Review Article

Thrombotic Risk in Cancer Patients: Diagnosis and Management of Venous Thromboembolism

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Abstract

Venous thromboembolism (VTE) represents a major health problem, especially in cancer patients, who experience a significantly higher incidence of both deep vein thrombosis and pulmonary embolism compared to the general population. Indeed, patients with cancer have a prothrombotic state resulting in both increased expression of procoagulants and suppression of fibrinolytic activity. In addition, VTE increases the morbidity and mortality of these patients. For all these reasons, the prevention and treatment of VTE in cancer setting represent major challenges in daily practice. In general, low-molecular-weight heparin monotherapy is the standard of care for the management of cancer-associated VTE, as Vitamin K antagonists are less effective in this setting. Direct oral anticoagulants offer a potentially promising treatment option for cancer patients with VTE, since recent studies demonstrated their efficacy and safety also in this peculiar setting.

Keywords: Cancer, direct oral anticoagulants, imaging, prevention, venous thromboembolism

Introduction

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a significant health problem with an estimated annual incidence of approximately 1–2 per 1000 people among the general population.[1]

Cancer represents an independent and major risk factor for VTE, accounting for about 18% of the total number of VTE cases.[2] Indeed, the estimated risk of developing VTE is approximately 4–6.5-fold higher in cancer patients compared to the general population, contributing significantly to their morbidity and mortality.[3] Thrombosis, in fact, represents the second leading cause of death in oncological patients.[4]

Thus, the most challenging aim for physicians will be to improve the awareness for an early detection and a correct management of VTE in order to prevent mortal complications.

Pathophysiology

Despite the association between cancer and thromboembolism was first reported by trousseau in the 19th century,[5] nowadays, its pathophysiology is still not entirely understood.

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Patients with cancer have a prothrombotic state resulting from the synergic activity of factors involved in the so-called Virchow's triad: first of all, stasis of the blood caused by bed rest or by the tumor compression, and second, vascular injury related to chemotherapy- and surgery-induced endothelial damage and a cancer-induced state of hypercoagulability itself.

In fact, cancer cells release coagulant factors such as tissue factor and inflammatory cytokines, which affect the hemostasis process, including platelet functions and clotting cascade.[6] This context represents a substrate favoring the development of deep vein thrombosis and PE.

Risk Stratification

Oncological patients should be periodically assessed for VTE risk. There is full agreement in literature about risk factors for

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cancer-related VTE that may be divided into three categories: cancer-related, treatment-related, and patient-related factors.

Cancer-related factors

Several studies demonstrated how the site of the primary tumor is an important risk factor for VTE. Particularly, the highest rates of VTE have been described in patients with primary brain tumors,[7] pancreatic,[8] stomach,[9] uterine,[10] and lung carcinomas.[11] A high incidence rate of VTE has been recently described also in association with hematologic malignancies.[12] Moreover, the stage of cancer is also important, since advanced stages confer an increasing risk.[3]

Treatment-related factors

Chemotherapy itself is associated with a 2–6-fold increase in the risk of VTE compared to the general population, accounting for 9% of deaths in patients starting new chemotherapeutic treatments.[13] Some chemotherapy agents appear to confer greater risk than others. Patients with multiple myeloma receiving thalidomide in combination with dexamethasone, for example, have a risk of developing DVT of about 28%.[14]

Behind chemotherapy, in hospitalized cancer patients, it is often necessary to transfuse blood and platelet products, both associated with an increased risk of thromboembolic events.[15] Central venous catheters, widely used in patients with cancer for the administration of chemotherapy, may also contribute to clot formation. A recent study showed that the incidence of symptomatic catheter-related DVT in adults is in a range from 0.3% to 28%, whereas catheter-related DVT screened by venography is from 275% to 66%.[16]

Patient-related factors

The overall risk of VTE is often influenced by a multitude of patient-related factors, including a history of prior thrombotic events, comorbid conditions, genetic factors, immobility, age, sex, and race. Particularly, both prior and concurrent thrombotic events, either venous or arterial, significantly increase future thrombotic risk in a wide range of cancer patients.[17] Probably, locally occurring thrombotic events may propagate pathways that result in systemic hemostatic activation. In addition, a detailed family history can underlie a number of predisposing genetic factors, such as Factor V Leiden and prothrombin gene mutations, known to confer an increased risk of VTE in oncological patients when compared to those without the mutations.[18]

