CONTINUING EDUCATION

EDUCATIONAL OBJECTIVES

After participating in this activity, clinicians should be better able to

- Describe the risk factors associated with cancer-related VTE development
- Identify three anticoagulants used for VTE prophylaxis and treatment in patients with cancer
- Apply four ASCO- and NCCN-recommended indications for VTE prophylaxis for hospitalized patients with cancer
- Describe six contraindications to anticoagulant therapy in patients with cancer

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Using anticoagulants to treat chemotherapy-related VTE

Lisa A. Thompson, PharmD, BCOP; Miryoung Kim, PharmD

STATEMENT OF NEED/PROGRAM OVERVIEW

Venous thromboembolism (VTE) is more prevalent in patients with cancer and metastatic disease. Critical oversight and coordination in the prevention and treatment of VTE are essential components of care for this patient population. Thorough patient education and early recognition of the signs and symptoms of VTE can reduce the morbidity and mortality associated with this complication. This article reviews the signs and symptoms, patient education needs, and pharmacologic and mechanical treatment options for VTE in the patient with cancer.

CE INFORMATION

Title: Using anticoagulants to treat chemotherapy-related VTE
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Target audience: This activity has been designed to meet the educational needs of registered nurses and nurse practitioners involved in the management of patients with cancer.

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Using anticoagulants to treat chemotherapy-related VTE

Signs and symptoms of venous thromboembolism in oncology patients should be heeded with prompt therapeutic and mechanical interventions.

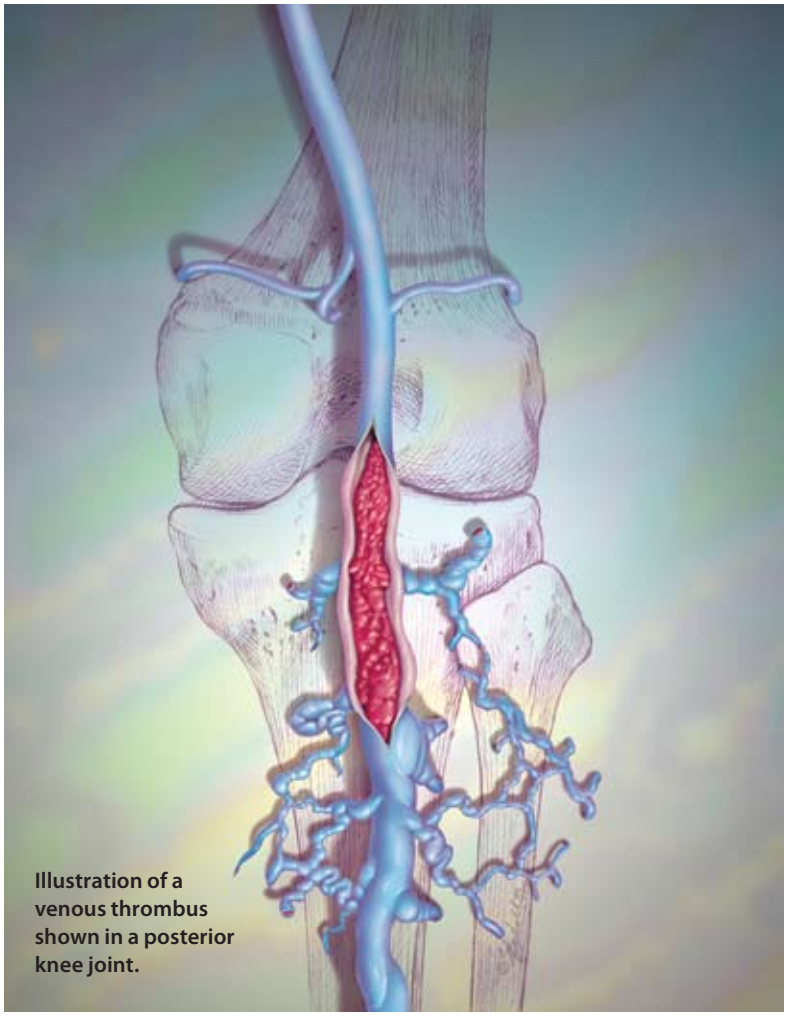

Illustration of a venous thrombus shown in a posterior knee joint.

