Direct Oral Anticoagulants and Cancer Thrombosis: What APs Need to Know

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Abstract

Patients with cancer are at high risk for developing cancer-associated blood clots. Mailey L. Wilks, DNP, APRN, NP-C, led a session at JADPRO Live Virtual 2021 on the risk of venous thromboembolism in patients with cancer, available anticoagulants, with a focus on direct oral anticoagulants, and what advanced practitioners should know about the prevention and the treatment of venous thromboembolism.

Cancer significantly increases the risk of developing venous thromboembolism (VTE), which is the second leading cause of death in people with cancer. During JADPRO Live Virtual 2021, Mailey L. Wilks, DNP, APRN, NP-C, of the Cleveland Clinic, reviewed the currently available anticoagulants, including direct oral anticoagulants (DOACs), used for prevention and treatment of VTE. Dr. Wilks also discussed optimal strategies for anticoagulation in special populations with cancer-associated thrombosis.

"It's very important for advanced practitioners to educate their patients with cancer about the risk of VTE, even before the diagnosis of blood clot, and to have a conversation with them about signs and symptoms," said Dr. Wilks. "Cancer-associated thrombosis can be very complex to treat."

RISK FACTORS FOR VTE

Venous thromboembolism, a disease that includes deep-vein thrombosis (DVT), pulmonary embolism (PE), splanchnic vein thrombosis, cerebral vein thrombosis, and superficial vein thrombosis, affects approximately 1 out of 1,000 people annually. Importantly, cancer increases the risk of developing VTE by 4 to 7 times, and cancer-associated VTE accounts for 20% of all VTE cases. Among people with cancer, VTE is associated with worse prognosis and early mortality if found within the first 4 cycles of chemotherapy (VTE occurs in 12.6% of patients during their first year of chemotherapy).

In addition to cancer and cancer treatments, age and male gender are risk factors for developing VTE. Protein C and S deficiency, antithrombin III deficiency, factor V Leiden gene mutation, and prothrombin gene mutation also increase the likelihood of a

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VTE event. Acquired diseases, such as antiphospholipid antibody, myeloproliferative disorders, autoimmune disorders/systemic inflammation, and paroxysmal nocturnal syndrome, and situational risk factors, such as hospitalization, immobilization (e.g., long flight/travel), recent trauma or surgery, obesity, smoking, hormone use, central venous catheters, infection, and prior VTE, also contribute to VTE risk.

Antineoplastic agents that are associated with the risk of VTE include tamoxifen, immunomodulatory drugs (IMiDs), L-asparaginase, and immunotherapies.

DIAGNOSIS

Clinical features of VTE include swelling, warmth, or redness of the lower extremities, and localized tenderness along the distribution of the deep venous system. According to Dr. Wilks, however, patients can also present asymptomatically.

"Sometimes, VTE is associated with very profound symptoms like unilateral swelling and is easy to diagnose, but other times, there may be bilateral swelling that is very equal in size," said Dr. Wilks. "Clots can also be detected incidentally with imaging for another medical reason."

"Trust your gut if your patient is presenting with mild symptoms," she added. "It doesn't hurt to check because the last thing you want to do is miss a DVT or a clot."

Providers can diagnose VTE with duplex ultrasound, CT scan, ventilation-perfusion scan, or venogram. Although D-dimer has a negative predictive value of 96% and a high sensitivity, NCCN guidelines do not recommend D-dimer in patients with cancer given increased likelihood of a false/positive result (D-dimer is elevated in patients with inflammation and with cancer).

TREATMENT OPTIONS: CHOICE OF INITIAL ANTICOAGULANT

According to Dr. Wilks, the goals of treatment for VTE are to prevent death from PE, prevent symptomatic recurrent VTE, reduce morbidity (from post thrombotic syndrome, which affects 1 in 4 people at 2 years and chronic pulmonary HTN, which has a rate of 4% at 2 years), and minimize risk of bleeding.