Predictive models have been established to assess the probability of developing VTE according to risk factors. The "Khorana score," for example, has been conceived to estimate the risk of VTE in ambulatory cancer patients receiving chemotherapy.[19] This score includes five predictive variables [Table 1]: tumor type (stomach or pancreatic cancer, +2 points), prechemotherapy hemoglobin level of <10 g/dL or use of erythropoietin-stimulating agents (+1 point), prechemotherapy leukocyte count >11 × 10^9/L (+1 point), prechemotherapy platelet count ≥350 × 10^9/L (+1 point), and a body mass index ≥35 kg/m^2 (+1 point).

Table 1: Khorana score: A predictive model for chemotherapy-associated venous thromboembolism

Patient characteristics	Risk score
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
Prechemotherapy platelet count ≥350×10^9/L	1
Prechemotherapy leukocyte count >11×10^9/L	1
Hemoglobin level <100 g/L or use of red cell growth factors	1
BMI ≥35 kg/m^2	1

BMI=Body mass index

Patients with a Khorana score >3 are considered at high risk for developing blood clots and may benefit from prophylactic anticoagulation.

Diagnosis and Evaluation

Deep vein thrombosis

Classic symptoms of lower extremity deep venous thrombosis (DVT) include pain, swelling, redness, warmness, and engorged superficial veins. However, many cancer patients with VTE may show no evident symptoms at presentation. More often, their signs might be masked by the underlying malignancy.[20]

D-dimer is a nonspecific marker of ineffective endogenous fibrinolysis and is elevated in VTE, as well as other systemic illnesses and conditions such as surgery and pregnancy. Thus, D-dimer is most useful in the evaluation of outpatients with suspected VTE because inpatients will frequently have elevated levels secondary to other conditions.[21]

For decades, venography represented the imaging test of choice for suspected DVT in the legs, pelvis, and inferior vena cava. On conventional venography, clot is identified as a filling defect. Potential problems with this technique include the need for the patient to travel to a radiology department, difficulty in obtaining venous access, pain from the procedure, contrast reactions, interobserver disagreement, technical limitations, and paradoxical postprocedure DVT in a minority of patients. With the introduction of ultrasound (US) in the 1980s, venography is almost never used for diagnosis alone, but in conjunction with therapeutic procedures, and has occasional use for upper extremity and central thoracic DVT imaging.[22]

Thus, venous US is nowadays the imaging test of choice in the first evaluation of suspected DVT.[23] It is useful for screening and to confirm/rule out DVT in both symptomatic and asymptomatic patients. Venous duplex US combines vein compression (B-mode imaging) and pulsed Doppler spectrum analysis with and without color. To diagnose directly, a clot is not always successful because clot echogenicity is variable and unpredictable, and a fresh clot is often anechoic [Figure 1]. With compression US, veins are compressed with the probe; in the absence of a DVT, a mild pressure with the probe causes

the venous lumen to collapse. The lack of compressibility of a venous segment under the probe, on the contrary, is diagnostic for DVT [Figure 2]. Color Doppler may serve as an additional technique in the diagnosis of thrombosis. It provides the visualization of flow, color-coded for velocity and direction; absent or partially absent color-coded flow is diagnostic for thrombosis. Using Doppler, proximal vein segments in the pelvis and abdomen that are difficult to assess with CUS may be evaluated.[24]

The advantages of US include very high accuracy for thigh and arm evaluation for acute DVT, relatively low cost, portability, absence of ionizing radiation, and ready repeatability. Anatomic limitations hinder the ultrasonographic evaluation of the pelvic veins and the upper extremity veins proximal to the clavicle.[23]

Alternative imaging modalities for assessment of patients with suspected acute DVT include computed tomography (CT), magnetic resonance, and contrast venography, when the evaluation by venous US is inconclusive.[24]

Pulmonary embolism

Like DVT, a high clinical suspicion is required, especially in patients with VTE risk factors such as cancer patients, to make a timely diagnosis of PE.

