

VENOUS THROMBOEMBOLISM AND CANCER: A TWO-WAY CLINICAL ASSOCIATION

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1. ABSTRACT

In recent years, a growing body of evidence has provided the convincing demonstration of a strong association between cancer and venous thromboembolism. This relationship is further supported by the risk of developing overt malignancy in patients with idiopathic venous thromboembolism. However, the cost-to-benefit ratio of an extensive diagnostic work-up aimed at identifying an occult cancer in patients with spontaneous thromboembolism still has to be demonstrated.

During prolonged immobilization from any cause, and following surgical interventions, patients with cancer are at a remarkably higher risk of venous thromboembolism than patients free from malignant disorders. Standard heparin in adjusted doses or a low-molecular-weight heparin in doses commonly recommended for high risk surgical patients represent the prophylactic treatment of choice for cancer patients undergoing an extensive abdominal or pelvic intervention. Furthermore, the risk of thrombotic episodes is increased in cancer patients by chemotherapy and by the use of indwelling central venous catheters. Recent data suggest a positive benefit-to-risk ratio with the systematical use of fixed mini-dose of warfarin in both conditions.

After experiencing an episode of thrombosis, cancer patients remain at risk of recurrence for as long as the cancer is active. Therefore, they should be protected by a long-term course of oral anticoagulation.

The risk of recurrent thrombotic events despite adequate anticoagulation is higher in patients with cancer than in those without cancer. The routine use of long-term subcutaneous heparin therapy rather than oral anticoagulants should be reserved for patients in whom warfarin has been ineffective.

Can antithrombotic drugs improve survival in cancer patients? In cancer patients affected by deep-vein thrombosis, the treatment with low-molecular-weight heparins has been reported to lower mortality at a higher extent than the standard heparin therapy. Such an observation suggests that these agents might develop an antineoplastic activity.

2. INTRODUCTION

Since the initial observation by Armand Trousseau in 1865, numerous studies have addressed the relationship between cancer and thrombosis. Post-mortem studies have demonstrated a markedly increased incidence of thromboembolic disease in patients who died of cancer, particularly those with mucinous carcinomas of the pancreas, lung, and gastrointestinal tract (1,2). Cohort studies of surgical patients showed that the incidence of deep venous thrombosis (DVT) was markedly higher in patients with malignant disorders than in patients with other

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(non-malignant) diseases (3-6). An increased risk of venous thromboembolism (VTE) is suggested by the high incidence of pulmonary embolism (7) and subclinical activation of the coagulation system in non-surgical patients with cancer (8-10). The relationship between cancer and thrombosis is further supported by the high risk of developing overt malignancy in patients with idiopathic VTE when compared with patients whose thrombotic episode is associated with a well recognized risk factor (11).

This article reviews the relation between cancer and VTE and highlights some relevant clinical implications.

3. PATHOGENESIS

Pathogenetic mechanisms accounting for the development of thrombotic disorders in patients affected by cancer were described by Virchow more than a century ago. They include hypercoagulability, due to tumor cell activation of clotting, vessel wall injury, and stasis.

3.1. Hypercoagulability

Neoplastic cells can activate the clotting system directly, thereby generating thrombin, or indirectly by stimulating mononuclear cells to produce and express procoagulants.

Several different procoagulant activities have been identified from tumor cell lines, extracts or sonicates of human and animal tumors. Best characterized tumor cell procoagulants are tissue factor, an integral membrane glycoprotein, which can activate the extrinsic pathway through interaction with factor VIIa, and Factor X activators (12,13). Tissue factor procoagulant activity has been identified in some acute leukemias (14) and in solid tumors of the ovary, stomach, and kidney (15). Direct factor X activation with the procoagulant cysteine proteinase has been found in some patients with lung, prostate, colon, breast, and kidney cancers and with leukemia (16,17). Mucin-secreting adenocarcinomas are frequently associated with thrombosis because the sialic acid moiety expressed by tumor cells can cause nonenzymatic activation of factor X to its active form, factor Xa (18). Consequently, adenocarcinomas of the lung, pancreas, gastrointestinal tract, and ovary are often associated with venous thrombosis (19).