LISA A. THOMPSON, PharmD, BCOP; MIRYOUNG KIM, PharmD

Venous thromboembolism (VTE) increases morbidity and mortality in oncology patients. The incidence of VTE is 5-fold higher in patients with cancer compared with other patients, and the condition is the second leading cause of death in oncology patients.[1-2] The risk of VTE in oncology patients is 0.5% per year and increases 6.5-fold for patients receiving chemotherapy.[3] The risk of recurrence is also higher in oncology patients (20.7% of cancer patients compared with 6.8% of patients without cancer).[4]

Types of venous thromboembolism include superficial venous thrombosis (SVT), deep-venous thrombosis (DVT), and pulmonary embolism (PE). SVT and DVT occur when a blood clot forms in the superficial or deep veins, respectively. The signs and symptoms of a DVT typically include unilateral limb redness, swelling, or pain. PE occurs when blood clots travel to the lungs and obstruct the pulmonary arteries. Symptoms of PE include shortness of

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breath, tachypnea, pleuritic chest pain, hypoxia, hemoptysis, tachycardia, or syncope.[5] The discussion of VTE in this article is confined to deep venous thrombosis and pulmonary embolism, as SVT is not typically treated via anticoagulation.

THROMBOSIS AND ANTICOAGULATION THERAPY

Cancer-associated mechanisms that can promote VTE include the release of prothrombotic factors, inflammation, local necrosis, and vascular stasis;[3] patient-related factors include age, comorbidities, or previous VTE (**Table 1**). The risk of VTE or VTE recurrence is higher for patients with advanced stage cancer; who are undergoing surgery; or who are receiving cytotoxic, hormonal, or antiangiogenic chemotherapy agents.[5-7]

The coagulation cascade is a series of reactions that produces a fibrin-containing clot. When the coagulation cascade is activated, tissue factor binds to cofactors to activate factor X. The activated factor X, referred to as *Xa*, interacts with other factors to convert prothrombin to thrombin. Thrombin then converts fibrinogen to fibrin, which forms the clot. Other factors that interact with this cascade include the vitamin K-dependent factors II, VII, and IX (factor X is also vitamin K-dependent). Some coagulation factors work to inhibit clot formation; these include antithrombin and the vitamin K-dependent proteins C and S.[3,7-9]

Patients who develop VTE are often treated with anticoagulants such as low-molecular-weight heparin (LMWH), unfractionated heparin (UFH), fondaparinux (Arixtra, generic), or warfarin (Coumadin, Jantoven, generics), a derivative of coumarin. UFH enhances the action of antithrombin, inactivating thrombin and preventing the conversion of fibrinogen to fibrin.[10] UFH may be administered subcutaneously for VTE prophylaxis, and intravenously as initial treatment of VTE in hospitalized patients. LMWH (enoxaparin [Lovenox, generics] and dalteparin [Fragmin]) also bind antithrombin to inhibit factor Xa and thrombin activity.[11,12] Although the LMWH products have not been compared in clinical studies, they are considered equivalent.[13] Fondaparinux inhibits factor Xa; the drug is used to treat VTE as well as prophylaxis in patients undergoing surgery.[14] Warfarin is an oral anticoagulant that inhibits synthesis of vitamin K-dependent coagulation factors and the anticoagulant proteins C and S.[15] Prophylaxis options include the anticoagulants discussed above as well as mechanical methods such as compression stockings, intermittent pneumatic calf compression, or mechanical foot pumps.[5,6] Oral direct thrombin inhibitors such as dabigatran (Pradaxa), are not recommended for prophylaxis or treatment in patients with cancer due to a lack of clinical data in these populations.[16]

In addition, some patients should not receive anticoagulants for treatment or prophylaxis of VTE. Contraindications to anticoagulation therapy include:

- Recent central nervous system (CNS) bleeding or intracranial or spinal lesions with a high risk of bleed;
- Active bleeding (acute or chronic)
- Thrombocytopenia with platelets less than 50,000/μL;
- Severe platelet dysfunction from uremia, medications, or dysplastic hematopoiesis;
- Recent major surgery with high risk for bleed;

TABLE 1. Risk factors for VTE or VTE recurrence in cancer patients[5-6]

