

Venous thrombosis in the cancer patient

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This summary was first published in SAJGO in 2012, but due to newer drugs available and the publication of a new guidance paper¹³ as well as the International Guideline for treatment and prophylaxis of VTE in the cancer patient,² on request of the publisher, an update is given.

Introduction

Armand Trousseau is often credited as being the first to describe the clinical sign of thrombosis associated with cancer¹ in 1865. Sadly, Trousseau within a year diagnosed this in himself and died of gastric cancer in 1867. Today, we know much more about this association, about mechanism of disease, risk stratification, prophylaxis and treatment of venous thromboembolism (VTE) in the cancer patient. Many articles and suggested guidelines have been written, but the ITAC (International initiative on Cancer and Thrombosis) group published a recent update to the **International Guideline for treatment and prophylaxis of VTE in the cancer patient**² in *Lancet Oncology* in October 2016. The initiative presents an educational platform for specialist physicians and nurses involved in the care of patients with cancer who are at risk of VTE or with established VTE, including central venous catheter-related thrombosis (CRT). Readers are strongly advised to visit the website www.itaccme.com and download the application that is available on the different smartphone operating systems.

Not only is the VTE risk increased in cancer patients (four to seven fold higher risk, depending on the stage of the cancer, histology and primary site) but cancer patients presenting with VTE have a poorer outcome than the patient with the same cancer without VTE (fourfold increase in mortality risk).³ Cancer patients are also more prone to recurrence of VTE as well as bleeding on anticoagulation therapy.³ Between 3–25% of patients who present with an idiopathic venous thrombosis are diagnosed with an active underlying malignancy (incidence varies in different studies depending on the level of aggressiveness of the diagnostic work-up) in the six months following the diagnosis of VTE,⁴ with ovarian, pancreas and liver the most common found underlying malignancies.⁵ Cytotoxic chemotherapy increases the risk for venous thrombo-embolism (1.8 fold risk increase),⁶ and surgery in the cancer patient has an approximate twofold increased risk for developing thrombosis, compared to patients undergoing the same surgery without underlying malignancy.⁷

Various analyses (data from registries, population-based databases and clinical trials) estimate the percentage of patients with active cancer that develop venous thrombo-embolism (VTE) between 1–30% and VTE is the second most common cause of death in the cancer patient.⁸ It is therefore necessary to individually evaluate each patient for VTE risk. The thrombosis may be in the form of idiopathic deep vein thrombosis or pulmonary embolism, migratory superficial thrombophlebitis (Trousseau syndrome), arterial thrombosis, disseminated intravascular coagulation, thrombotic microangiopathy and non-bacterial thrombotic endocarditis (marantic endocarditis).⁹

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

Why are cancer patients prone to thrombosis?

The well-known Virchow's triad of *endothelial damage, stasis and hypercoagulability* all play a role in many of these patients and each factor adds to the total thrombotic risk. Endothelial damage may be due to chemotherapy, indwelling catheters as well as changes in the endothelial cell function (these cells become more procoagulant with, amongst other changes, downregulation of thrombomodulin). Stasis may be due to patients being confined to bed, obstruction of venous flow by large tumours and prolonged theatre time in cases of surgery. Hypercoagulability in cancer patients has been extensively investigated and includes causes such as 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 clear cell variant), acute promyelocytic leukemia (APL), sarcoma, pancreatic and colorectal cancer and neuroblastoma.¹⁰ In a recent review article¹¹ by Mitrugno et al., several mechanisms are discussed including tissue factor expression by circulating tumour cells, malignant cells shedding procoagulant microparticles, platelet activation and generation of neutrophil extracellular traps.

It is thus 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.

How intensely should the patient with an idiopathic DVT be screened for an underlying malignancy?

A meta-analysis found an increased detection of cancers in patients who are extensively examined when presenting with idiopathic VTE (fourfold increase chance of finding an underlying malignancy compared to the provoked VTE patient).¹² Recommendations regarding extensive cancer screening in these unprovoked VTE patients are controversial, and it is unclear if extensive examination improves morbidity and mortality or patient's quality of life. In a recent guidance paper,¹³ the following recommendations are made:

- Patients with unprovoked VTE should undergo a thorough medical history and physical examination, basic laboratory investigations (complete blood counts, metabolic profile and liver function tests) and chest X-ray.
- We suggest that if not up-to-date, patients undergo age and gender-specific cancer screening (i.e. cervical, breast, prostate and colon).

