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Cancer-Associated Thrombosis: An Overview

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ABSTRACT: Venous thromboembolism (VTE) is a common complication in patients with malignant disease. Emerging data have enhanced our understanding of cancer-associated thrombosis, a major cause of morbidity and mortality in patients with cancer. In addition to VTE, arterial occlusion with stroke and anginal symptoms is relatively common among cancer patients, and is possibly related to genetic predisposition. Several risk factors for developing venous thrombosis usually coexist in cancer patients including surgery, hospital admissions and immobilization, the presence of an indwelling central catheter, chemotherapy, use of erythropoiesis-stimulating agents (ESAs) and new molecular-targeted therapies such as antiangiogenic agents. Effective prophylaxis and treatment of VTE reduced morbidity and mortality, and improved quality of life. Low-molecular-weight heparin (LMWH) is preferred as an effective and safe means for prophylaxis and treatment of VTE. It has largely replaced unfractionated heparin (UFH) and vitamin K antagonists (VKAs). Recently, the development of novel oral anticoagulants (NOACs) that directly inhibit factor Xa or thrombin is a milestone achievement in the prevention and treatment of VTE. This review will focus on the epidemiology and pathophysiology of cancer-associated thrombosis, risk factors, and new predictive biomarkers for VTE as well as discuss novel prevention and management regimens of VTE in cancer according to published guidelines.

KEYWORDS: cancer, thrombosis, management, low-molecular-weight heparin

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Introduction

Historically, in 1823, the French physician Jean-Baptiste Bouillaud published what appears to be the first report of an association between cancer and thrombosis.[1] In 1865, another French physician Armand Trousseau reported an association between gastric cancer and venous thrombosis.[2] These reports considered the beginning of attention that malignant disease and hemostasis interact together.

Currently, cancer and its treatments are well-recognized risk factors for venous thromboembolism (VTE). Evidence suggests that the absolute risk depends on the tumor type, the stage of the cancer, and treatment with antineoplastic agents.[3]

Venous manifestations of cancer-associated thrombosis include deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as visceral or splanchnic vein thrombosis, together described as VTE. In addition to VTE, arterial occlusion with stroke and anginal symptoms is relatively common among cancer patients, and is possibly related to genetic predisposition.[4]

Several risk factors for developing venous thrombosis usually coexist in cancer patients including surgery, hospital admissions, and immobilization; the presence of an indwelling central catheter; chemotherapy; and new molecular targeted therapies.[5,6] Furthermore, other comorbid features will also influence the overall of thrombotic complications, as they do in patients without cancer.[3]

In addition to the above-mentioned clinical factors, the presence of tumor cells induces a hypercoagulable state.[7] More recently, novel risk factors, including platelet and leukocyte

counts and tissue factor (TF), are associated with high risk of VTE in cancer patients.[8] Furthermore, cancer-associated thrombosis is linked with poor prognosis, and it is the second leading cause of death in cancer patients.[9,10]

Effective prophylaxis and treatment of VTE reduced mortality and morbidity, and improved quality of life. Low-molecular-weight heparin (LMWH) is preferred as an effective and safe means for prophylaxis and treatment of VTE. It has largely replaced unfractionated heparin (UFH) and vitamin K antagonists (VKAs).[11]

This brief review will focus on the epidemiology and pathophysiology of cancer-associated thrombosis, risk factors, and new predictive biomarkers for VTE as well as discuss novel prevention and management strategies of VTE in cancer.

Epidemiology of Cancer-Associated Thrombosis

Cancer patients are characterized by an acquired thrombophilic condition predisposing to increased risk of VTE.[12] VTE in patients with cancer may present as a vast range of clinically significant thrombotic complications including DVT, PE, arterial thrombosis, nonbacterial thrombotic endocarditis, superficial thrombophlebitis, catheter-related thrombosis, and hepatic veno-occlusive disease.[13–15]

It is well established that cancer patients are at an increased risk of VTE; the risk of VTE is four-fold to seven-fold higher in patients than in those without cancer[16] the reported incidence varies widely between studies depending on patient population, start and duration of follow-up, and the method of detecting and reporting thrombotic events.[17] The recent meta-analysis by Horsted et al described incidence rates of venous thrombosis in cancer patients, stratified by background risk of venous thrombosis; the incidence among cohorts with average-risk patients was estimated to be 13 per 1000 person-years (95% CI: 7–23). Among cohorts with high-risk patients, the overall incidence rate was 68 per 1000 person-years (95% CI: 48–96).[18]

