Venous thrombosis in the patient with cancer

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Abstract

The relationship between cancer and thrombosis has been known for many years. Thrombotic risk is increased in the patient with cancer, and the diagnosis of venous thromboembolism at the time that a malignancy presents influences patient outcome. Risk evaluation, prophylaxis and treatment of venous thromboembolism are practical issues that face doctors who are dealing with these patients.

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Introduction

Almost 150 years ago (1865), Armand Trousseau described the clinical signs of thrombosis associated with cancer.[1] Sadly, within a year he diagnosed this in himself, and died of gastric cancer in 1867. Overall, approximately one in six patients with cancer will experience a clinical thrombotic event during the course of their disease, and between 3-25% patients who present with an idiopathic venous thrombosis are diagnosed with an active underlying malignancy. A large difference exists in different studies, depending on the level of aggressiveness of the diagnostic work-up.[2] Cytotoxic chemotherapy increases the risk of venous thromboembolism (VTE) even more. The risk of developing thrombosis is 6.5-fold in these patients, compared to 4.1-fold in patients with cancer only.[3] Similarly, patients with cancer who are undergoing surgery have a two- to threefold increased risk of developing thrombosis, compared to patients undergoing the same surgery without underlying malignancy.[4]

Various analyses, including data from registries, population-based databases and clinical trials, estimate the percentage of patients with active cancer who develop VTE to be between 1-30%. Therefore, it is necessary to individually evaluate each patient for the risk of VTE. The thrombosis may be in the form of idiopathic deep vein thrombosis (DVT) or pulmonary embolism (PE), migratory superficial thrombophlebitis (Trousseau syndrome), arterial thrombosis, disseminated intravascular coagulation, thrombotic microangiopathy, and nonbacterial thrombotic endocarditis (marantic endocarditis).[5] VTE is the second leading cause of death in patients with cancer who are receiving chemotherapy, and it is likely that it is underdiagnosed in clinical practice.[6] Although anticoagulants are highly efficacious in most patients, patients with cancer have a higher risk of recurrent thrombosis and anticoagulant-related bleeding, compared to patients without cancer.[7]

Several practical questions arise when evaluating risk, and managing thrombosis in patients with cancer.

Why are patients with cancer prone to thrombosis?

The well-known Virchow's triad of endothelial damage, stasis and hypercoagulability causing thrombosis is present in many of these patients, and each factor adds to the total thrombotic risk. Endothelial damage may be due to chemotherapy, antiangiogenic drugs and indwelling catheters, as well as changes in the endothelial cell function. These cells become more procoagulant with, among other changes, the downregulation of thrombomodulin. Stasis may be due to patients being confined to bed, and the obstruction of venous flow by large tumours and prolonged theatre time, in surgery cases. Hypercoagulability in patients with cancer has been extensively investigated, and includes causes such as the expression of tissue factor (TF or factor III in the coagulation cascade) on tumour

cells. TF expression is seen in many tumours, including melanoma, lymphoma, ovarian cancer (especially the clear cell variant), acute promyelocytic leukemia (APL), sarcoma, pancreatic and colorectal cancer and neuroblastoma.[8] It is interesting that TF expression may inversely correlate with tumour differentiation, in part possibly explaining the higher thrombotic risk in poorly differentiated tumours.[9] Cancer procoagulant is a calcium-dependent cysteine protease that is present in malignant and foetal tissue, and that activates factor X directly, and has been shown to be present in malignant melanoma, APL, as well as cancers of the kidney, breast and colon.[10] Monocytes and platelets are also activated via tumour-specific antigens, immune complexes, or cytokines, in patients with cancer. It is clear that tumour-related factors, patient's host response to the tumour, inherited patient factors, as well as treatment-related factors, all add to the prothrombotic state in patients with active cancer.

Should all patients with idiopathic DVT be screened for cancer, and what tests should be carried out?

A meta-analysis found increased detection of cancers in patients who are extensively examined when presenting with idiopathic VTE.[11] No prospective studies have been carried out to show cost-effectiveness or improved survival, and these patients should have a careful history taken (as well as family history), and undergo a complete physical examination, including a rectal examination in men, and a pelvic examination in women. Laboratory testing should include a full blood count, UK and E, liver function test, calcium, urinalysis and faecal occult blood test, and prostate-specific antigen in men over 50 years' old. Iron studies, performed in the morning preferably, may indicate an early iron deficiency. A chest radiograph should be carried out. In patients with recurrent idiopathic thrombosis, extensive examinations are indicated. The more common occult malignancies associated with idiopathic VTE include ovary, pancreas and liver, as well as renal cell, stomach and haematological cancers (lymphoma).

