Thrombosis in Cancer

An Update on Risk Assessment, Prevention and Treatment

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Armand Trousseau, 1865

The first one who described the relation between Cancer and thrombosis

Tumour cells can trigger coagulation through different pathways, including procoagulant, antifibrinolytic and pro-aggregating activities; release of pro-inflammatory and pro-angiogenic cytokines and interaction with vascular and blood cells through adhesion molecules.

Arterial Thrombosis :

- Incidence is 1%,mostly in metastatic pancreatic, breast, colorectal and lung cancers
- The prothrombotic state may facilitate embolic events secondary to atrial fibrillation .
- Some cancer therapies, especially VEGF inhibitors, may favour thromboembolic complications .
- In patients with breast cancer under hormonal therapy, higher rates of arterial thrombotic events are reported under aromatase inhibitors compared with tamoxifen, (more favourable effects of tamoxifen on the lipid profile).

Pathophysiological mechanisms of coronary artery disease in cancer treatment :

- The mechanisms by which these drugs cause myocardial ischaemia are diverse and range from a direct vasospastic effect to endothelial injury and **acute arterial thrombosis**, to long-term changes in lipid metabolism and consequent premature arteriosclerosis . Previous mediastinal radiotherapy may accelerate drug-related coronary damage.

-Platinum compounds (cisplatin) :
Procoagulant status 2% risk of arterial thrombosis.

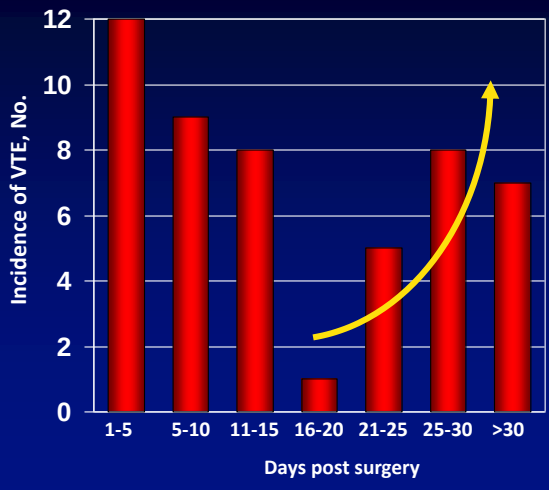
- VEGF inhibitors (bevacizumab, sorafenib, sunitinib): Risk of arterial thrombosis; bevacizumab 3.8%, sorafenib 1.7%, sunitinib 1.4% .

- The management of arterial thrombotic events in patients with cancer has been poorly addressed, and the use of antithrombotic therapies, thrombolysis and/or endovascular intervention should be discussed on a **case-by-case basis with multidisciplinary consultation involving the cardio-oncology team**, when available. In case of recurrences, control of cardiovascular risk factors and the search for anti-phospholipid antibodies has been proposed.

Venous thrombosis and thromboembolism :

- Incidence is 20% of hospitalized patients and are frequently underrecognized.
- VTE is the most common cause of death after surgery for cancer.
- Antithrombotic prophylaxis should be given for a minimum of 4 weeks after surgery.

Surgical Cancer Patients



Agnelli et al. Ann Surg 2006.

@RISTOS

Prospective cohort

N=2373

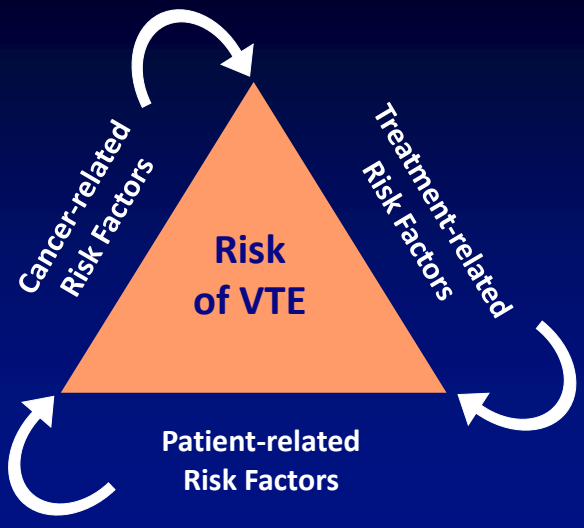
symptomatic VTE 2.1%

overall mortality 1.7%

46% due to fatal PE

- VTE is common in ambulatory patients with cancer (bladder, colon, ovary, lung, stomach and pancreas) during chemotherapy treatment; however, the role of prophylaxis is unclear. Improved patient selection and/or antithrombotic agents are required.
- The combination of chemotherapy and VEGF inhibitors increases the risk of VTE and recurrent VTE six-fold and two-fold, respectively.
- In patients with breast cancer, higher rates of VTE are reported under tamoxifen compared with aromatase inhibitors