Tumor cells can activate systemic coagulation by stimulating mononuclear cells to synthesize and express various procoagulant substances, including tissue factor and factor X activators. Normal monocytes and macrophages can be activated by tumor cells in the presence of lymphocytes (20). In patients with cancer, endothelial cells may be activated by cytokines such as tumor necrosis factor and interleukin-1 or interleukin-like

substances that may induce tissue factor production (21). A peptide produced by a human bladder cancer cell line stimulates tissue factor expression in endothelial cells (22).

The enhanced clotting activation in patients with cancer is confirmed by the demonstration of increased levels of systemic hypercoagulability markers, such as fibrinopeptide A, prothrombin fragment F₁₊₂ and thrombin-antithrombin complexes in most patients (23,24).

3.2. Vessel wall damage

There is increasing awareness that cancer cells can injure endothelium by direct vascular invasion, resulting in the onset of a prothrombotic state. Moreover, tumor cells may secrete vascular permeability factors which account for the extravascular accumulation of fibrinogen and other clotting proteins around tumor growth (23,24). The adhesion of tumor cells to endothelium was evaluated “*in vivo*” by Naschitz and associates, who observed a complex interaction among endothelium, platelets, and tumor cells (25).

A direct vessel wall injury, in association with rheologic abnormalities and catheter-associated thrombin formation, is the most likely explanation for the occurrence of the upper extremity DVT arising as a complication of central venous lines (26). Besides the reduction in the plasma concentration of natural anticoagulants, among mechanisms responsible for thrombotic events during the use of chemotherapeutic drugs, vascular endothelium damage is likely to play a major role (27-29).

3.3. Venous stasis

Venous stasis predisposes to venous thrombosis by preventing activated coagulation factors from being diluted and cleared by the normal blood flow. Moreover, hypoxic damage to endothelial cells due to stasis may produce prothrombotic alterations. Venous stasis develops as a consequence of immobility in severely debilitated cancer patients, in conjunction with cancer surgery, or as a result of venous obstruction due to extrinsic vascular compression in patients with bulky tumor masses (30).

4. CLINICAL IMPLICATIONS

4.1. Search for occult malignancies in patients with idiopathic VTE

Several studies, performed in recent years, have demonstrated that VTE carries a substantial risk of subsequent malignancies (11, 31-34). As clearly shown in table I, this risk in patients presenting with apparently spontaneous episodes of VTE (idiopathic VTE) is five times higher than that presented by

Table I. Incidence of cancer in the follow-up of patients with idiopathic and secondary VTE

	Frequency of cancer	
	Idiopathic VTE	Secondary VTE
Aderka <i>et al.</i> , 1986 (31)	12/35 (34%)	2/48 (4.0%)
Monreal <i>et al.</i> , 1988 (32)	8/21 (38%)	1/73 (1.0%)
Monreal <i>et al.</i> , 1991 (33)	7/31 (23%)	5/82 (6.0%)
Prandoni <i>et al.</i> , 1992 (11)	11/145 (7.6%)	2/105 (2.0%)
Bastounis <i>et al.</i> , 1996 (34)	5/68 (7.4%)	2/196 (1.0%)

Table II. Postoperative DVT following general surgery in patients with and without cancer

	Cancer patients	Non-cancer patients
Kakkar <i>et al.</i> , 1970 (3)	24/59 (41%)	38/144 (26%)
Hills <i>et al.</i> , 1972 (4)	8/16 (50%)	7/34 (21%)
Walsh <i>et al.</i> , 1974 (5)	16/45 (35%)	22/217 (10%)
Rosemberg <i>et al.</i> , 1975 (38)	28/66 (42%)	29/128 (23%)
Sue-Ling <i>et al.</i> , 1986 (6)	12/23 (52%)	16/62 (26%)
Allan <i>et al.</i> , 1983 (39)	31/100 (31%)	21/100 (21%)
Sasahara, 1984 (40)	9/37 (22%)	13/53 (24%)
TOTAL	128/346 (37%)	146/738 (20%)

patients in whom the thrombotic event is associated with the well recognized risk factors (secondary VTE).