It is estimated that about 4–20% of patients with cancer experience venous thrombosis[9] with the annual incidence of 0.5% in them compared to 0.1% in the general population.[19] Overall, cancer patients constitute 15–20% of the patients diagnosed with VTE.[20]

VTE and thrombotic complications are the second most frequent cause of mortality in patients with cancer.[14] Several studies have showed that the incidence of VTE is associated with the duration of the underlying illness. The highest rate of VTE is seen in the initial period after diagnosis,[21,22] and mortality from VTE is highest in one year after diagnosis.[23]

The heterogeneity of the studies makes it difficult to compare rates of venous thrombosis between these studies; but over the years, the incidence of VTE in cancer is on the rise.[24] Novel anti-cancer drugs, particularly antiangiogenic agents, may be contributing to this increase.[25,26] VTE in cancer is associated with a 21% annual risk of recurrent VTE, a 12% annual

risk of bleeding complications, requirement of long-term anticoagulation, and interruption of chemotherapy.[27,28]

A high incidence of VTE following chemotherapy was reported in cancers.[29] Chemotherapy increased the risk of VTE and recurrent VTE six-fold and two-fold, respectively, in patients with cancer, and it is estimated that the annual incidence of VTE in cancer patients undergoing chemotherapy is about 10.9%.[14]

Pathophysiology and Risk Factors for Cancer-Associated Thrombosis

The pathophysiology of cancer-associated thrombosis is not entirely understood. The hypercoagulable state in cancer involves several complex interdependent mechanisms (Fig. 1), including interaction among cancer cells, host cells, and the coagulation system.[30] Key roles in pathophysiology are played by TF, inflammatory cytokines, and platelets. Tumor cells can activate blood coagulation through multiple mechanisms, including production of procoagulant, fibrinolytic, and proaggregating activities; release of proinflammatory and proangiogenic cytokines; and direct interaction with host vascular and blood cells through adhesion molecules.[7] Novel risk factors include platelet and leukocyte counts and TF.[8]

Many tumors have been shown to activate blood coagulation through an abnormal expression of high levels of the procoagulant molecule TF.[31] In normal vascular cells, expression of TF is normally not expressed, except when induced by inflammatory cytokines or by bacterial lipopolysaccharides. In tumor cells, TF is expressed constitutively. Constitutive activation of the extrinsic pathway has been shown in patients with cancer. In a study conducted by Kakkar et al.[32] plasma levels of TF, factor VIIa, factor XIIa, the thrombin–antithrombin complex, and prothrombin fragments were elevated in patients with cancer compared with those in healthy controls. TF and factor VIIa levels were both significantly higher, suggesting that the extrinsic pathway was strongly activated. Levels of factor XIIa were only slightly elevated, suggesting that the intrinsic pathway is not involved to a significant extent in the hypercoagulable state seen in patients with cancer.[33] Also, Hoffman et al.[34] revealed that the majority of patients with cancer have increased levels of coagulation factors V, VIII, IX, and XI as well as increased levels of markers of coagulation activation.