Does thrombosis influence the outcome in patients with cancer?

A retrospective study has shown that patients have a poorer outcome when the malignancy develops within two years after VTE is diagnosed.[12]

Are there any biomarkers or laboratory tests that predict thrombotic risk in a patient with a known malignancy?

A full blood count showing a haemoglobin less than 10g/dl, platelet count more than 300 000/ml, and white cell count more than 11 000/ml, prior to starting chemotherapy, are predictors of thrombotic risk. Neutrophilia and monocytosis indicate increased risk, especially. An increased D-dimer also indicates increased thrombotic risk. Other thrombotic markers that are not available in routine laboratories are soluble P-selectin levels, Factor VIII levels, prothrombin fragment F1 and 2, as well as TF assays, e.g. circulating TF microparticles and TF antigen levels. Recently, thrombin-generation testing has been shown to help identify patients at high thrombotic risk.[13]

Is it possible to predict the thrombotic risk of an individual patient with cancer?

All patients should be individually evaluated for risks associated with:

- The specific malignancy (site, metastasis and histological differentation)
- Patients' inherited risk [body mass index, age, inherited thrombotic tendencies, e.g. Factor V, (Leiden), gender, and history of previous thrombosis]
- Treatment-related risks (surgery, chemotherapy, erythropoietin and indwelling catheters, antiangiogenic therapy such as lenolidomide or thalidomide, hormonal therapy, and tamoxifen and bevacizuma).

Different scoring systems have been developed, such as the Khorana score[14] (Table I) and the Vienna (Ay) risk score.[15] The Vienna risk score added increased D-dimer and soluble P-selectin as two additional biomarkers to the Khorana score.

Should ambulatory patients with cancer receive primary thromboprophylaxis?

Currently, only patients with myeloma who are receiving high-dose steroid therapy combined with thalidomide or lenolidomide have the National Institute for Health and Clinical Excellence (NICE) and American Society of Clinical Oncology (ASCO)

Table I: The Khorana scoring system

Risk factor	Risk score
Site of malignancy: Stomach and pancreas	2
Site of malignancy: Lung, lymphoma, gynaecological, bladder and testicular	1
Platelet count (pre-treatment) ≥ 350 000/ml	1
Haemoglobin < 10 g/dl or erythropoietin use	1
White cell count > 11 000/ml (pre-chemo-therapy)	1
Body mass index ≥ 35 kg/m^2	1

High risk = ≥ 3, intermediate risk = 1-2, low risk = 0

recommendation for outpatient thromboprophylaxis. The National Comprehensive Cancer Network (NCCN) guidelines also state that prophylaxis should be considered in other high-risk patients. The Khorana scoring system would be helpful in identifying these patients. Because of the risk of significant bleeding, generally it is not recommended that anticoagulation therapy is given to these patients. All patients should always be assessed for bleeding risk when anticoagulation therapy is considered. Different studies (PROTECHT, CONKO-004 and FRAGEM) have shown that low molecular weight heparin (LMWH) is effective in reducing thrombotic risk, but whether the current prophylactic dosage used in other patients, is high enough in patients with malignancies, is uncertain. In the elderly, warfarin showed lower efficacy. Current ASCO recommendations are against the use of aspirin to treat venous thromboprophylaxis, but a recent study showed it to have some effect in low-risk myeloma patients. Recent NCCN guidelines state that aspirin should not be used in non-myeloma patients for VTE prevention. It is also not recommended that patients receive prophylactic anticoagulation therapy due to the presence of indwelling catheters. Very close monitoring of ambulatory patients receiving chemotherapy and anticoagulation therapy is required.

Should all hospitalised patients with malignancies receive pharmacological thromboprophylaxis?

