than in non-cancer patients[19,20] and can occur despite appropriate anticoagulation. On the other hand, cancer patients seem to be prone to develop bleeding complications more frequently while receiving anticoagulant treatment. Recently, a randomized, controlled study in cancer patients demonstrated the efficacy and safety of secondary prevention of VTE with long-term administration of LMWH. In this study, dalteparin was shown to be more effective than oral anticoagulants in reducing the risk of VTE recurrence without increasing the risk of bleeding.[21] In this issue of the Journal Ageno *et al*. report their clinical experience on home treatment of DVT in 321 cancer patients. The results of this study demonstrate that home treatment of DVT in cancer patients is safe and feasible. Of interest, almost two-thirds of the cancer patients received only LMWH. Home treatment of DVT in cancer patients resulted to be effective without increasing the rate of recurrent VTE and deaths.

The optimal duration of antithrombotic treatment in cancer patients remains to be defined. The seventh ACCP consensus conference[22] recently recommended that anticoagulation for VTE occurring in cancer patients be continued indefinitely or for *as long as cancer is active*.

Conclusions

The management of VTE has been significantly improved in recent years. In particular diagnosis and treatment have been made easier and more reliable. It is of interest that most of the unsolved issues concern the management of VTE in cancer patients. It is to be hoped that the awareness of these unmet clinical needs will result in more extensive clinical research specifically targeting the association of cancer and thrombosis.

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