Cancer-related factors
Active cancer
Cancer diagnosis within the previous 3-6 months
Current metastatic disease or advanced stage of cancer
Extrinsic vascular compression from regional bulky lymphadenopathy
Primary site of cancer (eg, pancreatic ovarian cancers)
Patient-related factors
Age 65 years and older
Comorbid conditions (eg, obesity, infection, renal disease)
Elevated prechemotherapy platelet count
Familial and/or acquired hypercoagulability (including pregnancy)
Heritable prothrombotic mutations
Prior history of VTE
Prolonged immobilization, poor performance status
Race (incidence is higher in African Americans, lower in Asian-Pacific Islanders)
Receiving estrogen-containing medications (eg, HRT, OCs)
Treatment-related factors
Current ESA therapy (eg, darbepoetin alfa [Aranesp], epoetin alfa [Procrit, Epogen, Eprex])
Current hospitalization
Current or recent antiangiogenic therapy (eg, thalidomide [Thalomid], lenalidomide [Revlimid], bevacizumab [Avastin])
Currently receiving chemotherapy
Presence of central venous catheters
Recent major surgery
Receiving certain hormonal anticancer agents (eg, tamoxifen or raloxifene)

Key: ESA, erythropoiesis-stimulating agent; HRT, hormone-replacement therapy; OCs, oral contraceptives; VTE, venous thromboembolism.

- Underlying coagulopathy such as clotting factor abnormality (eg, factor VIII deficiency);
- Recent spinal anesthesia/lumbar puncture;
- High risk of falls or head trauma.[6]

Mechanical methods should be used for VTE prophylaxis in patients who meet any of these criteria. Patients with VTE for whom anticoagulant therapy is contraindicated or who have recurrent VTE despite optimal coagulation may be candidates for a vena cava filter to prevent emboli from traveling to the lungs.[5-6]

ANTICOAGULATION AS PROPHYLAXIS

Guidelines from the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) recommend VTE prophylaxis with anticoagulation therapy for hospitalized oncology patients, unless contraindicated (**Table 2**),[5-6] and it should be continued throughout the hospitalization. Patients undergoing major surgery (duration more than 30 minutes) for malignant disease should also receive VTE prophylaxis.

Ideally, anticoagulation therapy is initiated prior to surgery or as soon after surgery as possible.[5] VTE prophylaxis should be continued for at least 7 to 10 days after surgery, and may be extended up to 4 weeks in high-risk situations (eg, major abdominal or pelvic surgery with residual disease after surgery, obesity, prior VTE, older than 60 years, advanced cancer, surgery lasting more than 2 hours, or patient is bed bound for more than 3 days).[5-6] In patients who underwent major abdominal surgery, VTE rates were lower in those who received prolonged prophylaxis (4 weeks) with dalteparin compared with 1 week of prophylaxis (16.3% vs 7.3%, $P = 0.012$).[17]

The guidelines also recommend using mechanical methods in addition to pharmacologic agents, especially in high-risk surgical patients. However, mechanical methods should not be used alone unless anticoagulation is contraindicated.[5-6] VTE prophylaxis is not recommended for most ambulatory oncology patients, but it is recommended in ambulatory patients with multiple myeloma who are receiving thalidomide (Thalomid) or lenalidomide (Revlimid) in combination with chemotherapy or dexamethasone (Ciprodex, generics) due to the high risk of thrombosis in these patients.[5-6]

In vitro data and animal studies suggested that LMWH and UFH may have antineoplastic effects by interfering with angiogenesis and inhibiting metastases.[8,18] However, clinical trials did not show a consistent improvement in overall survival of patients without VTE.[19-20] Therefore, anticoagulation is not currently recommended to improve survival in oncology patients without a previous VTE.[5]

ANTICOAGULATION AS TREATMENT

The ASCO and NCCN guidelines recommend acute and chronic anticoagulation therapy for VTE in oncology patients

TABLE 2. Anticoagulants for VTE prophylaxis in patients with cancer[5-6]

Setting	Drug	Dose
Hospitalized or surgical cancer patients	LMWH • Dalteparin (Fragmin)	• 5,000 units SQ daily
	• Enoxaparin (Lovenox, generics)	• 40 mg SQ daily
	Unfractionated heparin	5,000 units SQ every 8 hours
	Fondaparinux (Arixtra, generics)	2.5 mg SQ daily
Ambulatory patients receiving thalidomide or lenalidomide	LMWH[a] • Dalteparin	• 5,000 units SQ daily
	• Enoxaparin	• 40 mg SQ daily
	Warfarin[a] (Coumadin, Jantoven, generics)	Adjust to INR of 2.0-3.0

Key: INR, international normalized ratio; LMWH, low-molecular-weight heparin; SQ, subcutaneous.