Risk Stratification

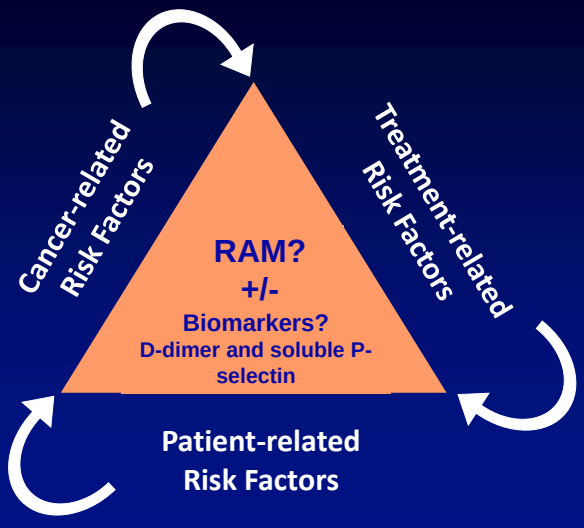


Risk Factors for VTE in Cancer

- Risk varies from 1 – 30% depending on:

Patient-related	Cancer-related	Treatment-related
• Older age • Race • Prior VTE • Platelet count • Comorbid conditions	• Primary site • Histology • Metastatic disease • Time interval since diagnosis	• Surgery • Chemotherapy • Hormonal therapy • Antiangiogenic therapy • ESA • Hospitalization • Catheters

Risk Stratification

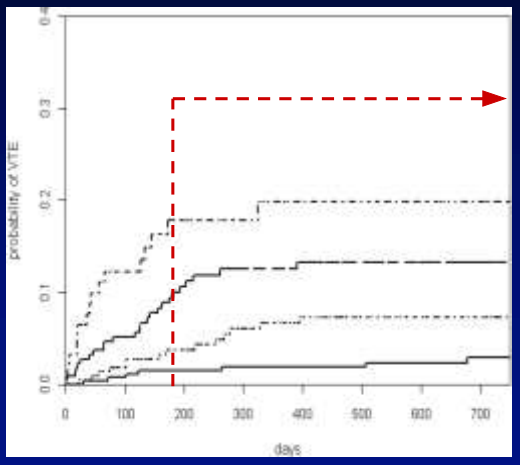


Khorana Model for Outpatients

Patient Characteristic	Score
Site of Cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, GU excluding prostate)	1
Pre-chemotherapy platelet count $\geq$ 350,000/mm^3	1
Hb < 10g/dL or use of RBC growth factors	1
Prechemotherapy leukocyte count > 11,000/mm^3	1
BMI $\geq$ 35 kg/m^2	1

Khorana Model Validation

- Prospective follow up of 819 patients
- Median observation time/follow-up: 656 days



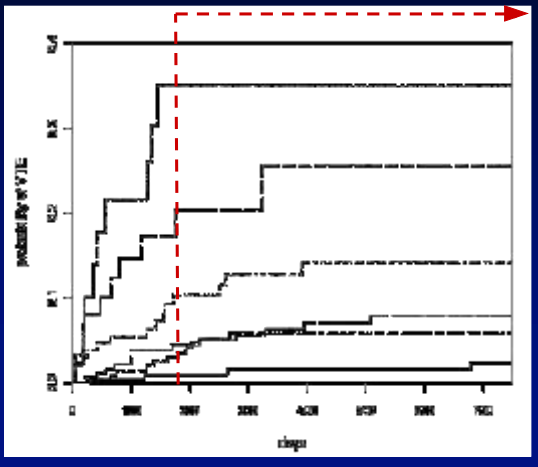
6-mo cumulative VTE rates:

	Patients n	Events %
Score ≥3	93	17.7%
Score 2	221	9.6%
Score 1	229	3.8%
Score 0	276	1.5%

Ay et al Blood 2010.

Ay Model for Outpatients

- Addition of D-dimer and soluble P-selectin to Khorana model:



6-mo cumulative VTE rates:

	Patients, n	Events, %
Score ≥5	30	35%
Score 4	51	20.3%
Score 3	130	10.3%
Score 2	218	3.5%
Score 1	190	4.4%
Score 0	200	1.0%

Ay et al Blood 2010.

Surgical Cancer Patients

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Risk factors for VTE	Odds Ratio (95% CI)
previous history of VTE	6.0 (2.1 – 16.8)
anesthesia lasting ≥ 2 hours	4.5 (1.1 – 19.0)
bed rest post-op ≥ 4 days	4.4 (2.5 – 7.8)
advanced tumour	2.7 (1.4 – 5.2)
age ≥ 60	2.6 (1.2 – 5.7)

Agnelli et al. Ann Surg 2006.