The risk factors associated with the development of thromboembolic complications can be divided into patient characteristics, tumor factors, and treatment-related factors (Table 1).[35] Patient characteristics include old age; female sex; black ethnicity; elevated D-dimer levels; C-reactive protein and soluble P-selectin (sP-selectin); platelet count over 350×10^6/L or leukocyte count over 11×10^6/L; prothrombotic mutations, factor V Leiden, and prothrombin 20210A;[23,35–37] and commonly recognized risk factors for the development of thromboembolism, such as obesity and a history of VTE. Tumor-related factors include anatomical
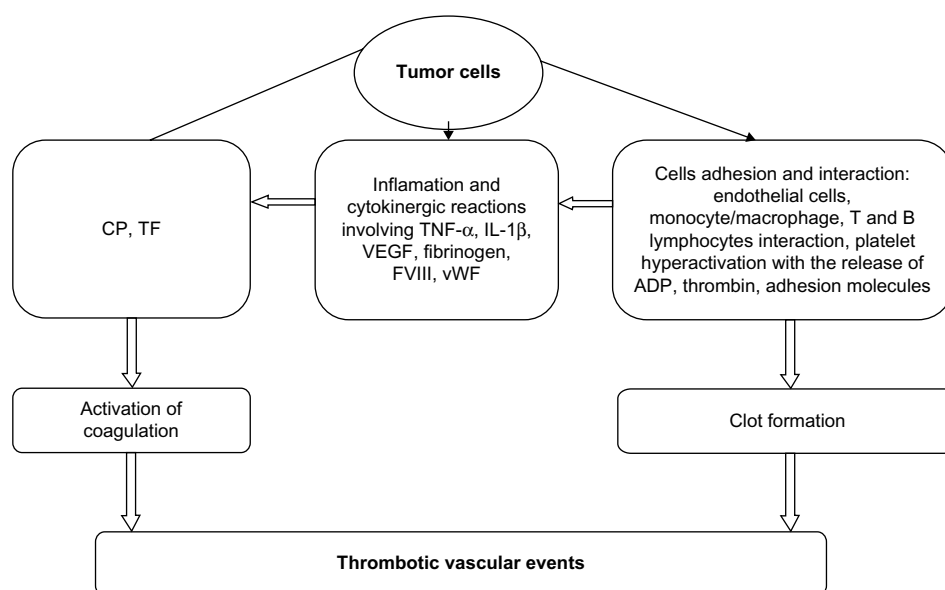
Figure 1. Factors involved in cancer-associated thrombosis.
Abbreviations: CP, Cancer procoagulant; TF, Tissue factor; TNF-α, Tumor necrosis factor-α; IL-1β, Interleukin-1β; VEGF, Vascular endothelial growth factor; FVIII, Factor VIII; vWF, Von Willebrand factor; ADP, Adenosine diphosphat.
Source: Karimi M, Cohan N. Cancer-Associated Thrombosis. *The Open Cardiovascular Medicine Journal* 2010;4:78–82. doi:10.2174/1874192401004020078.

site of tumor, and tumor histology, stage, and duration of cancer.[38,39] Treatment-related factors include both pharmacologic agents, such as chemotherapeutic agents, hormonal agents, antiangiogenic agents, and erythropoiesis-stimulating agents (ESAs), and mechanical causes like surgery and central venous catheters.[35,39]

According to a systematic review, up to 10% of patients presenting with idiopathic VTE are subsequently diagnosed with cancer during the first year of follow-up.[38,39]

Management of Cancer-Associated Thrombosis

Initial treatment of cancer-associated VTE. The treatment of VTE in cancer patients aims at reducing mortality and morbidity, and improving quality of life. Until the mid-2000s, the standard treatment for acute VTE consisted of initial therapy with LMWH or UFH followed by long-term therapy with an oral anticoagulant, namely VKAs.[11] Oncology patients have a higher rate of VTE recurrences during oral-anticoagulant therapy with VKAs and a higher anticoagulation-associated hemorrhagic risk as compared with non-cancer patients.[40]

The most important guidelines, namely, from the American Society of Clinical Oncology (ASCO), the European Society of Medical Oncology (ESMO), the American College of Chest Physicians (ACCP), and the National Cancer Comprehensive Network (NCCN) recommend LMWH-based therapy over warfarin-based therapy as the preferred VTE treatment in cancer patients for the initial therapy (Table 2).[40,41]

The initial treatment of cancer-associated thrombosis includes LMWH, UFH, or fondaparinux.[41] Data analysis of trials showed no difference in efficacy between LMWH and

UFH in patients with cancer.[42] However, LMWH is preferred as an effective and safe for treatment of VTE. It has largely replaced UFH and VKAs because LMWH does not need hospitalization and laboratory monitoring like UFH. Also, LMWH is associated with a lower risk of heparin-induced thrombocytopenia (HIT) and simple dosing (once-daily, weight-based subcutaneous injection).[43] Moreover, a statistically significant reduction in mortality risk with LMWH at three months of follow-up has been noted. The reason for this survival benefit is unknown. Some studies of the efficacy of LMWH in the treatment of malignancy-associated VTE have reported a survival benefit not only because of resolution of the thrombus but also because of an antineoplastic effect.[44,45] However, the reduction in mortality observed in favor of LMWH has been found in a subgroup analysis of a systematic review and has never been confirmed in subsequent randomized clinical trials.