Although these studies have demonstrated a significant association between idiopathic VTE and cancer, the clinical implications of these findings are yet unclear. As suggested by these results, an extensive diagnostic work-up might be justified at the time of referral for the venous thrombosis. However, the design of this study does not allow to answer whether the malignant disease which develops during follow-up can be detected by such a diagnostic procedure. Furthermore, it remains unclear whether the identified malignancy is potentially treatable and whether treatment can favorably influence life expectancy or the quality of life. Since extensive screening procedures for malignancy are associated with high costs, and themselves carry some morbidity, they are only acceptable if they are life-saving (35).

To verify whether an extensive diagnostic work-up aimed at identifying occult malignancies in patients with spontaneous VTE is cost-effective, a large randomized trial is being carried out in Europe. Patients with idiopathic VTE are assigned to either an extensive diagnostic work-up or to standard medical practice. Cancer-related mortality is the main end-point of this study. While waiting for the results of this trial, the current approach which can be recommended is that of maintaining a high index of

clinical suspicion, performing an array of systematic non-invasive investigations in all patients presenting with spontaneous VTE. Further tests should be based on patient's symptoms and signs or on the results of the first-line investigations. This approach has received a recent support from the retrospective analysis of a wide cohort of patients with idiopathic DVT, conducted in the Boston area (36).

4.2. Primary prophylaxis of VTE

Because VTE is often encountered in patients with cancer, some clinicians have proposed that all patients with cancer should receive pharmacological prophylaxis (37). However, further trials are needed before this approach can be endorsed.

Currently, primary prevention should be considered for cancer patients in certain circumstances, such as surgical interventions, chemotherapy, and the insertion of indwelling central venous catheters.

4.2.1. Surgical interventions

Patients with cancer are at a markedly high risk of developing DVT. As shown in table II, the overall incidence of postoperative DVT in patients with cancer is about twice as high as that of patients free of malignancy (3-6, 38-40). As recently demonstrated by Huber *et al.*, the incidence of postoperative pulmonary embolism is remarkably higher in patients with cancer than in those without cancer (41).

Table III. Arterial and Venous thrombosis in patients with breast cancer undergoing chemotherapy

Author	No of Patients	Stage	Thrombosis (%)	Type of thrombosis
Weiss <i>et al.</i> 1981 (46)	433	II	5	V
Goodnough <i>et al.</i> 1984 (47)	159	IV	15	V+A
Levine <i>et al.</i> 1988 (48)	205	II	7	V+A
Wall <i>et al.</i> 1989 (49)	1014	Variable	1.3	A
Fisher <i>et al.</i> 1989 (50)	383	II	3	V
Saphner <i>et al.</i> 1991 (51)	2352	Variable	5	V+A
Clahsen <i>et al.</i> 1994 (52)	1292	Variable	2	V
Rifkin <i>et al.</i> 1994 (53)	603	II	2.5	V+A
Pritchard <i>et al.</i> 1996 (55)	353	II	9.6	V+A
Tempelhoff <i>et al.</i> 1996 (54)	50	II	10	V

V = venous thrombosis

A = arterial thrombosis

In order to reduce the risk of venous thrombosis, the European Consensus Statement, recently held in London, has recommended the use of low-dose heparin, low-molecular-weight heparin (LMWH) at low doses, or physical measures in patients with cancer when confined to bed from any cause, and when undergoing low-risk surgical procedures (42). Extensive abdominal or pelvic surgery places patients with cancer at a remarkably high risk for developing post-operative DVT and pulmonary embolism. Therefore, these patients require prophylactic measures comparable to those usually recommended for major orthopaedic surgery. These measures include adjusted-dose heparin, higher doses of heparin fractions (average twice as high as those suggested for general surgery), or oral anticoagulants (42). Danaparoid (a mixture of dermatan and heparan sulphate) has recently been shown to be as effective and safe as the standard heparin for prevention of DVT after elective surgery for malignant disease (43).