Clinical trials, such as Prophylaxis in Medical Patients with Enoxaparin (MEDENOX), Prevention of Recurrent Venous Thromboembolism (PREVENT) and Arixtra for Thromboembolism Prevention in a Medical Indications Study (ARTEMIS), confirmed the need for medical patients at high risk of VTE to receive thromboprophylaxis. No specific randomised controlled trials in patients with cancer only have been carried out, but a percentage (5-15%) of the medical patients had malignancies. No separate bleeding complications were reported in the clinical trials. Unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) may be used. It is recommended that medical patients at high risk of VTE, such as those with malignancies, receive thromboprophylaxis. Dosages for prophylaxis may be given as fixed dosages, or weight-adjusted dosages (see Table II).

What about mechanical prophylaxis for hospitalised patients?

Mechanical prophylaxis includes aggressive mobilisation, electrical calf stimulation, venous foot pumps, graduated static compression stockings, and intermittent pneumatic compression devices. All these methods have the advantage of not increasing the risk of bleeding, and may be used in cases where the bleeding risk is temporarily too high for pharmacological thromboprophylaxis. It may also be used in addition to pharmacological thromboprophylaxis, but on its own is not adequate to prevent thromboprophylaxis in high-risk group patients. It reduces the risk of deep DVT, but not PE. The Clots in Legs or Stockings After Stroke (CLOTS) study,[16] that was carried out in medical patents with strokes, showed a non-significant absolute reduction of thrombotic risk with thigh-length compression stockings, and more skin complications such as ulcers, blisters and necrosis.

What are the contraindications for pharmacological thromboprophylaxis?

The contraindications for pharmacological thromboprophylaxis are thrombocytopenia (less than 50 000/ml), bleeding (active major, as well as chronic bleeding lasting longer than 48 hours), decreased platelet function, e.g. medication and uraemia, recent major surgery, being still at risk of bleeding, and recent central nervous system bleeding, as well as patients at a high risk of head injuries (falls). Care should also be taken with regard to spinal anaesthesia. Specific suggestions for each type of drug exist.

How should patients with cancer be prepared for surery?

Planned surgery in these patients carries a very high risk of thrombosis, and this risk persists for a long period postoperatively. Preoperative prophylaxis is indicated, and has been shown to be superior to starting prophylaxis postoperatively. Different clinical trials have shown that extended prophylaxis, up to four weeks post-surgery, is safe and effective. In the @RISTOS study that followed 2 373 patients who underwent surgery for cancer, 40% of symptomatic VTE events occurred more than three weeks after surgery, and 46% of deaths were due to PE.[17] The NCCN and ASCO guidelines both suggest that all high-risk patients should be considered for extended prophylaxis.

The NCCN defines these patients as those:

- Undergoing surgery for gastrointestinal malignancies
- Undergoing anaesthesia for more than two hours
- Partaking in bed rest for longer than four days
- In the advanced stage of the disease
- With a previous history of thrombosis
- Who are elderly (older than 60 years) and undergoing major abdominopelvic surgery.

Specific drugs and dosages for treatment are shown in Table II.

Table II: Pharmacological drugs used for prophylaxis and venous thromboembolism treatment

Drug	Prophylaxis dosage	Treatment dosage	Testing	Comment
Warfarin	According to INR rather use low molecular weight heparin	According to INR, rather use low molecular weight heparin	Regular INR testing Target INR 2-3	Difficult-to-control INR Bleeding and thrombosis, despite therapeutic INR
Clexane® (enoxaparin)	40 mg subcutaneous daily, or 1mg/kg subcutaneous daily for high-risk patients	1 mg/kg 12 hourly	Anti-Factor Xa level three hours after subcutaneous low molecular weight heparin: *Prophylaxis*: 0.3-0.5 IU/ml *Therapeutic*: 0.5-1.0 IU/ml	Suggest platelet count after 5 days
Unfractionated heparin	5 000 units 8 hourly subcutaneous	80 units/kg load, then 18 units/kg/hour, adjust according to PTT	PTT for therapy: target PTT 2-2.5 x control PTT performed 6 hours after initiation, and after each dose adjustment	Risk of heparin-induced thrombocytopenia highest (platelet counts are important)
Fragmin® (dalteparin)	5 000 units subcutaneous daily	200 units/kg daily	As with Clexane®	As with Clexane®
Arixtra® (fondaparinux)	2.5 mg subcutaneous daily	< 50 kg: 5 mg 50-100 kg: 7.5 mg > 100 kg: 10 mg		Use carefully in older patients and those with renal dysfunction

INR: international normalised ratio, PTT: partial thromboplastin time

How should a VTE be treated in a patient with a malignancy?