[a] For high risk patients with multiple myeloma receiving thalidomide (Thalomid) or lenalidomide (Revlimid) with high dose dexamethasone (Ciprodex, generics; more than 480 mg per month)

TABLE 3. Anticoagulants for VTE treatment in cancer patients[5-6]

Drug	Dose
LMWH[a] • Dalteparin (Fragmin)	• 200 units/kg SQ daily for 30 days, then 150 units/kg SQ daily
• Enoxaparin (Lovenox, generics)	• 1 mg/kg SQ every 12 hours
Fondaparinux (Arixtra, generics)[b]	• <50 kg: 5 mg SQ daily • 50-100 kg: 7.5 mg SQ daily • >100 kg: 10 mg SQ daily
Unfractionated heparin (IV)[b]	80 units/kg loading dose, then 18 units/kg per hour[c]
Warfarin[d]	Adjust dose to INR 2.0-3.0

Key: INR, international normalization ratio; LMWH, low-molecular-weight heparin; SQ, subcutaneous; VTE, venous thromboembolism.

[a] LMWH preferred for first 6 months in patients with proximal deep venous thrombosis or pulmonary embolism and to prevent recurrent VTE.

[b] Acute setting

[c] Adjust to PTT 2 to 2.5 x control per institution protocol

[d] Chronic setting; requires bridge therapy with unfractionated heparin or LMWH for 5 days and INR higher than 2.0 for 2 consecutive days

unless contraindicated.[5-6] Anticoagulation therapy should be initiated in patients with VTE as soon as possible (**Table 3**). A low-molecular-weight heparin is the preferred agent for initial treatment; however, fondaparinux or parenteral UFH may be used. The guidelines recommend administration of anticoagulation therapy for at least 3 to 6 months for DVT and 6 to 12 months for PE. LMWH is preferred for continuing treatment of VTE, although fondaparinux or warfarin (to a target international normalization ratio [INR] of 2.0 to 3.0) may be another option. If warfarin is used, *bridge therapy* (concomitant administration of LMWH or parenteral UFH) is necessary due to the initial hypercoagulability of warfarin. To administer bridge therapy, the patient should achieve therapeutic levels of anticoagulation with LMWH or UFH before initiating warfarin, which is continued until warfarin has been administered for at least 5 days and two consecutive INR measurements are 2.0 or higher.[5-6]

Both ASCO and NCCN guidelines recommend indefinite anticoagulation (beyond 6 months) for patients with VTE who have active cancer with metastatic disease, are receiving chemotherapy, or have persistent risk factors.[5-6] Mechanical devices such as a vena cava filter may be used if pharmacologic anticoagulation is contraindicated or if VTE recurs while the patient is receiving the LMWH.[5]

Although warfarin is an option for continuing treatment of VTE, multiple complexities are associated with its use in patients with cancer. As mentioned above, warfarin therapy requires bridging with another agent (eg, LMWH). In addition, warfarin doses are titrated for individual patients to a target INR range. If the INR is too low or too high, patients are at risk for recurrent VTE or bleeding, respectively.[4,21] Oncology patients are more prone to fluctuating INR due to drug interactions with other medications; altered dietary intake as a result of vomiting, decreased appetite, or poor GI absorption; or altered metabolism due to liver metastases and impaired hepatic function.[22] The CLOT (Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer) Trial compared the efficacy and safety of secondary prophylaxis with dalteparin with an oral coumarin (warfarin or acenocoumarol, including bridge therapy) in the prevention of recurrent VTE in cancer patients.[22] The INR of patients receiving warfarin was within the targeted range only 46% of the time.[22] The incidence of recurrent VTE was significantly greater in the oral anticoagulant arm (17%) than the dalteparin arm (9%). No difference was seen in the rate of any type of bleeding or mortality at 6 months. This study concluded that dalteparin prevented recurrent VTE more effectively than oral coumarin derivatives without increasing the risk of bleeding.[22]

Comprehensive listings of foods high in vitamin K

USDA National Nutrient Database for Standard Reference, Release 17
Vitamin K (phylloquinone) (µg) content of selected foods per common measure, sorted by nutrient content
www.nal.usda.gov/fnic/foodcomp/Data/SR17/wtrank/sr17w430.pdf