Clinical predictive models such as the Wells' criteria have been evaluated and were proven useful in the diagnosis of VTE.[25] Thus, Wells' criteria can be used to rapidly assess the likelihood of PE at the bedside. A score of 4.0 or lower makes PE unlikely (PE risk <5%). The seven features are:

1. Clinical signs and symptoms of DVT (3 points)
2. An alternative diagnosis is less likely than PE (3 points)
3. Heart rate >100 bpm (1.5 points)
4. Immobilization or surgery in the preceding 4 weeks (1.5 points)
5. Prior VTE (1.5 points)
6. Hemoptysis (1 point)
7. Cancer treated currently or within the previous 6 months or palliative (1 point).

However, in patients with cancer, it is unclear whether this scoring system is valid because only a minority of patients with cancer were included in models of this score.

Thus, the diagnosis of acute PE remains often challenging because the disease is characterized by a wide spectrum of clinical presentation ranging from pleuritic pain or dyspnea to cardiac arrest and is strongly influenced by the grade of the pulmonary pressure increment, leading to overload and systolic dysfunction of the right ventricular. Anyway, the classic clinical signs include unexplained shortness of breath, chest pain, tachycardia, apprehension, tachypnea, syncope, and hypoxia.[26]

Contrast-enhanced chest CT is the predominant diagnostic imaging technique for the evaluation of suspected PE [Figure 3]. The enhanced resolution of newer multidetector CT scanners

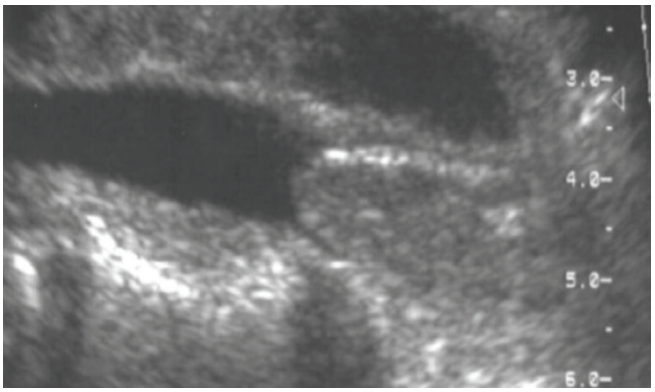

Figure 1: A fresh anechoic clot

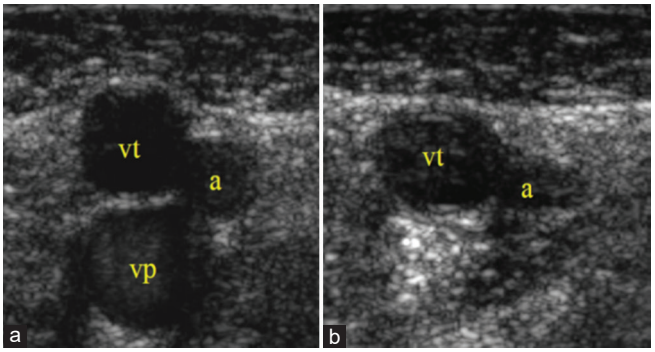

Figure 2: The lack (a) and the presence (b) of compressibility of a venous segment under the probe, the first diagnostic for deep vein thrombosis

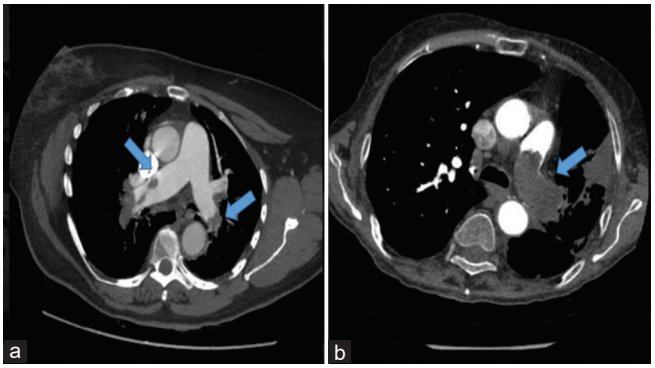

Figure 3: Contrastenhanced chest computed tomography of pulmonary embolism; arrows show bilateral (a) and left main pulmonary artery (b) embolism

increased the detection rate of subsegmental PE and reduced the frequency of nondiagnostic studies when compared with older single-detector model.[27]

