Review Article

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Cancer-Associated Venous Thromboembolism

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Abstract:

Venous thromboembolism (VTE) presents a significant clinical challenge in the management of cancer patients, marked by a notably higher incidence compared to the general population. This article focuses on cancer-associated venous thromboembolism, exploring its multifaceted nature and the complexities encountered in both diagnosis and treatment. Additionally, the evolution of anticoagulant therapy, including the emergence of low molecular weight heparin (LMWH) and direct oral anticoagulants (DOACs), is examined for their efficacy in preventing recurrent cancer-associated VTE. Emphasizing the need for personalized treatment approaches. Through a comprehensive understanding of these challenges and advancements, clinicians can optimize therapeutic strategies to enhance outcomes for cancer patients at risk of VTE.

Keywords: Venous thromboembolism, Cancer, Management

Introduction

Blood clots in the veins, a condition known as venous thromboembolism, pose a growing challenge in modern medicine. While medications can dissolve these clots, they also carry a significant risk of causing bleeding incidence. VTE strikes cancer patients at a much higher rate than the general population, both at the time of diagnosis and upon later treatment duration. Treating VTE in cancer patients is particularly complex due to a confluence of factors. The cancerous condition itself, the direct complications it brings, and the side effects of treatments like surgery, radiation, and chemotherapy all contribute to VTE. Furthermore, even with anticoagulants for secondary prophylaxis, cancer patients have a sharp risk of recurrent blood clots and also higher potential for hemorrhage after treatment requires a different treatment approach for VTE in cancer patients compared to the general population.

Burden of venous thromboembolism in patients with cancer

Venous thromboembolism most commonly forms in the deep veins of the legs which this called deep vein thrombosis (DVT). These clots can then dislodge and travel to the lungs, blocking pulmonary arteries called pulmonary embolism (PE). Symptoms can range from leg swelling and

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pain to fever, shortness of breath, and even coma in severe cases. The general population experiences VTE at a rate of crudely 1 per 1,000 people.[1] However, this incidence elevates to 4-8 fold in cancer patients compared to those in the same age group.[2] Among the entire population of cancer patients, VTE occurs in up to 15%.[3] As high as 20% of newly diagnosed VTE cases involve patients with underlying cancer. In individuals diagnosed with VTE without a clear trigger (unprovoked venous thromboembolism), follow-up care reveals up to 10% of these patients develop cancer within 1-2 years.[4]

Pathogenesis and risk factors for VTE in cancer patients

The exact origins of VTE involve multiple theories. The most widely accepted explanation is Virchow's triad, proposed by Rudolf Virchow.[5] This triad identifies three key factors:

1. Stasis of blood: When blood flow slows in certain areas of the veins, such as around the valve cusps in the legs, or in cases of prolonged immobilization, the risk of clotting increases.

2. Endothelial injury: Damage to the endothelium allows platelets to come into contact with collagen, a protein in connective tissue. This contact triggers platelet activation and the clotting cascade, leading to clot formation.

3. Hypercoagulability: Certain genetic factors can predispose individuals to abnormal blood clotting. Conditions with Protein C, Protein S, and antithrombin deficiency fall into this category.

The current understanding suggests that multifactorial causes work together to cause VTE.[6] Cancer patients often have several of these risk factors, making them more susceptible to VTE compared to the general population. These risk factors can be categorized based on their origins as shown in table1.

Table 1 Risk factors of VTE in cancer patients

Patient-based factors	Cancer-based factors	Treatment-related factors
Age	Type of cancer	Chemotherapy
Underlying	Cancer stage	Radiation therapy
medical conditions	Metastatic	Surgery
Previous VTE	organ involvement	Hormone therapy
Genetic thrombophilia		Central venous catheter insertion
Obesity		

Symptoms, signs and diagnosis

The symptoms and signs of VTE in cancer patients are generally similar to those in the general population. The diagnostic tests used for VTE, such as D-dimer, ultrasound, CT scan, and venography, are also the same for both cancer patients and the general population. The choice of tests depend on the individual patient's clinical presentation and risk factors which are not mentioned here.

However, diagnosis of VTE in cancer patients can be challenging due to the

presence of other symptoms and signs related to the cancer itself or its complications. Such as edema from malnutrition, fever from infection, dyspnea from infection or anemia caused by chemotherapy and complications from cancer surgery. It is important to consider VTE in the differential diagnosis of any cancer patient with symptoms or signs that could be suggestive of VTE. A careful assessment is essential to avoid misdiagnosis.

