Cancer-Associated Thrombosis: Risk Assessment, Prevention, and Treatment

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Presenters' disclosures of conflicts of interest are found at the end of this article.

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Abstract

The risk of developing venous thromboembolism (VTE) is four to seven times higher in patients with cancer than in those without. At JADPRO Live 2022, presenters discussed risk factors and assessing patients for VTE, as well as how to protect patients against VTE in both the inpatient and outpatient clinic settings. They reviewed selecting an appropriate anticoagulation treatment, including the choice of agent and duration of treatment for the patient with cancer, and finally the steps needed to assess and treat patients experiencing therapeutic anticoagulation failure.

Cancer-associated thrombosis, a life-threatening complication of cancer, can strike without warning and turn a patient's fight against the disease into a harrowing battle on multiple fronts. During JADPRO Live 2022, Keri Halsema, NP, and Brandon McMahon, MD, of the University of Colorado, discussed venous thromboembolism (VTE) prophylaxis for the inpatient and ambulatory patient with cancer, including risk assessment and the available pharmacologic options. The presenters also explained the diagnostic workup and appropriate anticoagulation treatment, including choice of agent and duration of treatment for the patient with cancer presenting with acute deep vein thrombosis and pulmonary embolism. Finally, Ms. Halsema and Dr. McMahon summarized the steps needed to assess and treat the patient with cancer experiencing therapeutic anticoagulation failure.

CANCER-ASSOCIATED THROMBOSIS

Cancer-associated thrombosis is a condition in which blood clots form in the blood vessels of individuals with cancer. The risk of developing a blood clot, or VTE, is four to seven times higher in patients with cancer than in those without, and approximately 15% of cancer patients will develop thromboembolism at some point during their treatment course (Connors, 2014).

Patients with cancer who develop VTE are more likely to have metastatic disease than those without thrombosis. They are also at higher risk for VTE recurrence and for bleeding complications on anticoagulation compared to their counterparts with VTE who do not have cancer.

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According to Ms. Halsema, the incidence of cancer-related thrombosis seems to be increasing, which is likely due to a combination of factors such as patients living longer and treatments becoming more prothrombotic. Patients who develop a VTE while being treated for cancer have a decreased 1-year overall survival rate of 12%, compared to a rate of 36% for those without thrombosis. Additionally, patients with cancer-associated thrombosis can die of the thrombosis itself, said Ms. Halsema.

A prospective study that looked at almost 4,500 cancer patients receiving outpatient chemotherapy found that the most common cause of death among these patients was progression of disease (71%), but death due to thromboembolism was also common, accounting for more than 9% of deaths (Khorana et al., 2007).

"The increased mortality with cancer-associated thrombosis is seen across numerous cancer types and in patients with localized or metastatic disease," summarized Ms. Halsema.

RISK FACTORS AND PATIENT ASSESSMENT

According to Ms. Halsema, several risk factors can contribute to thrombosis in cancer patients, including age, prior thrombosis, intrinsic hypercoagulability, cardiovascular risk factors, disease-specific issues such as tissue factor and vascular compression, high white and red blood cell counts, and complications and interventions such as central venous catheters and immunomodulatory drugs.

In addition, several studies have explored the relationship between chemotherapy and the risk of VTE in cancer patients. One retrospective trial involving 1,200 patients in Minnesota found that patients with cancer receiving chemotherapy have an increased risk of VTE with an odds ratio of 6.5 compared with cancer patients not receiving chemotherapy (Heit et al., 2000). Another large cohort study of 66,000 patients estimated that patients receiving chemotherapy have a 2.2 times increased risk of developing thrombosis (Blom et al., 2006).

In fact, in a prospective clinical trial of 3,003 ambulatory patients receiving chemotherapy for the first time, 9.65% of patients developed VTE within the first 2 to 3 months (Khorana et al., 2005). The cancer types that were associated with the highest risk of VTE were upper gastrointestinal cancers, lung cancer, and lymphoma.

