Clinical Practice

Five things to know about cancer-associated thrombosis

Yousef Bolous, MD[1]

Allen Tran, MD[2]

1. Department of Medicine, Dalhousie University, Halifax, NS

2. Division of General Internal Medicine, Department of Medicine, Dalhousie University, Halifax, NS

Correspondence to
Dr. Yousef Bolous;
yousef.bolous@dal.ca

Cancer-associated thrombosis (CAT) is common and is the second leading cause of death in patients with cancer.

20-30% of first venous thromboembolic (VTE) events are associated with cancer.[1] This can occur in patients with cancer who otherwise do not have risk factors for VTE. Patients with cancer have a 4-7-fold higher risk of VTE compared to the general population.[1] The risk of VTE is greatest during the first three months after diagnosis due to a multitude of factors, including patient-related risk factors (e.g. reduced mobility, comorbidities, older age), cancer-related risk factors (e.g. cancer type, disease burden), and treatment-related risk factors (e.g. surgery, chemotherapy, central venous catheters).[1]

Incidental CAT requires treatment because this diagnosis carries a high risk of recurrence and high mortality rate.

28% of CAT diagnoses are identified incidentally on routine imaging.[2] A post-hoc analysis of the Hokusai VTE Cancer Study population found that incidence of VTE recurrence after 12 months of anticoagulation was similar between patients with incidental CAT and symptomatic CAT (7.9% vs. 10.9%, aHR 0.68, 95% CI 0.42-1.11).[3] Likewise, both populations had a similar all-cause mortality rate (37.2% vs. 38.1%, aHR 0.83, 95% CI 0.65-1.05). These findings are in alignment with current guidelines which recommend treatment of incidental CAT like symptomatic CAT.

Low molecular weight heparin (LMWH) and direct acting oral anticoagulants (DOACs) are the preferred agents to treat CAT.

LMWH was the preferred treatment option for CAT prior to recent studies assessing the role of DOACs for CAT. This recommendation was based on data showing a reduced VTE recurrence rate and non-significant increased risk of bleeding when comparing LMWH to vitamin K antagonists.[4] The Hokusai VTE,[5] SELECT-D,[6] CARAVAGGIO,[7] and ADAM-VTE[8] trials compared individual DOACs against LMWH for the treatment of VTE in patients with cancer.[9] These studies demonstrated that DOACs were non-inferior to LMWH with respect to VTE recurrence and major bleeding.

DOACs might not be suitable in certain circumstances.

DOACs are now regarded as the treatment of choice for CAT. However, DOACs should not be considered interchangeable in patients with gastrointestinal (GI) malignancies. Specifically, compared with LMWH, edoxaban and rivaroxaban are associated with increased risk of bleeding in patients with GI malignancies whereas apixaban does not have this association. In the Hokusai VTE population, patients in the edoxaban arm had a greater incidence of major bleeding events (6.1% vs. 3.1%, HR 2.0, 95% CI 1.09-3.66, p=0.025).[10] The group's elevated risk was attributed to an increased rate of upper GI bleeding events primarily occurring in patients with GI malignancies (12.7% vs. 3.6%, HR 4.0, 95% CI 1.5-10.6, p=0.005). Similarly, SELECT-D showed that rivaroxaban was associated with a greater cumulative major bleeding rate at six months (6% vs. 4%, HR 1.83, 95% CI 0.68-4.96) compared to LMWH,[6] and the patients with GI malignancies tended to experience more major bleeding events (36% vs. 11%). In contrast, the CARAVAGGIO trial did not show a significant difference in major bleeding events (3.8% vs. 4.0%, HR 0.82, 95% CI 0.40-1.69) or major GI bleeding events (1.9% vs 1.7%, HR 1.05, 95% CI 0.44-2.50) between apixaban and LMWH treated groups.[7]

Finally, patients who have GI tract resections, take medications that alter P-glycoprotein and/or CYP3A4 metabolic pathways, and/or are at the extremes of weight may have DOAC levels outside of the expected range. There is a paucity of high-quality evidence for these situations.[11]

Most patients with CAT will receive anticoagulation for six months. After this period, patients require reassessment for the benefits and harms of continuation.

Patients with CAT require follow up at least every three months to consider the need for ongoing anticoagulation.[11] This should be guided by a clinician comfortable in VTE man-

agement as this requires evaluation of the risk of recurrence and bleeding. Expert guidelines recommend continued anticoagulation if the patient is receiving systemic chemotherapy, has active disease, or has risk factors of recurrent thrombosis and a low bleeding risk.[12]

Table 1. Treatment Options for Cancer-Associated Thrombosis*

	Drug	Dosage	Interactions	Considerations
DOACs	Apixaban	10 mg BID p.o. for 7 days then 5 mg BID p.o.	Contraindicated with CYP3A4 and Pgp inhibitors	CrCl <15 mL/min – not recommended CrCl 15-29 mL/min – use with caution
	Edoxaban	60 mg daily p.o. after 5 days of parenteral LMWH at therapeutic doses	Avoid with CYP3A4 and Pgp inducers	CrCl <30 mL/min – not recommended CrCl 30-50 mL/min or ≤60kg – 30 mg daily p.o.
	Rivaroxaban	15 mg BID p.o. for 3 weeks then 20 mg daily p.o.	Contraindicated with CYP3A4 and Pgp inhibitors	CrCl <30 mL/min – not recommended Take with largest meal to maximize absorption
LMHWs	Dalteparin	200 units/kg daily s.c. for first month then 150 units/kg daily s.c. or 200 units/kg daily s.c. for duration of treatment	Bleeding risk with ASA and oral anticoagulants	Dose based on actual weight Use with caution in patients with renal dysfunction

*Adapted from Carrier et al,[11] Thrombosis Canada,[12] and Compendium of Pharmaceuticals and Specialties[13]
Abbreviations: ASA, acetylsalicylic acid; BID, twice daily; CrCl, creatinine clearance; DOAC, direct oral anticoagulant; LMWH, low molecular weight heparin; p.o., by mouth; s.c., subcutaneously

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