Treatment of venous thromboembolism in cancer patients

The duration of anticoagulant therapy in cancer patients with thrombosis is not different from that of general patients. However, even with anticoagulant therapy, the recurrence rate of deep vein thrombosis (DVT) in cancer patients is still higher than in non-cancer patients.[7] In addition, after stopping anticoagulant therapy after completing treatment, cancer patients are twice as likely to have recurrent thrombosis as patients with DVT from other correctable causes.[8]

Anticoagulation Phase

1. Initial Phase (5 days-21 days) considered parenteral low molecular weight heparin (LMWH), unfractionated heparin (UFH) or direct oral anticoagulants (DOACs) such as rivaroxaban or apixaban.

2. Long-term Phase (5 days to 3-6 months) consider anticoagulation for all patients unless contraindicated.

3. Extended Phase (after 3-6 months) individualized decision-making depend on cancer status (active disease), treatment complications, bleeding risk, age and patient preference. Collaboration between healthcare providers and patients is essential. General recommendation is continuing anticoagulation if cancer is active or ongoing treatment is needed.

Evolution of anticoagulant options

The type of long-term anticoagulant therapy initially did not significantly differ from that recommended for non-cancer patients, where Vitamin K antagonists were the standard. Until 2003, Lee AY, et al.[9] reported findings from a randomized controlled trial comparing the efficacy of preventing recurrent VTE in cancer patients with DVT and PE who received either warfarin or dalteparin, a low-molecular-weight heparin (LMWH). It was found that the use of warfarin led to a higher incidence of recurrent VTE in cancer patients compared to dalteparin, with a hazard ratio (HR) of 0.48, though the probability of death did not significantly differ. A systematic review of 8 studies consistently showed that LMWH was more effective than warfarin in preventing recurrent VTE in cancer patients. Consequently, treatment recommendations largely advocate for the use of LMWH as the first-line therapy in managing cancer-associated thrombosis.[10]

However, LMWH has limitations for long-term use due to its subcutaneous administration, which may be inconvenient for medication management and could potentially exacerbate pain in cancer patients who commonly experience cancer-related pain. Currently, there are direct oral anticoagulants (DOACs) available, which have been studied for their efficacy in preventing recurrent venous thromboembolism (VTE) in cancer patients. Several randomized controlled trials, including the Hokusai VTE Cancer study[11], SELECT-D trial[12] and Caravaggio study[13] have compared the efficacy of DOACs (specifically edoxaban, rivaroxaban, and apixaban, respectively) versus dalteparin. The consistent finding across these studies is that DOACs are non-inferior to dalteparin in preventing recurrent VTE and can be used as anticoagulant therapy in cancer patients. However, patients

using edoxaban and rivaroxaban may have an increased risk of gastrointestinal bleeding in gastrointestinal cancer patients. Recently, a CANVAS study in 2023 compared the effectiveness of DOACs versus LMWH in preventing recurrent VTE in cancer patients. They found that DOACs were noninferior to LMWH in preventing recurrent VTE. Both groups had similar rates of major bleeding and adverse events.[14]

Although DOACs offer the convenience of oral administration and eliminate the need for monitoring coagulation levels, they still have limitations such as cost, accessibility, and interactions with other medications, predominantly through the cytochrome P450 enzyme system, particularly CYP3A4 and P-glycoprotein. These interactions include medications such as carbamazepine, phenytoin, protease inhibitors for HIV, azole antifungals, rifampicin, amiodarone, verapamil, diltiazem, and dronedarone.[15]

Current treatment recommendations for cancer patients with thrombosis suggest LMWH or DOACs over vitamin K antagonists.[16,17,18] Choice of anticoagulants take into account various factors including cancer type, disease status, bleeding risk, comorbidities, medication accessibility and convenience, financial status, and patient preference.

Table 2 Dosage and administration use of anticoagulant in VTE

ANTICOAGULANTS	DOSE
ENOXAPARIN	1 mg/kg SC every 12 hours (can consider decreasing to 1.5 mg/kg SC daily after first month)
TINZAPARIN	175 IU/kg SC once Daily
FONDAPARINUX	• 5 mg SC daily (< 50 kg) • 7.5 mg SC daily (50–100 kg) • 10 mg SC daily (> 100 kg)
BEMIPARIN	115 IU/kg SC once daily
UNFRACTIONATED HEPARIN (UFH)	80 units/kg IV bolus, followed by 18 units/kg/hour adjusted to target aPTT of 2–2.5 X control, followed by SC 250 units/kg every 12 hours
EDOXABAN	Initial therapy with heparin for at least 5 days followed by edoxaban 60 mg PO daily (or 30 mg PO daily in patients with estimated CrCl 30–50 mL/min or weight < 60 kg or concomitant potent p-glycoprotein inhibitors)
RIVAROXABAN	15 mg PO every 12 hours for the first 21 days followed by 20 mg daily
APIXABAN	10 mg PO every 12 hours for 7 days followed by 5 mg PO every 12 hours
DABIGATRAN	Initial therapy with heparin for at least 5 days followed by dabigatran 150 mg PO every 12 hours
WARFARIN	Initial with heparin, initial 2.5-5 mg PO daily adjusted to INR 2-3