The National Institute for Health Care Excellence (NICE) guidelines¹⁴ on managing VTE adds urinalysis to the above, as well as a CT abdomen/pelvis and, mammography for women, in patients aged over 40.

What risk stratification schemes are available for VTE prediction in the cancer patients?

All patients should be individually evaluated for risks associated with:

- the specific malignancy (site, metastasis, histological differentiation)
- patient's inherited risk (BMI, age, inherited thrombotic tendencies e.g. F V (Leiden), gender, history of previous thrombosis)
- treatment related risks (surgery, chemotherapy, erythropoietin, indwelling catheters, antiangiogenic therapy such as lenalidomide / thalidomide).

Biomarkers predicting VTE risk include haemoglobin, white cell count, platelet count, D-dimer value as well as less commonly available markers such as soluble P-selectin and microparticle-associated activity. Initially developed to evaluate the VTE risk in patients receiving chemotherapy, the Khorana score¹⁵ (Table 1) uses easily available markers and clinical factors to predict VTE risk. This score has also recently been evaluated in the hospitalised cancer patient.¹⁶ Two scores as expansion of the Khorana score have been proposed: the extended Vienna CATS score¹⁷ adds D-dimer and soluble P-selectin, and the PROTECH score¹⁸ includes platinum-based and gemcitabine-based chemotherapy to the predictive variables.

When should primary VTE prophylaxis be prescribed to cancer patients? Which drugs should be used?

These guidelines are suggested in the International Guideline for treatment and prophylaxis of VTE in the cancer patient² (see Table 2).

Table 1. Khorana scoring system

Risk factor	Risk score
Site of malignancy: Stomach & pancreas	2
Site of malignancy: Lung, lymphoma, gynaecologic, bladder, testicular)	1
Platelet count (pretreatment) \geq 350 000/mL	1
Haemoglobin < 10 g/dl or EPO use	1
White cell count > 11 000/ml	1
BMI \geq 35 kg/m ²	1

High risk: \geq 3, intermediate risk 1–2, low risk: 0.

a. Ambulatory patients²

- Primary prophylaxis is not recommended for ambulatory patients receiving chemotherapy.
- Exceptions are patients with
 - locally advanced or metastatic pancreatic cancer treated with systemic anticancer therapy and who have a low bleeding risk
 - or possibly patients with locally advanced or metastatic lung cancer treated with systemic anticancer therapy and who also have a low bleeding risk.
- VTE primary pharmacological prophylaxis is also recommended in the patients treated with thalidomide and lenalidomide combined with steroids or other systemic anticancer therapies (myeloma treatment).

In the medical patients, prophylactic doses of low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) are indicated.

b. Hospitalized patients²

- Cancer patients who are medically treated and hospitalised with reduced mobility should be considered for prophylaxis, taking bleeding risk into consideration.

In these patients the use of LMWH, but also UFH, or fondaparinux is suggested.

c. Cancer patients undergoing surgery²

- Postoperative VTE prophylaxis in patients with cancer undergoing surgery should be given and continued for at least 7–10 days. The recent International guidance suggests pre-operative initiation of prophylaxis (12 hours pre-operatively).
- Extended prophylaxis is indicated (4 weeks) with LMWH after major laparotomy and laparoscopic surgery in patients with cancer with a high VTE risk and low bleeding risk.
- Mechanical methods are not recommended as monotherapy, except when pharmacological methods are contraindicated.
- Inferior vena cava filters are not recommended for routine prophylaxis.

Low-molecular-weight heparin (LMWH) once per day (highest prophylactic dose) or low-dose unfractionated heparin (UFH) three times per day is recommended to prevent postoperative VTE. Insufficient evidence is available for the use of fondaparinux post-operatively.

d. Cancer patients with indwelling catheters²

- Routine VTE prophylaxis in patients with indwelling catheters is not recommended.
- To decrease VTE risk, it is suggested that catheters be inserted on the right side, in the jugular vein, with the distal extremity of the central catheter located at the junction of the superior vena cava and the right atrium.