As compared to standard heparin regimen that is used in the prevention of thromboembolism in patients with cancer who undergo surgery, no selective advantage has yet been shown with LMWHs (44). A recent study compared two doses of a LMWH (dalteparin, 5000 and 2500 units once daily) for thromboprophylaxis in 2070 patients undergoing

elective general surgery for abdominal diseases, 63% of whom had malignant disease (45). The higher dosage schedule reduced the incidence of DVT from 12.6 to 6.7% at the expense of more hemorrhagic complications (4.7 versus 2.7%). This higher rate of bleeding was not seen among patients undergoing operation for cancer.

4.2.2. Chemotherapy

As shown in table III, patients with breast cancer are at a particularly high risk of developing both venous and arterial thrombosis when receiving chemotherapeutic drugs (46-55). Moreover, a recent trial randomized a wide series of women with breast cancer to receive tamoxifen alone or a 6-month course of chemotherapy (54). During the study period, thromboembolic events were observed much more frequently in women who received chemotherapy much than in women who only received tamoxifen. Thromboembolism related to chemotherapy represents, therefore, a relatively common and serious complication that may outweigh any benefits by this additional therapy.

Recently, a prospective double-blind randomized study showed that during chemotherapy very-low-dose warfarin (1 mg/day) for six weeks, followed by doses that maintained the International

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Table IV. Venous thromboembolism and bleeding complications during 3-month oral anticoagulation. A prospective cohort study in 355 consecutive patients with DVT treated with heparin followed by warfarin

	Cancer (n=58)	No Cancer (n=297)	p value
Recurrence of VTE	6 (10.3%)	14 (4.7%)	0.12
Recurrence of VTE despite adequate anticoagulation (INR=2.0-3.0)	5 (8.6%)	4 (1.3%)	< 0.01
Bleeding	5 (8.6%)	29 (9.8%)	> 0.2
Major bleeding	2 (3.4%)	9 (3.0%)	> 0.2

VTE = venous thromboembolism
from Prandoni *et al.* (63)

Table V. Cancer-related mortality in patients with proximal-vein thrombosis.
Analysis of two prospective randomized trials comparing standard heparin with LMWH treatment

Series	UFH	LMWH	p value
Prandoni <i>et al.</i> 1992 (68)	8/18	1/15	
Hull <i>et al.</i> 1992 (69)	13/49	6/47	
TOTAL	21/67 (31%)	7/62 (11%)	0.005

UFH = unfractionated heparin
LMWH = low-molecular-weight heparin
from Green *et al.* (70)

Normalized Ratio (INR) at 1.3 to 1.9, was an effective and safe method for prevention of thromboembolism in patients with metastatic breast cancer (56). Based on data from this trial, a cost-effectiveness analysis was performed, showing that with no increase in health care costs, warfarin, at low doses, can be given to women with metastatic breast cancer receiving chemotherapy (57). Whether this strategy may also be utilized in patients with other cancer remains to be demonstrated.

4.2.3. Central venous catheters

A few studies using venography demonstrated an unexpectedly high incidence of upper limb venous thrombosis following the insertion of indwelling central venous catheters in patients with cancer (58,59).

Two randomized, controlled studies have documented the benefit of a similarly low-dose of warfarin sodium in decreasing the incidence of thrombosis related to indwelling central venous catheters (59,60). Subcutaneous administration of LMWH (dalteparin) at the dosage of 2500 IU once

daily for 90 days has proven to be highly beneficial in the prevention of upper limb DVT in cancer patients with venous access devices (61).