A risk score developed for predicting the risk of VTE in cancer patients receiving chemotherapy, called the Khorana VTE risk score, considers various factors such as tumor type, platelet count, anemia, white blood cell count, and obesity. Points are assigned to each factor and the total score can range from 0 to 6. A prospective study of more than 800 patients found that those with a score of 0 had a relatively low incidence of VTE in the first 6 months (1.5%), while those with a score of 3 or higher had an incidence of nearly 18% (Table 1; Ay et al., 2010).

ANTICOAGULANT

As Ms. Halsema explained, there are several anticoagulant therapies available for cancer patients. Fondaparinux, a synthetic pentasaccharide with similar antithrombin inhibition as heparin and low molecular weight heparins, has the longest half-life of around 20 hours among the various options. The half-life of the agent and renal function of the patients are important considerations when deciding on anticoagulant therapy, said Ms. Halsema, who noted that most anticoagulant options have a reversal therapy available.

With respect to VTE prophylaxis in hospitalized cancer patients, the National Comprehensive Cancer Network Guidelines recommend the use of unfractionated heparin or low-molecular-weight heparins for VTE prophylaxis in cancer patients. Direct oral anticoagulants (DOACs) such as apixaban or rivaroxaban may be considered in patients who were already taking them before being hospitalized or in the case of heparin-induced thrombocytopenia. However, aside from these cases, the guidelines recommend the use of heparin over DOACs for patients hospitalized for malignancy.

"Fondaparinux should be avoided in patients who weigh less than 50 kilograms but is acceptable for use in patients with a history of heparin-induced thrombocytopenia," said Ms. Halsema.

TREATMENT OF ACUTE VTE IN CANCER PATIENTS

The randomized, phase III CLOT study was practice-changing for the treatment of cancer-associated thrombosis. This trial compared the

Table 1. Risk of Cancer-Associated Venous Thromboembolism

Risk factor	Points	
Site of cancer		
Very high risk (stomach, pancreas)	2	
High risk (lung, lymphoma, GYN, bladder, testicular)	1	
Pre-chemo platelet > 350 K/µL	1	
Hemoglobin < 10 g/dL OR use of ESA	1	
Pre-chemo WBC > 11 K/µL	1	
BMI ≥ 35 kg/m^2	1	
Points	**VTE incidence 2.5 months**	**VTE incidence 6 months**
0 (low)	0.3%–0.8%	1.5%
1–2 (intermediate)	1.8%–2%	3.8% (1 point) 9.6% (2 points)
≥ 3 (high)	6.7%–7.1%	17.7%

Note. ESA = erythropoiesis-stimulating agent. Information from Ay et al. (2010); Khorana et al. (2008).

low-molecular-weight heparin, dalteparin, with warfarin and found that patients on dalteparin had half the rate of recurrent VTE at 6 months compared with warfarin (Lee & Peterson, 2013). Other studies using different low-molecular-weight heparins were also found to be effective, with patients showing lower recurrence of VTE at 3 months compared with warfarin.

According to Dr. McMahon, however, the main disadvantage of low-molecular-weight heparins is that they are parenteral.

"Not everyone likes to self-administer a shot, which led to the emergence of a new drug option—DOACs—which have similar efficacy as low-molecular-weight heparins and have the advantage of oral administration," he said.

Several studies have looked at the safety and efficacy of DOACs in cancer patients with thrombosis. An open-label, noninferiority trial with 1,050 patients, over half of whom had metastatic disease, found that edoxaban was as effective as dalteparin but had a slightly higher rate of bleeding problems (Raskob et al., 2018). A smaller study also found that rivaroxaban had a better efficacy than dalteparin in terms of recurrent VTE but had higher rates of bleeding, particularly in patients with gastrointestinal or gastroesophageal junction tumors (Young et al., 2018). Lastly, one study found that apixaban had a lower rate of recurrent VTE and lower rates of major bleeding than dalteparin.

"Overall, while the DOACs, particularly apixaban, rivaroxaban, and edoxaban had better efficacy, they still had higher rates of bleeding, particularly gastrointestinal or genitourinary bleeding," said Dr. McMahon (Table 2).