How should VTE be treated in a patient with a malignancy? Which drugs should be used in these patients?

These guidelines are suggested in the International Guideline for treatment and prophylaxis of VTE in the cancer patient² (see Table 2).

a. Initial treatment (first 10 days)²

- Recommended treatment is LMWH, but fondaparinux and unfractionated heparin may also be used.
- Only on a case-by-case basis, thrombolysis may be considered, but a high risk of bleeding is present in these patients.
- Inferior vena cava filters are only indicated in cases where a contraindication to anticoagulation is present, or possibly in case of pulmonary embolism recurrence despite optimal anticoagulation. Anticoagulation should be resumed as soon as it is deemed safe.

b. Early maintenance therapy (10 days to 3-6 months)²

- LMWHs are preferred over vitamin K antagonists (warfarin), and should be given for a minimum of 3 months. VKAs may be considered, if LMWH cannot be used, but interaction with chemotherapy is a problem and a higher bleeding risk is present.

- Direct oral anticoagulants may be considered in patients with stable cancer not receiving systemic anticancer therapy when VKAs are considered.

c. Long term treatment (> 6 months)²

- The decision to continue or discontinue treatment is based on individual assessment. This includes activity of the malignancy, underlying risk factors (e.g. family history) that are persistently present and preference of the patient (higher value on thrombotic or bleeding event). LMWH, heparin or DOACs may be used, depending on individual contra-indications.

d. Catheter related thrombosis²

- Anticoagulant treatment is given for a minimum of 3 months and LMWHs are preferred drugs.
- The central venous catheter can be kept in place if functional, well positioned, and non-infected. Close surveillance must be kept.

e. Treatment of recurrent VTE²

- Once the VTE recurrence has been confirmed, alternative therapy should be started (in case of a patient on LMWH, an increase in dosage of 20–25% is given; the patient on VKA is switched to LMWH).

The cause should be determined, being possibly¹⁹:

- subtherapeutic anticoagulation (non-adherence, discontinuation due to recent bleeding or thrombocytopenia)
- Intrinsic resistance (heparin-induced thrombocytopenia, Trousseau's syndrome)
- Extrinsic resistance (anatomic compression).

Table 2. Pharmacological drugs used for prophylaxis and VTE treatment

Drug	Prophylaxis dosage	Treatment dosage	Testing	Comment
Warfarin	Suggested to use rather LMWH	According to INR, rather LMWH use	Regular INR testing	Difficult to control INR. Bleeding and thrombosis despite therapeutic INR.
Unfractionated heparin	5000 U 8 hourly s/c	80 U/ kg load, then 18 U/h, adjust according to PTT	PTT for therapy: target PTT 2-2.5 x control AntiFXa test	Risk of heparin induced thrombocytopenia (Suggest platelet count after 5 days)
Clexane (Enoxaparin)	40 mg s/c daily or 1 mg/kg s/c daily for high risk patients	1 mg/kg 12 hourly or 1.5 mg/kg once a day	Anti-FXa level 3 h after s/c LMWH: Prophylaxis: 0.3-0.5 IU/ml Therapeutic: 0.5-1.0 IU/ml	Consider platelet count after 5 days.
Fragmin (Dalteparin)	5 000 U s/c daily	200 U/kg daily	Anti-FXa level 3 h after s/c LMWH: Prophylaxis: 0.3-0.5 IU/ml Therapeutic: 0.5-1.0 IU/ml	Consider platelet count after 5 days.
Fraxiparine (Nadroparin)	0.3 ml (2,850 anti-Xa IU)	Target dose of 86 anti-Xa IU per kg body weight, e.g 0.4 ml bd if < 50kg, up to 0.9 ml bd if >90 kg.	Anti-FXa level 3 h after s/c LMWH: Prophylaxis: 0.3-0.5 IU/ml Therapeutic: 0.5-1.0 IU/ml	Consider platelet count after 5 days.
Arixtra (Fondaparinux)	2.5 mg s/c daily. Suggested rather use LMWH	5 mg (< 50 kg) 7.5 mg (50-100 kg) 10 mg (> 100kg)	Arixtra level may be done 3-4h post s/c	Careful with older patients and renal dysfunction. Problem with long halflife.
NOAC's: Xarelto (Rivaroxaban) Pradaxa (Dabigatran)	Not approved for use, studies being done at present	May be considered after initial treatment, if patient is stable and not receiving systemic chemotherapy.	Levels may be done.	Interaction with chemotherapy drugs a problem, as well as absorption with nausea and vomiting.