4.3. Treatment and secondary prophylaxis of VTE

Patients with cancer developing an acute thromboembolic disorder should receive a proper course of full-dose unfractionated heparin (62). Alternatively, therapeutic doses of a LMWH can be employed. Thrombolytic drugs are rarely indicated. The limited cases in which thrombolysis may be considered include massive pulmonary embolism, extension of venous thrombosis despite extensive anticoagulation, and upper-extremity thrombosis in patients who have an indwelling central venous catheter, which must be kept patent.

Whenever possible, heparin should be administered as soon as there is a reasonable possibility that venous thrombosis exists. Heparin should be overlapped and followed by an oral anticoagulant drug (62).

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What are the main questions clinicians confront when facing cancer patients with an episode of venous thrombosis? The main controversies deal with the most appropriate duration and intensity of anticoagulation; the risk of extension and/or recurrence of venous thromboembolism during anticoagulation; and the potential for an increased risk of bleeding during the course of proper anticoagulant therapy.

4.3.1. Duration and intensity of anticoagulation

It is a common experience that patients with active cancer remain at a high risk of developing thromboembolism after discontinuation of warfarin therapy (62). In view of the persisting high risk for recurrent thrombotic events and the acceptable risk of bleeding, prolongation of warfarin should be considered for as long as the cancer is active. The suggested policy is to administer warfarin to maintain the INR between 2.0 and 3.0 (62).

4.3.2. Recurrence of venous thromboembolism during oral anticoagulation

The literature contains many reports of persistent or recurrent thrombosis in cancer patients despite administration of therapeutic doses of oral anticoagulants. However, the exact frequency of these failures is unknown.

Recently, we reported the data from the long-term follow-up of a large series of patients with DVT (63). All patients received oral anticoagulation for at least three months. The frequency of thromboembolic recurrences during the first three months of anticoagulation was higher in patients with cancer (table IV). These findings have been confirmed by a recent report (64).

The anticoagulation strategy in the treatment of patients with recurrent venous thromboembolism during oral anticoagulation is not rigidly standardized. Our policy is to administer a new course of full-dose (LMW) heparin, followed by a higher dose of warfarin (INR 3.0 to 4.5). We recommend the use of subcutaneous heparin in adjusted doses for patients in whom warfarin has proven to be ineffective. In patients with a very poor prognosis, it seems reasonable to replace warfarin with heparin, without waiting for the eventual failure of higher doses of warfarin. If heparin therapy fails, the only option remains the insertion of a vena cava filter.

4.3.3. Hemorrhagic risk related to anticoagulation

It is generally agreed that cancer patients are at high risk of haemorrhagic complications while receiving oral anticoagulant drugs (65). However, in our cohort of patients with DVT, the risk of bleeding during oral anticoagulant therapy was not different in patients with cancer than those without cancer (table

IV) (63). This finding is supported by a recent study (66). The practical implication of these studies is that there is no need to reduce the intensity of anticoagulation in cancer patients, as often performed in many centres because of fear of hemorrhagic complication.

4.4. Reduction of mortality

Anticoagulant treatment of cancer patients, particularly those with lung cancer, has been reported to improve survival (67). These interesting, although preliminary, results of controlled trials lend some support to the argument that activation of blood coagulation plays a role in the natural history of tumor growth.

Recently, two studies compared the effectiveness of standard heparin with LMWH in the treatment of DVT (68,69). In both studies, mortality rates were lower in patients randomised to LMWH (70). The analysis of these deaths reveals a striking difference in cancer-related mortality (table V). This difference cannot solely be attributed to thrombotic or bleeding events. Since large numbers of cancer patients were included in the studies, it seems unlikely that ones with more advanced tumors were present in the standard heparin group. While it is also possible that standard heparin increases cancer mortality, such an adverse effect has not been reported previously. These considerations suggest that LMWH might exert an inhibitory effect on tumor growth that is not apparent with standard heparin.

The evidence of lowered cancer mortality in patients on LMWH has stimulated renewed interest in these agents as antineoplastic drugs. A multicentre study with the intent of investigating this fascinating hypothesis is now being carried out.

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