Diagnostic and therapeutic management

- The detection of thrombotic events in patients undergoing chemotherapy is based mainly on clinical symptoms.
- No systematic screening strategy has shown any benefit.
- Incidental pulmonary embolism or venous thrombosis can be detected during imaging for cancer (e.g. chest PET or CT).
- The management of these silent thrombotic events is still unclear.
- As the risk for (symptomatic) recurrence and mortality is increased, these cases are usually treated in a similar manner to symptomatic VTE

- The decision to administer anticoagulation for VTE prevention in patients with cancer should always take into consideration the patient's bleeding risk (6 times higher) and life expectancy; these may change over time, requiring periodic reassessment.

- Treatment of a confirmed episode of acute VTE in haemodynamically stable patients consists of LMWH given over a period of 3 –6 months. This strategy is superior to VKA therapy in patients with cancer in terms of reduced VTE events, with no difference regarding mortality or bleeding in clinical trials

chronic anticoagulation after the acute phase of treatment, and until the cancer is considered cured :

- The choice of anticoagulation discontinuation or maintenance under LMWH or switching to VKAs should be discussed on an individual basis after considering the cancer therapy success, the risk of VTE recurrence and bleeding, as well as the patient's preference.

- Current data on NOACs are limited (subgroup analysis)
- Results from specific trials involving NOACs in patients with cancer are awaited.
- No comparison between NOACs and LMWH is currently available.
- Different NOACs may differ because of potential drug interactions and sensitivity to renal or hepatic dysfunction

- Recurrent VTE may still occur despite VKA or LMWH therapy in patients with cancer, and may be managed by switching from VKA to LMWH or increasing the LMWH dose.

- Vena cava filter may be implanted (2b) when anticoagulation is contraindicated or failing. However, the risk of filter thrombosis and occlusion leading to distal propagation of thrombosis with PTS should be considered. No clinical advantage was found in the systematic placement of a vena cava filter in addition to anticoagulation with fondaparinux in patients with cancer

- **There is no conclusive evidence on the benefits of thrombolysis in case of haemodynamically unstable pulmonary embolism in patients with cancer**
- Thrombolysis may still be considered (2b) .
- It is important to keep in mind contraindications to fibrinolytic therapy in patients with brain tumours or metastasis.
- Surgical embolectomy (2b) but surgery imparts significant morbidity, and cardiopulmonary bypass requires aggressive anticoagulation.

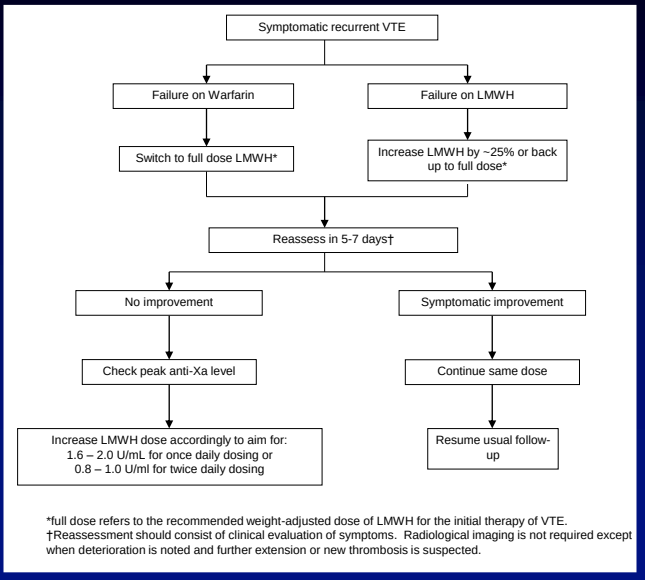
Prevention of thromboembolic events:

- Currently, primary prevention, mainly LMWH, should be proposed in high-risk ambulatory patients receiving chemotherapy (with multiple myeloma receiving anti-angiogenic agents or locally advanced or metastatic pancreatic or lung cancers) with low bleeding risk. (2a)

- Hospitalized patients, several guidelines advocate the use of thromboprophylaxis, although a recent meta-analysis of subgroups of trials including patients with cancer hospitalized for medical conditions failed to find evidence of any global benefit or risk of primary thromboprophylaxis. (MEDENOX trial)
- Studies are underway to validate thromboprophylaxis based on risk factors and biomarkers.
- Meanwhile, it is reasonable to consider thromboprophylaxis with LMWH based on individual benefit– risk assessments.

- For patients with **central venous catheters**, there is a reduction in symptomatic deep vein thrombosis with the use of heparin and of asymptomatic deep vein thrombosis with VKA compared with no anticoagulation. However, heparins are associated with a higher risk of thrombocytopaenia and asymptomatic deep vein thrombosis compared with VKA, and therefore treatment decisions should be individualized.

Approach to Recurrent VTE



Lee. Hematology Education Program Book 2014.

Thrombosis in Cancer Summary

- VTE is a very common complication that increase morbidity and mortality in cancer patients
- Use a validated RAM to estimate risk of VTE in ambulatory patients with new or progressive disease
- Selected cancer patients benefit from extended prophylaxis after surgery
- Prophylaxis in hospitalized patients is a patient safety priority
- LMWH is the “best” agent available for prevention and treatment