Fondaparinux is administered as a once-daily, weight-based subcutaneous injection as LMWH, and is also rarely associated with drug-induced thrombocytopenia.[46] However, its use in cancer patients is limited because of long half-life of 17–21 hours, the lack of a reversal agent, and 100% dependence on renal clearance.[47] However, UFH can be used in those with severe renal impairment as it depends on hepatic clearance and fondaparinux is a reasonable choice in patients with a history of HIT.[41]

Long-term management of cancer-associated VTE. According to current international recommendations,[48–50] LMWH is the standard anticoagulant therapy during the first three months after the VTE. LMWH is also routinely recommended for 6–12 months or indefinitely for patients with

Table 1. Summarize the risk factors for cancer associated thrombosis.

PATIENT CHARACTERISTICS	TUMOR -RELATED FACTORS	TREATMENT-RELATED FACTORS	BIOMARKERS
Female gender	Anatomical site of tumor	Major surgery	High TF expression by tumor cells[31]
Older age	Tumour histology	Hospitalization	Pre-chemotherapy platelet count >350,000/mm[38,35]
Race (black ethnicity)	Advanced stage of cancer	Cancer therapy	Pre-chemotherapy leukocyte count >11,000/mm[38]
Common comorbidities: DM, Obesity, Previous VTE, atherosclerosis, inflammation, others	Initial period after diagnosis of cancer	Erythropoiesis-stimulating agents	Elevated D-dimer[34,35]
Inherited prothrombotic mutations	–	Central venous catheters	High level of[35] - TF plasma levels - soluble P-selectin - C-reactive protein

Abbreviations: TF, Tissue factor; DM, Diabetic mellitus; VTE, Venous thromboembolism.

active neoplastic disease, for patients receiving chemotherapy, if thrombosis is recurrent in patients, or if the patient had inherited thrombophilia.[44]

VKAs have been the mainstay agents for long-term management and secondary prophylaxis of acute VTE in patients without cancer.[50] However, its use is problematic in oncology patients because of lower efficacy and high rates of recurrence (three times than in patients without cancer) despite maintenance of the international normalized ratio (INR) within the therapeutic range.[27]

In CLOT trial,[11] patients with cancer who had acute VTE were randomly assigned to receive LMWH (dalteparin) at a dose of 200 IU/kg of body weight subcutaneously once daily for five to seven days and a coumarin derivative for six months (target INR, 2.5) or dalteparin alone for six months (200 IU/kg once daily for one month, followed by a daily dose of approximately 150 IU/kg for five months). During the six-month follow-up, 27 of 336 patients in the dalteparin group had recurrent VTE, compared with 53 of 336 patients in the oral-anticoagulant group (hazard ratio, 0.48; $P = 0.002$). The probability of recurrent VTE at six months was 17% in the oral-anticoagulant group and 9% in the dalteparin group. No significant difference between the dalteparin group and the oral-anticoagulant group was detected in the rate of major bleeding (6% and 4%, respectively) or any bleeding (14% and 19%, respectively), and the authors conclude that dalteparin was more effective than an oral anticoagulant in reducing the risk of recurrent VTE without increasing the risk of bleeding.

Table 2. Summary of guidelines on treatment of VTE in patients with cancer.

	NCCN 2011	ACCP 2012	ASCO 2013
Initial treatment	LMWH Dalteparin 200 U/kg OD Enoxaparin 1 mg/kg BID Tinzaparin 175 U/kg OD Fondaparinux 5 mg (<50 kg), 7.5 mg (50–100 kg), or 10 mg (>100 kg) OD APTT-adjusted UFH infusion	Not addressed in cancer patients	LMWH is recommended for the initial 5 to 10 days of treatment for DVT and PE in patients with a CrCl>30 mL/min.
Long-term treatment	-LMWH is recommended for first 6 months as monotherapy without warfarin in patients with proximal DVT or PE and metastatic or advanced cancer. -Warfarin 2.5–5 mg every day initially with dynamic dosing strategy based on INR value targeted at 2–3.	-LMWH preferred to VKA -In patients not treated with LMWH, VKA therapy is preferred to dabigatran or rivaroxaban -Patients receiving extended therapy should continue with the same agent used for the first 3 months of treatment	-LMWH is recommended for long-term therapy for DVT and PE -VKAs (target INR, 2–3) are acceptable for long-term therapy if LMWH is not available. -Use of novel oral anticoagulants is not recommended -Patients with cancer should be periodically assessed for VTE risk
Duration of therapy	Minimum 3 months. Indefinite anticoagulant if active cancer or persistent risk factors.	Extended therapy is preferred to 3 months of treatment	At least 6 months duration. Extended anticoagulation with LMWH or VKA beyond 6 months for patients with: -metastatic disease -receiving chemotherapy -recurrent thrombosis

Note: Adapted from Khorana AA2009,[8] Lee AY 2013.[41]
Abbreviations: ACCP, American College of Chest Physicians; BID, twice-daily dosing; OD, once-daily dosing; NCCN, National Comprehensive Cancer Network; OD, once-daily dosing; ASCO, American Society of Clinical Oncology; ESMO, European Society of Medical Oncology; ACCP, American College of Chest Physicians; NCCP, National Cancer Comprehensive Network; DVT, Deep vein thrombosis; PE, Pulmonary embolism.