Echocardiography is useful in detecting right ventricle (RV) dysfunction in the setting of PE with advanced RV pressure overload. Typical echocardiographic findings among patients with acute PE include RV dilation and hypokinesis, paradoxical interventricular septal motion toward the left ventricular, tricuspid regurgitation, and pulmonary hypertension. Regional RV dysfunction with severe free wall hypokinesis and apical sparing (McConnell sign) is a specific finding for PE [Figure 4].[28] Although poor sensitive for diagnosis,

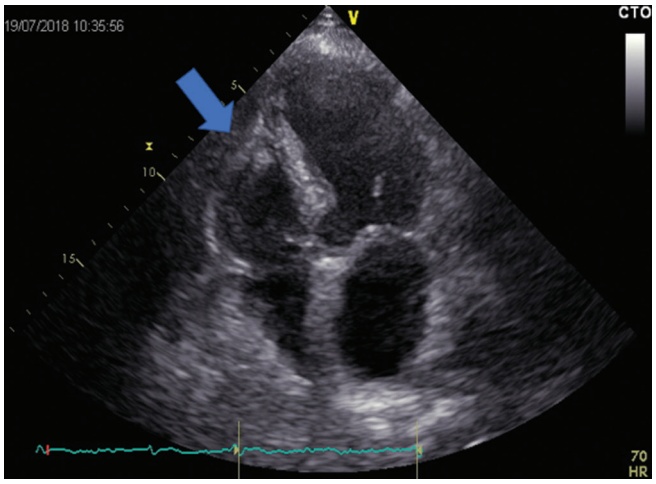

Figure 4: Transthoracic echocardiography can show regional right ventricle dysfunction with severe free wall hypokinesis and apical sparing (McConnell sign) as a specific finding for pulmonary embolism

transthoracic echocardiography is crucial for risk stratification in patients with proven acute PE.[29]

Prevention and Treatment

The prevention and treatment of VTE in cancer patients represent major challenges in daily practice. In general, all of the treatment options for primary prevention and acute treatment of VTE in the general population are potentially also available for cancer patients with VTE [Table 2]. Actually, oncological patients often present a variety of risk factors and comorbidities, making difficult the appropriate management of VTE.[30] In addition, not only the risks of recurrent thrombosis but also those related to increased bleeding are higher among patients with cancer than those without cancer; both significantly contribute to hospitalization, morbidity, and mortality and may interfere with cancer treatment.[4]

Treatment of established venous thromboembolism and secondary prophylaxis

Traditionally, Vitamin K antagonists (VKAs) has been considered the treatment of choice in the management of VTE.[31] Particularly, the standard treatment consists of initial therapy with low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) followed by long-term therapy with an oral anticoagulant as secondary prophylaxis. However, in cancer patients, VKA treatment is associated with an increased risk of recurrence of thrombosis and higher rates of bleeding compared to the general population.[32]

Thus, the efficacy and safety of parenteral anticoagulants in cancer patients have been investigated in numerous clinical trials with generally favorable results.[33-35] A recent meta-analysis[36] of these clinical trials reported that LMWH was associated with a reduced risk of recurrent VTE and no difference in the risk of major bleeding relative to VKA in cancer patients who experienced an acute VTE episode.

Table 2: Potential treatment options in venous thromboembolism

Treatment options	Route of administration
VKA (warfarin, acenocoumarol)	Oral
Unfractionated heparin	Parenteral
Low-molecular-weight heparin (dalteparin, enoxaparin)	Parenteral
Indirect factor Xa inhibitors (fondaparinux)	Parenteral
DOAC - Direct thrombin inhibitors (dabigatran)	Oral
DOAC - Direct factor Xa inhibitors (apixaban, rivaroxaban, edoxaban)	Oral

VKA=Vitamin K antagonists, DOAC=Direct oral anti-coagulant

Currently, guidelines agree in using LMWH as the first choice in the management of established VTE in cancer patients.[37-43] Treatment is recommended for the initial 5–10 days of treatment for patients with established deep vein thrombosis and/or PE and should be continued for 3–6 months, or indefinitely, as long as there is clinical evidence of active malignant disease. In patients with complete remission, treatment can be stopped after 6 months. In patients with active cancer (for example, the presence of metastatic disease and/or ongoing anticancer treatment), treatment can be continued beyond 6 months.