Anticoagulant-related bleeding in CA-VTE; risk factors and management

Cancer patients with VTE face a difficult situation. While anticoagulant medications are essential to prevent new blood clots, they also increase the risk of bleeding. Recent large cohort studies have shown an approximation of a 10% bleeding event rate within a 12-month period of anticoagulant use. The most common clinically significant bleeding sites are the gastrointestinal tract, genitourinary tract, and intracranial hemorrhage, respectively.

Risk factors associated with anticoagulant-related bleeding in CA-VTE were: history of bleeding, estimated glomerular filtration rate (eGFR) < 60 ml/min, uncontrolled hypertension, predisposition to falling, history of ischemic stroke, alcohol abuse, anemia and liver disease had the highest association with anticoagulant-related bleeding. Of cancer specific variables, GI cancer, GU cancer and metastatic cancer was most predictive.[19]

The acute management of bleeding in cancer patients with VTE is generally similar to that in non-cancer patients. This may involve discontinuation of anticoagulant, specific antidotes, blood product replacement, using of bypassing agents and local control bleeding source, which is not mentioned in detail in this article.

The decision to restart anticoagulation therapy after a bleeding event depends on a careful evaluation of several factors; bleeding severity, risk of recurrent VTE is weighed against the risk of future bleeding. The likelihood of restarting anticoagulation therapy increases if the bleeding source has been effectively identified and addressed.

Patients should be informed about bleeding signs and symptoms and empowers patients to participate in a shared decision-making process with healthcare providers.

Recurrent VTE in cancer patients and consideration of extended therapy duration

The rate of recurrent VTE is higher in patients with persistent or unprovoked risk factors compared to those with transient risk factors. In cancer patients, several factors affect treatment continuity and VTE recurrence outcomes. These factors include: discontinuing anticoagulant medication early or not receiving the appropriate dosage, active cancer, particularly cancers of the pancreas, lung, ovary, or brain and needing to stop anticoagulation due to bleeding complications.

A 2018 COMMAND VTE registry study showed that the rate of discontinuing anticoagulation within a 1-year treatment period was highest in the cancer group compared to the transient risk factor and unprovoked groups (transient: 37.3%, unprovoked: 21.4%, cancer: 43.5% at 1 year, $P < 0.001$). Additionally, the cumulative 5-year incidences of recurrent VTE, major bleeding, and all-cause death were highest in the cancer group. The overall recurrent VTE rate in cancer patients was nearly 18% over the 5-year study period, which is 2.8 times higher than the transient risk factor group.[20]

In DOACs era, the COMMAND VTE Registry-2 study, conducted during 2015-2020, collected data from 5,197 patients. The study found that 79% of patients receiving oral anticoagulants were administered DOACs. Although cancer patients still had the highest bleeding event rate compared to the unprovoked or transient risk groups, the cumulative 5-year incidence of recurrent VTE in cancer patients was nearly 12%, which is a lower rate compared to the previous study.[21]

Due to the complexities of managing cancer patients, extended anticoagulation therapy should be considered for patients with active cancer who are undergoing ongoing cancer treatment without a high

risk of bleeding. Additionally, prolonged anticoagulation after cancer remission can be individualized for patients with an increased VTE risk and a low bleeding risk.

Conclusion

Cancer patients face a significantly higher risk (4-8 times greater) of developing blood clots (VTE) compared to the general population. This is due to the cancer itself, its complications, and side effects from treatments. Anticoagulants are crucial to prevent blood clots, but they also increase bleeding risk (around 10% within a year). Newer medications like LMWH and DOACs offer advantages over older options, but have limitations. Managing VTE in cancer patients requires careful consideration. Treatment decisions weigh factors like cancer type, bleeding risk, and ongoing treatment. Extended use of anticoagulants might be necessary for some patients with active cancer to manage their VTE risk. This underlines the importance of collaboration between healthcare providers and patients to create individualized treatment plans and achieve the best outcomes.

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