In addition to lower efficacy, VKAs also need laboratory monitoring of their anticoagulant activity; and their absorption affected by food interactions has a longer half-life that makes interruption for procedures, or thrombocytopenia is difficult.

Whenever possible, outpatient management of the VTE is preferred. Criteria for hospital admission were adapted in Siragusa et al.[51] study: poor clinical conditions because of the VTE event and/or concomitant medical comorbidities, poor compliance, high risk of bleeding or active bleeding, renal insufficiency, and platelet count less than $50 \times 109/L$.

In brief, LMWH is recommended for both initial and long-term anticoagulation in cancer-associated thrombosis by major consensus guidelines.[40,50,52,53] If LMWH is unavailable, the ASCO 2013 VTE Prevention and Treatment Guideline recommends the use of VKAs with a target INR of 2–3 as an acceptable alternative.[54]

Duration of anticoagulant therapy. Studies regarding the optimal duration of anticoagulant therapy are lacking in oncology patients. The decision regarding the continuation of anticoagulation beyond the first three to six months is largely based on weighing the risk for recurrent thrombosis against the risk of major bleeding. The patient assessment should be done to determine whether biomarkers, radiologic imaging, and clinical prediction models can identify patients with a sufficiently high risk for recurrent thrombosis to benefit from extended anticoagulation.[55]

Management of Selected Cases of Cancer-Associated VTE

Treatment of patients with renal impairment. Abnormal renal function is a common condition in patients with malignancy. Because LMWH is partially cleared by renal excretion and metabolism, drug accumulation is expected with long-term management in those with significant renal insufficiency. Limited data are available on the use of LMWH in patients with significant renal dysfunction, but they do indicate that the risk of bleeding is higher in patients with renal impairment.[56] Manufacturer-recommended dose reduction in renal impairment exists for enoxaparin but not for other LMWH preparations.[57] Compared with other LMWHs, tinzaparin does not exhibit significant accumulation in patients with renal impairment, allowing for utilization without dose adjustment.[58] The difference favoring tinzaparin clearance in patients with severe renal insufficiency compared to other LMHWs is possibly related to the drug's metabolism by hepatic mechanisms because of the higher molecular weight of tinzaparin.[59,60]

However, the results regarding tinzaparin have not been confirmed in a clinical trial.

Most experts and guidelines recommend dose adjustment based on anti-factor Xa activity in patients with a CrCl <30 mL/minute.[50,52] If anti-factor Xa monitoring is not readily available, VKA therapy is likely a safer option for long-term anticoagulation in these patients.

Inferior vena cava (IVC) filters insertion. Data on the efficacy and safety to insert IVC filters in oncology patients are limited, and its use remains controversial. Complications associated with IVC filters include recurrent VTE up to 32%, and fatal PE has been well documented.[28] Also, insertion problems occur in 4–11% of patients, and long-term adverse effects, such as thrombosis, which can occur proximally or distally to the filter, occur in 4–32% of patients.[61] So, because of the absence of data to support their efficacy and high rates of complications, IVC filters should be restricted to patients with acute VTE when anticoagulant therapy is not tolerated or contraindicated. Abdel-Razeq et al revealed that the IVC filter should be considered for patients who are currently bleeding or are at high risk for bleeding, patients who have recurrent VTE despite anticoagulation or develop VTE immediately postoperatively, and patients who present with a large primary or metastatic CNS tumor or present with cor pulmonale.[62]

Treatment of incidental VTE. Incidental or unsuspected VTE is defined as evidence of thrombosis detected on imaging studies performed for other indications such as cancer staging.[63] Retrospective studies in unselected oncology patients demonstrated incidental VTE rates of up to 6%.[64] Currently, based on published literature, it is recommended that patients with incidental DVT and PE receive therapeutic anticoagulation if there are no contraindications.[50,54] However, confirming the diagnosis with the appropriate testing is strongly required in such cases.