Indeed, recently, the DALTECAN (dalteparin sodium for the long-term management of VTE in cancer patients) study, following patients with active cancer and newly diagnosed VTE treated with dalteparin for 12 months, showed that the incidence of major bleeding and recurrent VTE with LMWH was similar between 7 and 12 months and 2–6 months.[44]

Venous thromboembolism primary prophylaxis

Studies report the prophylactic use of anticoagulant agents to be safe and effective in decreasing VTE-related mortality/morbidity, especially in postoperative cancer patients.

Current guidelines[37-43] recommend either LMWH, UFH, or, in some cases, fondaparinux in the primary thromboprophylaxis of most hospitalized patients with cancer during hospitalization. Particularly, guidelines recommend that patients undergoing major cancer surgery should receive prophylaxis starting dose before surgery and continuing for at least 7–10 days. Extending postoperative prophylaxis up to 4 weeks should be considered in those with high-risk features. On the other hand, thromboprophylaxis is not routinely recommended for ambulatory patients with cancer undergoing chemotherapy; in this case, it may be considered for very select high-risk patients, such as in solid tumors or in myeloma patients receiving immunomodulatory agents.

Direct oral anticoagulants in cancer patients

Direct oral anticoagulants (DOACs) represent a new important therapeutic goal in the management of thrombosis-related problems. Unlike parenteral anticoagulants, DOACs, including direct thrombin inhibitors such as dabigatran and direct factor Xa inhibitors such as apixaban, rivaroxaban, and edoxaban, offer the convenience of oral administration and have more predictable pharmacodynamics, besides requiring less frequent

laboratory monitoring than VKAs.[45] Although these agents are now used for the treatment of VTE in the general population, for cancer patients most guidelines continue to recommend LMWH monotherapy for at least 3–6 months after an acute episode, owing to the lack of sufficient clinical data in patients with cancer.[37-43] Actually, it is important to underline that these old guidelines, still based on previous evidence in literature, will be soon revised, taking into account the more recent favorable results about the use of DOAC in the prevention and treatment of VTE in oncological patients.

In fact, in the pivotal phase 3 clinical trials for DOACs in acute treatment of VTE, only approximately 6% of the patients had active cancer; of those patients, approximately 20%–30% had metastatic cancer and approximately 30% were receiving chemotherapy.[46-49] As such, the patient population included in these trials was nonrepresentative of the patient population at risk for cancer-associated VTE. However, two small studies directly assessing the safety of DOACs in primary or secondary prevention of cancer-associated VTE showed that both apixaban[50] and dabigatran[51] versus placebo and acenocoumarol, respectively, were safe and efficacy in preventing VTE in patients with metastatic cancer.

More recently, the largest trial published to date in this patient population, the HOKUSAI-VTE Cancer study, compared the use of dalteparin with edoxaban in patients with cancer diagnosed with an acute symptomatic or incidental VTE.[52] This is an open-label, noninferiority, randomized clinical trial of 1050 patients that assigned participants to receive either subcutaneous dalteparin for 5 days followed by oral edoxaban 60 mg or 30 mg once daily based on the Summary of Product Characteristics or a single subcutaneous dalteparin 200 units/kg injection daily for 1 month. After 1 month, the dalteparin dose was reduced to 150 units/kg once daily for the remainder of the study period. Both arms of the study were treated for at least 6 months, up to a maximum of 12 months. The primary outcome was a composite of VTE recurrence or major bleeding, based on the International Society on Thrombosis and Hemostasis definition, during the 12-month study period. This study found that edoxaban was noninferior to dalteparin in the primary composite outcome of recurrent VTE or in major bleeding at 12 months. There was a nonsignificant reduction in the recurrence of VTE in the edoxaban group, coupled with a higher rate of major bleeding. Bleeding was primarily seen in patients with gastrointestinal cancers, whereas a subgroup analysis showed no difference in bleeding in patients without gastrointestinal cancers.