Patients are treated with LMWH, e.g. enoxaparin 1mg/kg twice daily, as standard therapy. LMWH is more efficacious than warfarin therapy, and reduces the risk of symptomatic recurrent VTE by 52%.[18] The NCCN guidelines also suggest that LMWH is preferred as monotherapy without warfarin, for the first six months, in patients with proximal DVT or PE, if financially possible. If patients are put on warfarin, it should overlap with LMWH as needed for at least five days, and until international normalised ratio (INR) values are more than 2. The INR control may be difficult in many of these patients, especially with nausea, vomiting and drug interaction. Up to nine per cent of patients with cancer treated with LMWH, and 20% of those treated with warfarin, can develop recurrent VTE.[19] Although randomised control trials are lacking, observational data support the use of LMWH in this setting. The recommended practice is to switch patients, who develop a recurrence while on warfarin therapy, to LMWH. Raising the intensity of warfarin therapy is not recommended. Dose escalation of LMWH appears to be effective in the majority of patients who develop a recurrence while on LMWH.[20]

Should all patients with cancer continue secondary thromboprophylaxis after a VTE?

Patients with a DVT should receive at least three to six months of anticoagulation therapy, and those with a PE, at least six to 12 months. If active cancer or persistent risk factors are present, indefinite anticoagulation therapy is indicated.[21]

What about new drugs and cancer treatment?

At present, the new oral anticoagulants (dabigatran and rivaroxiban) have not been approved for use other than in orthopaedic surgery in South Africa. Semuloparin, a new ultra-low-molecular-weight heparin was evaluated in the Prevention of Venous Thromboembolism in Cancer Patients Undergoing Chemotherapy (SAVE-ONCO) study,[22] a large study with more than 3 000 patients receiving chemotherapy for a locally advanced or metastatic solid tumour (lung, colon-rectum, stomach, ovary, pancreas or bladder cancer). This drug is a new anti-Factor Xa drug, with a higher anti-Factor Xa activity, and showed a 64% reduction, compared to placebo, in composite of symptomatic deep VTE, non-fatal PE, or VTE-related death, without increasing the risk of bleeding.

Conclusion

The relationship between cancer and thrombosis has been known for a long time. VTE has a negative predictive value in the outcome of a patient with cancer. Various factors in patients with cancer contribute to the risk, and some types of cancer have a higher thrombotic risk, including haematological malignancies, ovarian cancer, and tumours of the kidney, brain, pancreas, stomach and lungs. Although mechanical thromboprophylaxis carries much less bleeding risk, it does not protect the high-risk patient against developing a PE.

Aspirin should not be used as a pharmacological thromboprophylactic agent, except in low-risk myeloma patients. Currently, LMWH is the preferred drug for prophylaxis, as well as treatment, as it is often difficult to control the INR values in patients on warfarin who have cancer. After surgery in patients with cancer, at least seven to 10 days, and up to four weeks, of antiocoagulation is indicated. Newer drugs are being developed, such as semuloparin, to be used as prophylaxis in high-risk patients.

In summary:

- Patients with cancer are at high risk of developing a thrombotic event.
- Scoring systems are available to evaluate the ambulatory patient who is undergoing chemotherapy, but patients should be individually evaluated for tumour-related, patient-related and therapy-related risks. At present, the only absolute indication in the group of ambulatory patients who should receive thromboprophylaxis are those with myeloma on high-dose steroid therapy and thalidomide regimens.
- Mechanical prophylaxis may be used temporarily when the bleeding risk is high, but is not adequate on its own in the high-risk group of patients, and causes skin complications.
- All admitted patients with active cancer should be considered for pharmacological thromboprophylaxis, unless contraindicated.
- Patients undergoing surgery who have an underlying malignancy should be considered for pharmacological thromboprophylaxis, unless contraindicated, and extended prophylaxis is indicated.
- Treatment of VTE and PE are the same for patients without a malignancy, but LMWH is preferred as monotherapy, if possible. If active cancer or persistent risk factors are present, indefinite anticoagulation therapy must be considered.
- The following guidelines, dealing in detail with various aspects of VTE in malignancies, are available online: ASCO (www.asco.org); NCCN (www.nccn.org); NICE (www.nice.org.uk).

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