Treatment of catheter-related thrombosis. To date, published data and clinical experience suggest that catheter-related thrombosis is associated with a low risk for thrombosis recurrence and postthrombotic syndrome.[65] Therefore, conservative treatment is recommended. Also, removal of the catheter is indicated if there is evidence of concomitant DVT, line-related sepsis is suspected or documented, or the access is no longer required or nonfunctioning. Anticoagulant therapy should be given using either LMWH alone or LMWH followed by warfarin therapy. A short period of anticoagulation (three to five days of LMWH) may even salvage some thrombosed catheters and obviate the need to remove and replace the line. Anticoagulation is recommended for a minimum of three months while the catheter remains in place.[41]

Management of Challenging Cases of Patients with Cancer-Associated Thrombosis

Management of VTE in patients with thrombocytopenia. Thrombosis is commonly diagnosed in patients with malignancy and thrombocytopenia.[66] The possible etiologies of the thrombocytopenia in cancer patients are HIT, thrombotic thrombocytopenic purpura, immune thrombocytopenia, or chemotherapy effect. Clinicians need to assess the severity; whether there are potentially reversible causes that can be corrected; and whether there are other risk factors for bleeding, such as advanced age or renal insufficiency. Anticoagulation

in patients with thrombocytopenia should be applied on an individual patient basis after assessment of the risks and benefits. In the initial month following the diagnosis of VTE, the risk of recurrent thrombosis is highest.[11,67] Consequently, giving maximal or therapeutic anticoagulant therapy is important. In patients with acute cancer-associated thrombosis and platelet count $\geq 50 \times 10^9/L$, full therapeutic anticoagulation without platelet transfusion is appropriate. But, in patients with a platelet count $< 50 \times 10^9/L$, platelet transfusion support to maintain a platelet count $\geq 50 \times 10^9 L$ to allow full, therapeutic anticoagulation should be considered.[68] The cut-off of $50 \times 10^9/L$ is empirical, but there is general consensus that the risk of spontaneous bleeding is very low above this level.

However, platelet transfusion support to maintain a platelet count of $\geq 50 \times 10^9 L$ just to allow full, therapeutic anticoagulation may not be practical. In retrospective study of 53 patients with cancer-associated thrombosis and thrombocytopenia $< 50 \times 10^9/L$, the impact of anticoagulation dose reduction on the risk of recurrent cancer-associated thrombosis appeared to be minor. In all, 23 patients received anticoagulation for less than three months, including 11 patients who received it for < 14 days. Fifteen patients had $\geq 25\%$ dose reductions of anticoagulants. At six-month follow-up, the recurrent thrombosis rate was 1.8%.[69]

In such cases, most experts agree that dynamic dosing strategy for anticoagulants, irrespective of the initial one-month period, appeared the best option[70]: for a platelet count of $\geq 50 \times 10^9/L$, full therapeutic anticoagulation; for a platelet count of $25–50 \times 10^9/L$, reducing the dose of LMWH to 50% of the therapeutic dose or using a prophylactic dose of LMWH in patients with a platelet count of $25–50 \times 10^9/L$; and for a platelet count of $< 25 \times 10^9/L$, no anticoagulation.[68,70]

Treatment of recurrent VTE during anticoagulant therapy. Recurrent VTE despite appropriate anticoagulation is common among cancer patients. Approximately 10–17% of patients with cancer-associated thrombosis treated with a VKA and 6–9% of patients treated with LMWH will have recurrent VTE during follow-up.[11,67,71] The causes for VKA failure are multifactorial, and cancer patients can develop recurrent VTE despite maintaining therapeutic INR values.[11] LMWHs for at least the first three months are known to be more effective than VKAs in the treatment of cancer-associated thrombosis.[11,67] Raising the anticoagulation target of the VKA (eg, INR 2.5–3.5) is not recommended, given the lack of cancer-specific data and the increase in the risk of bleeding with a higher target INR.[27]

Once recurrent VTE is confirmed, it is essential that HIT be excluded in patients who were first exposed to LMWH or UFH within the past 10–14 days and also to confirm drug compliance. An approach to managing cancer patients with symptomatic recurrent VTE despite anticoagulation has been proposed.[72,73] Patients with recurrent event who are being treated with VKAs should be switched to LMWH monotherapy or continuation of VKA after a bridging period with LMWH (or UFH) and those managed with LMWH should have their dose increased by 25% (or increased to therapeutic, weight-adjusted doses if they are receiving lower doses). A retrospective study of 70 patients with cancer with recurrent VTE demonstrated that transition to LMWH (in patients receiving VKA therapy at the time of recurrence) or LMWH dose escalation by 20–25% (in patients receiving LMWH at recurrence) prevented additional VTE in 91% of patients during a minimum of three months of follow-up.[74]