Choosing an anticoagulant can be challenging due to an abundance of treatment options, which include unfractionated heparin, low-molecular-weight heparin (e.g., enoxaparin and dalteparin), fondaparinux, and several DOACs (e.g., rivaroxaban, apixaban, edoxaban, and betrixaban).

"There is no cookie-cutter approach to choosing an initial anticoagulant," said Dr. Wilks. "You have to look at the whole clinical scenario, have a talk with the patient to understand their wishes, and then weigh the risks vs. benefits of bleeding vs. risk of VTE."

DOACs: DETAILS TO CONSIDER

Dr. Wilks listed several details to consider when using DOACS to treat cancer patients with thrombosis. Renal function must be considered because most DOACs are cleared renally, she said, and cost can be a huge concern.

"A lot of the DOACs now come with a free 1-month supply and have programs in place to mitigate costs," said Dr. Wilks. "I encourage you to work with your social work team and other financial advocates at your centers to really make sure you can find coverage for patients."

Providers should also consider the half-life of the drug, especially if there are upcoming procedures that increase the risk of bleeding (e.g., surgeries or port placements). Some anticoagulants may require proper bridging, said Dr. Wilks, who emphasized the importance of patient preference.

"Always have a conversation with the patient, give them all the options, and tell them why you think one vs. another anticoagulant would be better," she said. "Most of these patients already have so many other comorbidities and a laundry list of medications they're taking, so it's important to remember that you're adding one more to the mix."

Dr. Wilks also underscored the importance of discussing compliance with patients, as missing a dose could lead to a life-threatening situation. Although there are fewer food/drug interactions to consider vs. other anticoagulants, Dr. Wilks noted that potent inhibitors or inducers of P-glycoprotein and cytochrome P450 CYP3A4 are known to influence metabolism of DOACs (Table 1).

DURATION OF ANTICOAGULATION

According to Dr. Wilks, patients frequently ask questions about the duration of treatment of cancer thrombosis. Close follow-up is important to monitor patients and analyze the risk factors of

stopping vs. continuing treatment. At the Cleveland Clinic's outpatient clinic, Dr. Wilks noted that patients are followed at 1 month, 3 months, 6 months, and beyond to help the primary oncology team determine whether a patient should remain on anticoagulation.

"We typically treat our patients with cancer-related thrombosis for at least 3 to 6 months, and then we analyze the risk factors," said Dr. Wilks. "The conversations with the primary oncologist about the risks of bleeding vs. the risks of VTE are always very patient specific."

PULMONARY EMBOLISM

Incidental detection is common in the cancer thrombosis population because of the number of scans for disease progression.

Most patients in clinical practice are treated with anticoagulation, especially those with a history of cancer. In patients with a high suspicion for VTE/PE and no known contraindications to anticoagulation, anticoagulation can be started pending imaging studies (Kraaijpoel & Carrier, 2019).

If proximal, incidental PE should be treated as symptomatic, said Dr. Wilks, who also noted controversy regarding asymptomatic subsegmental PE. In cancer, subsegmental PEs have been associated with VTE recurrence (O'Connell, 2015).

"When in doubt, call a radiologist to consult with the scan or get another lower extremity ultrasound," she said.

ROLE OF DOACs IN CANCER

The Hokusai-Cancer trial, which randomized 1,050 patients with cancer who had acute symptomatic or incidental VTE to edoxaban or dalteparin, showed that DOACs perform favorably in the cancer population, unless they have gastrointestinal cancer (Raskob et al., 2018). Oral edoxaban was noninferior to dalteparin, with a lower rate of recurrent VTE but a higher rate of major bleeding. The risk of major bleeding was 6.9% with edoxaban and 4% with dalteparin, and patients with gastrointestinal cancers had the highest risk of bleeding.