How do we manage anticoagulation in cancer patients with thrombocytopenia and VTE?

These guidelines are suggested in the International Guideline for treatment and prophylaxis of VTE in the cancer patient²

VTE Prophylaxis in a cancer patient²

- Pharmacological prophylaxis might be used in platelet count > 80 000 /mL; if the platelet count is < 80 000/mL, pharmacological prophylaxis should only be considered on a case-by-case basis and careful monitoring is recommended.

VTE Treatment in a cancer patient²

- Full doses of anticoagulant if the platelet count is > 50 000/mL and bleeding is not evident; with a platelet count < 50 000/mL, decisions on a case-by-case basis with the utmost caution.

Successful LMWH dose reductions (administering full dose enoxaparin for a platelet count > 50 000/mL, half-dose enoxaparin for a platelet count of 25 000–50 000/mL, and hold anticoagulation for a platelet count < 25 000/mL) has been shown²⁰ to be effective as well as safe.

Conclusion

The relationship between cancer and thrombosis has been known for a long time. VTE has a negative predictive value in outcome of a cancer patient. Various factors in the cancer patient contribute to the risk, including tumour-related factors, patient's inherited factors, and treatment related factors. Although mechanical thromboprophylaxis carries much less of a bleeding risk it does not protect these high risk patients from developing VTE, and LMWHs are the current standard drug to use in prophylaxis and treatment of VTE. Aspirin should not be used as pharmacological thromboprophylactic agent except in the low risk myeloma patients. VKA (warfarin) has a higher bleeding and VTE recurrence risk, as well as being difficult to control in patients receiving chemotherapy. NOACs should not be used at present for VTE prophylaxis and may only be considered for long term VTE management in stable patients not receiving active chemotherapy, where LMWH cannot be used and warfarin is considered. Post-surgical prophylaxis in cancer patients should be given for at least 7–10 days and up to 4 weeks in patients with low bleeding risk after major laparotomy and laparoscopic surgery.

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IN SUMMARY:

1. Cancer patients are at high risk of developing a thrombotic event.
2. Scoring systems are available to evaluate the ambulatory patient receiving chemotherapy, but patients should be individually evaluated for tumour-related, patient-related and therapy-related risks.
3. Mechanical prophylaxis may be used temporarily when the bleeding risk is high, but is not adequate on its own in the high risk group patients, and may have skin complications.
4. VTE prophylaxis should not be given to ambulatory cancer patients, unless specifically indicated due to other factors, or to patients with locally advanced or metastatic pancreatic cancer treated with systemic anticancer therapy and who have a low bleeding risk, or possibly patients with locally advanced or metastatic lung cancer treated with systemic anticancer therapy and who also have a low bleeding risk.
5. VTE primary pharmacological prophylaxis is also recommended in patients treated with thalidomide and lenalidomide combined with steroids or other systemic anticancer therapies (myeloma treatment).
6. All hospitalized patients with active cancer, and reduced mobility, should be considered for pharmacological thromboprophylaxis, unless contra-indicated. Bleeding risk should be evaluated in all patients receiving anticoagulation prophylaxis.
7. Patients undergoing surgery who have an underlying malignancy should receive pharmacological thromboprophylaxis for at least 7–10 days, unless contra-indicated, and extended prophylaxis may be indicated.
8. Treatment of VTE and PE are the same as for the patient without a malignancy, but LMWH is preferred as monotherapy, if possible. If active cancer or persistent risk factors are present, indefinite anticoagulation must be considered.
9. The International clinical practice guidelines including guidance for direct oral anticoagulants in the treatment and prophylaxis of venous thromboembolism in patients with cancer² is an excellent resource with downloadable free application for use on smartphones / tablets.

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