Important information to know when you are taking Coumadin and vitamin K
http://ods.od.nih.gov/pubs/factsheets/coumadin1.pdf

Warfarin diet: What foods should I avoid?
www.mayoclinic.com/health/warfarin/AN00455

MONITORING AND PATIENT EDUCATION

Nurses have an important role in educating patients about anticoagulants and monitoring their therapy. Patients should be counseled on the signs and symptoms of bleeding such as blood in the urine, black tarry stools, bloody sputum, or severe headache, as well as symptoms of recurrent VTE. Frequent CBCs are also recommended.[11,12,14] Patients receiving anticoagulation therapy via injections should be counseled on administration technique and syringe disposal. In addition to these general instructions, each therapeutic option includes its own specific counseling points and monitoring parameters.

Unfractionated heparin Patients receiving UFH should have their dose titrated according to aPTT results. aPTT test results are laboratory-specific; therefore, dose titration should follow institution-specific nomograms. UFH does not require dose adjustments in renal or hepatic failure.[10] UFH (as well as LMWH and, in rare cases, fondaparinux) has been associated with heparin-induced thrombocytopenia (HIT), which can occur 5 to 10 days after initiation of heparin products. Delayed onset HIT may occur up to 3 weeks after heparin exposure.[23,24] HIT is an immune-mediated disorder that causes platelet activation and aggregation, resulting in lower platelet counts. Patients receiving these agents should have their platelet counts monitored. If platelets decrease significantly,[3] discontinuation of therapy and close monitoring is recommended.[25]

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Low-molecular-weight heparin LMWH does not affect aPTT or INR but can be monitored via anti-Xa levels. LMWH produces predictable degrees of anticoagulation, thus anti-Xa levels are not routinely monitored. However, patients who are obese or have renal impairment may have variable levels of anticoagulation; therefore, anti-Xa may be monitored in these populations.[11,12] Serum creatinine monitoring is recommended for patients receiving LMWH (enoxaparin, dalteparin), as these agents require dose adjustments or anti-Xa monitoring in patients with creatinine clearance of less than 30 ml/min.

Guidelines recommend LMWH as the preferred agent for VTE prophylaxis, although warfarin or fondaparinux may be used.

Fondaparinux Anti-Xa activity may be measured for fondaparinux, but this is not routinely performed.[14] Serum creatinine should be monitored, as fondaparinux is contraindicated in patients whose creatinine clearance is less than 30 ml/min. Fondaparinux should not be used for VTE prophylaxis in patients who weigh less than 50 kg.[14]

Warfarin Patients using warfarin should be counseled on the importance of adhering to a regular INR monitoring schedule, and their dose should be titrated to a goal INR of 2.0 to 3.0 (unless they have a mechanical heart valve or other indications).[6] Warfarin has many drug-drug interactions that cause INR fluctuations, especially medications and herbal supplements (eg, St. John's wort) that inhibit or induce warfarin metabolism. Patients should contact their health care providers before taking a new medication or herbal supplement, or if their current medications are changed. Vitamin K intake also affects INR, therefore, patients should be advised to keep the amount of vitamin K in their diet consistent. Foods high in vitamin K include dark, leafy green vegetables; brussel sprouts; broccoli; asparagus; and scallions (**Comprehensive listings of foods high in vitamin K**). Patients should be advised to discuss any multivitamins and nutritional supplements they may be taking or consider taking because these products may also contain vitamin K.

IN SUMMARY

Within the context of this article, VTE refers to deep venous thrombosis and pulmonary embolism. Superficial venous thrombosis is not generally treated with anticoagulation therapy. Patients with cancer are at increased risk of developing new and recurrent VTE. Routine prophylaxis is not recommended for oncology patients without a previous VTE. However, hospitalized, surgical, and certain ambulatory oncology patients should receive VTE prophylaxis. ASCO and NCCN guidelines recommend LMWH as the preferred agent for VTE prophylaxis, although warfarin or fondaparinux may be used. Treatment with LMWH or other anticoagulants should be administered to oncology patients who develop VTE. Clinicians should keep in mind the increased risk of bleeding from anticoagulants; therefore, their use is not appropriate for all patients, and the benefits of anticoagulant treatment should outweigh the harms. Appropriate patient education and monitoring is crucial. ■

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