A systematic review of observational and randomized controlled trials also demonstrated a lower rate of recurrent VTE with the use of DOACs as compared with low-molecular-weight heparin or warfarin (Li et al., 2019). The bleeding rate was also higher on DOACs, but many of these early trials of DOACs in the cancer population included patients with gastrointestinal cancer.

"Treatment with DOACs is preferred for patients with low risk of bleeding and no drug-drug interaction, but low-molecular-weight heparins are an acceptable alternative," said Dr. Wilks. "The final treatment recommendation should be made after shared decision-making with the patient regarding fewer VTE recurrence events but greater bleeding rates with rivaroxaban and edoxaban compared with low-molecular-weight heparin."

"We're still very cautious about using DOACs in patients with gastrointestinal cancer, especially if it's a luminal cancer," she added.

For cancer patients with luminal gastrointestinal cancers, cancers at risk of bleeding from genitourinary tract, patients with active mucosal abnormalities such as duodenal ulcers, metastasis to GI tract, gastritis/esophagitis or colitis, Dr. Wilks recommended avoiding DOACs and using low-molecular-weight heparins instead to minimize bleeding risks.

The SELECT-D trial was a prospective, open-label multicenter trial that randomized 406 patients with active cancer and symptomatic lower

Table 1. Direct Oral Anticoagulants

DOAC	Enzyme target	Renal clearance	Half-life	Approved for	Dose
Rivaroxaban	Xa	36%	7–11 hr	DVT/PE	15 mg bid × 21 days then 20 mg daily
Apixaban	Xa	27%	8–12 hr	DVT/PE	10 mg bid × 7 days then 5 mg bid
Edoxaban	Xa	50%	8–10 hr	DVT/PE	60 mg qd after 5–10 days of heparin

extremity DVT or symptomatic/incidental PE to receive rivaroxaban vs. dalteparin for 6 months. This trial showed a statistically significant reduction in recurrent VTE at 6 months in the rivaroxaban arm compared with dalteparin (4.0% vs. 11.0%, respectively. Major bleeding was higher with rivaroxaban than with dalteparin (6.0% vs. 4.0%, respectively), although not statistically significant (Young et al., 2018).

The CARAVAGGIO trial examined the use of DOACs for the treatment of cancer-associated thrombosis. This open-label trial randomized 1,170 cancer patients to receive apixaban or dalteparin for 6 months. This trial showed that apixaban was noninferior to dalteparin with respect to recurrent VTE (5.6% vs. 7.9%, respectively). Major bleeding rates were similar between apixaban and dalteparin (3.8% vs. 4.0%, respectively; Agnelli et al., 2020).

PRIMARY VENOUS THROMBOEMBOLIC PROPHYLAXIS

The CASSINI and the AVERT trial also showed that DOACs can be used effectively for the prevention of cancer-associated thrombosis (Khorana et al., 2019; Carrier et al., 2019).

The Khorana score predicts risk of VTE and the need for prophylaxis for cancer patients depending on type of cancer and other risk factors. These risk factors include platelet count, hemoglobin, red cell growth factors, leukocyte count, and body mass index (BMI). Patients with Khorana score greater than 2 should be considered for primary prophylaxis with DOACs or low-molecular-weight heparin to reduce the risk of VTE (Bosch et al., 2020).

"Weight is another important consideration," said Dr. Wilks. "Patients with a BMI greater than 40 or weight greater than 120 kg can use DOACs, but may need to be considered for warfarin."

CONSIDERATIONS FOR PATIENTS UNDERGOING SURGERY

Finally, Dr. Wilks noted considerations for patients undergoing major surgery for cancer.

"Pharmacologic VTE prophylaxis should start as soon as possible after surgery and be continued for at least 7 to 10 days," she said. "Low-molecular-weight heparin is recommended for up to 4 weeks post-op for patient undergoing major abdominal or pelvic surgery for cancer who have other high-risk features."

Disclosure

The presenter had no conflicts of interest to disclose.

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