All patients should be reassessed in five to seven days to ensure symptomatic improvement. Patients without symptomatic improvement should be considered for another dose escalation, and the anti-FXa level can be used to estimate the next dose escalation, although there is no published evidence to support this strategy.[41]

Other therapeutic options, including the insertion of an IVC filter or switching to a different anticoagulant (eg, fondaparinux or VKA), have been proposed.

Thromboprophylaxis in Patients with Cancer

Prediction of VTE in cancer patients. Multiple clinical risk factors including primary site of cancer and systemic therapy, and biomarkers including leukocyte and platelet counts and TF are associated with increased risk of VTE. However, risk cannot be reliably predicted based on single risk factors or biomarkers, and the patients with cancer should be assessed for VTE risk at the time of chemotherapy initiation and periodically thereafter.[75] Based on known risk factors, a simple model for predicting chemotherapy-associated VTE in ambulatory cancer patients was developed by Khorana et al.[76] The study included patients with breast, colorectal, lung, gynecologic, gastric, and pancreatic cancers, and lymphoma who were to receive systemic chemotherapy. Other cancer sites made up the 10% of remaining patients. The five predictive variables identified included cancer site, elevated prechemotherapy platelet count, anemia or use of red blood cell growth factors, elevated prechemotherapy leukocyte count, and elevated body mass index (BMI).[8,76]

This risk model was subsequently validated in another cohort of cancer patients and expanded with two additional laboratory markers, sP-selectin and D-dimer, to increase the predictive value of estimating a patient's risk of chemotherapy-associated thrombosis (Table 3).[77,78] The patient population used to generate the expanded risk model consisted of 819 patients from Vienna Cancer and Thrombosis Study (CATS) enrolled at the time of newly diagnosed cancer or progression of the disease. The median follow-up was much longer in this study than in that of Khorana et al (21.4 months vs 73 days). Primary brain tumors were added to the very-high-risk category. Kidney cancer and multiple myeloma were added to the high-risk category. This model was better able to stratify high-risk patients from low-risk patients. Yet the application of this extended risk-assessment tool is limited by the fact that the sP-selectin assay is not routinely performed in clinical centers

Table 3. Predictive model for chemotherapy-associated VTE.[8,77]

PATIENT CHARACTERISTICS	VTE RISK SCORE
Site of cancer	
Very high risk (primary brain, stomach or pancreas)	2
High risk (lung, lymphoma, gynecologic, genitourinary excluding prostate or multiple myeloma)	1
Low risk (breast, colorectal or head and neck)	0
Other characteristics	
Platelet count $\geq 350 \times 10^9/l$	1
Hemoglobin <100 g/l or use of red blood cell growth factors	1
Leukocyte count $>11 \times 10^9/l$	1
BMI ≥ 35 kg/m^2	1
sP-selectin ≥ 53.1 ng/ml	1
D-dimer ≥ 1.44 µg/ml	1

Notes: 0 score, Low risk. 1 or 2 score, Intermediate risk. 3 or higher, High risk.

and that there is significant variability of D-dimer assays employed.[79]

In a multicenter trial (SAVE-ONCO),[80] once-daily, subcutaneous semuloparin (a hemisynthetic, ultra-LMWH with high anti-Xa activity) at 20 mg administered to 1608 patients receiving chemotherapy for locally advanced or metastatic solid tumors significantly prevented VTE without increasing major bleeding. In this trial, the median treatment duration was 3.5 months. VTE occurred in 20 of 1608 patients (1.2%) receiving semuloparin, as compared with 55 of 1604 (3.4%) receiving placebo (hazard ratio, 0.36; 95% confidence interval [CI], 0.21–0.60; $P < 0.001$). The incidence of clinically relevant bleeding was 2.8% and 2.0% in the semuloparin and placebo groups, respectively (hazard ratio, 1.40; 95% CI, 0.89–2.21). Major bleeding occurred in 19 of 1589 patients (1.2%) receiving semuloparin and 18 of 1583 (1.1%) receiving placebo (hazard ratio, 1.05; 95% CI, 0.55–1.99). The authors show that semuloparin is safe and effective for prophylaxis against VTE in patients receiving chemotherapy for solid tumors.