Moreover, another recent trial, the Select-D study, showed favorable results in favor of DOAC use in this peculiar setting.[53] Select-D is a prospective, randomized, open-label, multicenter pilot trial randomizing 406 cancer patients with acute VTE to dalteparin (200 units/kg injections daily in month 1 and 150 units/kg daily in months 2–6) and rivaroxaban (15 mg twice daily for 3 weeks, and then 20 mg once daily, for 6 months in total). The 6-month rates of recurrent VTE were 11% and 4% for patients receiving dalteparin and rivaroxaban, respectively, whereas major bleeding rates were similar between the two subgroups; gastric/esophageal cancer patients were especially at risk for major bleeding, and these patients were excluded toward the end of the study.

Indeed, a meta-analysis of the two previous randomized controlled trials (RCTs)[54] showed that rates of recurrent VTE in patients who received DOACs were lower when compared with LMWH, but this outcome was paired with an increased risk of bleeding, specifically in patients with gastrointestinal cancers. Improved compliance with DOACs compared with LMWH was noted to explain the differences in the effectiveness and safety of the two interventions.

According to all these new evidence-based results, nowadays, in multiple guidelines, data suggest that edoxaban or rivaroxaban may be reasonable alternatives to LMWH for cancer patients with an acute diagnosis of VTE. The National Comprehensive Cancer Network guidelines,[55] for example, recommend the use of edoxaban or dalteparin as the first choice in this kind of patient. Moreover, the Associazione Italiana Di Oncologia Medica guidelines[56] for solid tumors suggest the use of heparin followed by DOACs as a first therapeutic option in patients affected by Venous thromboembolism (VTE), with a strong positive recommendation; edoxaban and rivaroxaban as a first therapeutic option in TEV treatment, but with a weak positive evidence; and only heparin and edoxaban for the prolongation of treatment beyond 6 months. In addition, the ISTH Scientific and Standardization Committee on Hemostasis and Malignancy[57] confirmed the efficacy and safety of the use of edoxaban or rivaroxaban in this peculiar setting, with attention to carcinomas and clinical conditions with high risk of bleeding.

Of note, it is important to underline that currently edoxaban and rivaroxaban are the only DOACs that have been compared with LMWH in RCTs in cancer populations; given the differences in anticoagulant mechanisms and in metabolic clearance, a class effect of DOACs should not be readily assumed. In addition, the efficacy and safety of the use of DOACs in cancer patients with intake difficulties and/or absorption of orally administered drugs has not yet been fully demonstrated. Similarly, the possible drug interactions between DOACs and chemotherapeutic drugs, especially for cytochrome- and glycoprotein P-inducing/inhibiting drugs, are currently poorly explored.

Hence, the use of DOACs in cancer population will likely be increasing in the near future soon, especially when further investigation will further confirm the already established efficacy and safety in this peculiar setting.

The PE guidelines published recently[58] suggest that patients with acute PE and cancer, particularly those with gastrointestinal cancer or severe renal insufficiency, and those where oral treatment is not possible due to intake or absorption problems, should be encouraged to continue LMWH for

3–6 months. In all other cases, especially in patients with a low expected risk of bleeding, the choice between LMWH and edoxaban or rivaroxaban, it is left to the discretion of the physician's and the patient's preferences.

Conclusions

The correct management of VTE in cancer patients represents several difficulties in daily practice. Diagnosis could be challenging because the disease presents a variety of clinical signs that could be masked by the underlying malignancy. Regarding the optimal treatment, LMWH monotherapy is the standard of care for the management of cancer-associated VTE, as VKAs are less effective in cancer patients. DOACs offer a potentially promising treatment option for cancer patients with VTE, since recent studies demonstrated their efficacy and safety also in this peculiar setting.

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Conflicts of interest

There are no conflicts of interest.

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