For patients who have active cancer and develop deep vein thrombosis, which is a blood clot that forms in the deep veins of the body, often in the legs, there are pros and cons to each treatment option. According to Dr. McMahon, the data for these options are helpful but must be applied to the individual patient's case.

"One of the benefits of DOACs is that they are very convenient and reliable with respect to the degree of anticoagulation they provide," said Dr. McMahon. "However, there are some nuances to consider when choosing a DOAC."

"Apixaban, for example, has the least renal clearance compared with the others, and monitoring the levels of Xa inhibitors in the blood can be difficult," he added.

ANTICOAGULATION FAILURE

Anticoagulation failure in cancer patients is a common problem. Despite receiving adequate anticoagulation treatment, up to 15% of patients with cancer experience recurrent VTE (Lee, 2017). According to Dr. McMahon, this issue is often associated with malignancy progression and portends a worse outcome for the patient. Risk factors for

Table 2. Treatment of VTE in Active Cancer

Agent	Pros	Cons
Warfarin	• Considerable experience • Monitoring available • Readily reversible • Oral	• Extremely variable dosing • Long acting • Extensive drug interactions • Dietary issues
Low-molecular-weight heparin (enoxaparin, dalteparin)	• Reliable activity • Weight based • Monitoring available • Short acting • No significant drug or food interactions	• Subcutaneous • Renal dependent (caution w/ CrCl < 30 mL/min) • HIT (risk/contraindicated with history) • Partial reversal (protamine)
Fondaparinux	• Reliable activity, weight based • Monitoring available • Safe in HIT • No significant drug or food interactions • Once-daily dosing	• Subcutaneous • Renal dependent (contraindicated w/ CrCl < 30) • Long-acting
DOAC	• Oral • Safe in HIT	• Stomach, small bowel absorption (may pose problem with past resection, UGI cancers); apixaban partially absorbed in colon • More GI/GU bleeding seen
Apixaban	• Least renal clearance • Readily reversible (andexanet)	• Contraindicated with AST/ALT > 3 ×, tbili > 2 × ULN • Interaction w/strong dual inhibitor/inducer CYP3A4, P-gp • Bid, half-life ~12 hr • Limited monitoring
Dabigatran	• Monitoring available (dilute thrombin time) • Readily reversible (idarucizumab)	• Long acting • Most renal dependence (contraindicated w/ CrCl < 30 mL/min) • Contraindicated w/ AST/ALT > 2 × ULN • Limited bioavailability (pH dependent) • P-gp inducer/inhibitor
Edoxaban	• Readily reversible (andexanet)	• Contraindicated w/ CrCl < 30 mL/min • P-gp inducer/inhibitor
Rivaroxaban	• Shortest acting • Readily reversible (andexanet)	• Contraindicated w/ CrCl < 30 mL/min • Contraindicated w/ AST/ALT > 3 × ULN • Interaction w/ strong dual inhibitor/inducer CY3A4, P-gp

Note. CrCl = creatinine clearance; HIT = heparin-induced thrombocytopenia; UGI = upper gastrointestinal; GU = genitourinary; AST = aspartate aminotransferase; ALT = alanine aminotransferase; P-gp = P-glycoprotein; tbili = total bilirubin; ULN = upper limit of normal.

recurrent VTE include advanced disease and certain types of cancer.

Dr. McMahon highlighted the need to evaluate various reasons for anticoagulation failure, such as patient noncompliance, drug-drug interactions, heparin-induced thrombocytopenia, disease progression, and malabsorption issues. However, he also noted that there are limited data on what to do for patients who have recurrent VTE and that changes in the choice of anticoagulant don't necessarily result in better outcomes.

"Increasing the dose or switching agents is often done, but there are no data to suggest that this leads to better outcomes," said Dr. McMahon.

A study of over 200 patients who had breakthrough clots while on anticoagulation showed increasing the intensity of anticoagulation did not result in better outcomes at 90 days compared with those who stayed on the same dose (Schulman et al., 2015). ●

Disclosure

Ms. Halsema has no relevant financial relationships to disclose. Dr. McMahon has served as a consultant for CTI Biopharma and Curio Science.

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