Thromboprophylaxis in cancer patients. The risk for recurrent thrombosis in patients with active cancer is high even while they are receiving anticoagulation; it is generally recommended that extended anticoagulation prophylaxis be considered in this population.[50,54] Patients given extended anticoagulation require frequent reassessment to review the risk–benefit balance of continuing anticoagulant therapy.

Despite the existence of several evidence-based guidelines that delineate appropriate anticoagulation regimens for primary and secondary prophylaxis of VTE and long-term anticoagulation in cancer patients,[49,81–84] up to 75% of cancer patients do not receive appropriate prophylaxis.[85]

Indeed, the use of thromboprophylaxis in cancer patients is complicated by the fact that although they are at an increased risk of VTE, they are also at an increased risk of

bleeding.[86] So, the use of antithrombotic agents that provide stable anticoagulation while minimizing bleeding complications is especially important in this high-risk group.

Controversy exists regarding the benefits of extended prophylaxis on an outpatient basis for ambulant patients receiving chemotherapy, as guidelines currently do not recommend routine prophylaxis for this group or are not always consistent in their recommendations.[81–84]

Both UFH and the LMWHs are recommended for primary prophylaxis following cancer surgery. Studies show that the LMWHs are at least as effective as UFH in this setting, but associated bleeding tendency is lower than UFH.[44]

The LMWHs are recommended for use in secondary/long-term prophylaxis where, compared with warfarin, they display increased efficacy with a good safety profile and reliability, and are associated with increased quality of life. In addition, the LMWHs have been associated with potential antineoplastic effects that may contribute to improved survival times in cancer patients.[44,45] However, more studies are needed to understand this effect and the potential role of the LMWHs as antineoplastic therapy.

Novel Oral Anticoagulants

Recently, the development of novel oral anticoagulants (NOACs) that directly inhibit factor Xa (eg, rivaroxaban, apixaban, or betrixaban) or thrombin (for example, dabigatran etexilate) is a milestone achievement in the prevention and treatment of VTE.[87] Unlike LMWHs and warfarin, which inhibit multiple coagulation factors, NOACs target specific clotting cascade factors; NOACs are more attractive to patients and clinicians because they do not require laboratory monitoring to achieve therapeutic anticoagulation, they can be taken orally in fixed doses once or twice daily, and they have minimal food and drug–drug interactions.[41,54,88] The major limitation is the lack of specific antidotes to reverse the anticoagulant effect and the absence of readily available assays to measure the anticoagulant effect, which can be an issue when facing bleeding events or treatment failure.[55,87] To date, NOACs have not been rigorously evaluated in cancer patients. A recent randomized phase II trial of apixaban for the prevention of thromboembolism in patients with metastatic cancer[89] showed that apixaban is safe and feasible to use as VTE prophylaxis for high-risk cancer patients receiving chemotherapy. However, no published clinical trials have specifically addressed the treatment of cancer-associated VTE using these direct inhibitors. Also, ASCO guideline does not recommend the use of these new agents.[41,54]

Summary

VTE is a serious complication, and the second most frequent cause of death in patients with cancer and adversely affects quality of life. Studies showed that anticoagulant therapy and thromboprophylaxis are efficacious and can protect patients from VTE.

Based on clinical trial findings, subcutaneous LMWH is the first-line therapy for VTE in patients with cancer and

has largely replaced UFH and VKAs. The treatment should be delivered for an extended period between three and six months, or even indefinitely, in the presence of active neoplastic disease or a very high risk of recurrence. The results of the studies indicate that patients demonstrate a survival benefit with LMWH, but these possible benefits must be weighed against the risks, costs, and inconvenience of chemopreventive anticoagulation. Recently, the results of clinical trials of use of NOACs that directly inhibit factor Xa or thrombin are promising in the prophylaxis of high-risk cancer patients receiving chemotherapy.

Author Contributions

Conceived and designed the experiments: GE. Analyzed the data: GE, AMA, EB. Wrote the first draft of the manuscript: GE, AMA. Contributed to the writing of the manuscript: GE, AMA, EB. Agree with manuscript results and conclusions: GE, AMA, EB. Jointly developed the structure and arguments for the paper: GE, AMA, EB. Made critical revisions and approved final version: GE, AMA, EB. All authors reviewed and approved of the final manuscript.

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