Cancer and Thrombosis

Thrombosis Canada
Thrombose Canada

Objective:

To assist health care professionals in the management of cancer-associated thrombosis (CAT).

Background:

Low molecular weight heparin (LMWH) and anti-factor Xa direct oral anticoagulants (DOACs), including apixaban, edoxaban, and rivaroxaban, are recommended for the treatment of CAT. The major barriers for LMWH use are drug cost and discomfort of daily injections; however, studies have shown that it is well tolerated. Both LMWH and the DOACs are superior to warfarin in terms of efficacy, bleeding risk, and quality of life measures. There are some instances where treatment with LMWH is preferred over a DOAC:

- Malignancy of the GI/GU tract or GI/GU bleeding
- Significant thrombocytopenia (e.g. platelet count 25-50x10^9/L)
- Pregnancy & breastfeeding
- Upfront treatment for VTEs with large clot burden (e.g. submassive PE)

Management approaches to Deep Vein Thrombosis (DVT) and/or Pulmonary Embolism (PE) in cancer patients:

LMWH:

Therapeutic dosing varies depending on the specific LMWH. While only dalteparin has regulatory indication in Canada for extended treatment of CAT, the other LMWHs have also been used successfully for this indication. The following are the recommended doses for LMWHs:

- Dalteparin 200 U/kg daily for the first month then continue at ~150 U/kg daily.
- Tinzaparin 175 IU/kg daily.
- Enoxaparin 1 mg/kg twice daily or 1.5 mg/kg once daily.

The calculated dose should be rounded up to the nearest prefilled syringe available. The dose of LMWH in obese patients should not be capped but based on actual body weight. For patients weighing more than the upper limit accommodated by a single pre-filled syringe (i.e., 90 kg for dalteparin, 100 kg for enoxaparin and 103 kg for tinzaparin), twice daily dosing or use of multi-dose vials (available for all 3 LMWHs) is recommended.

LMWH is renally dependent and in patients with severe renal insufficiency (creatinine clearance [CrCl] <30 mL/min), use should be reassessed to ensure safety. The following options may be considered for patients on a case-by-case basis:

1. Continue tinzaparin at standard dosing. For tinzaparin, available evidence demonstrates no accumulation in patients with CrCl levels down to 20 mL/min. A recent systematic review provided evidence that there was no bioaccumulation of tinzaparin over a short time period in patients with significant renal impairment, including CrCl < 20 mL/min.
2. Continue LMWH with anti-Xa level measurement to guide dose adjustment. Some experts suggest that a dose reduction should be considered if the trough anti-Xa level is >0.5 IU/mL; however, high quality data showing a correlation between these levels and poor clinical outcomes are lacking.
3. Warfarin may also be used if usage of LMWH or DOACs is not feasible in patients with chronic kidney disease. Consultation with a hematologist or thrombosis expert is recommended.

Direct Oral Anticoagulants (DOACs):

Edoxaban (HOKUSAI-VTE Cancer), rivaroxaban (SELECT-D), and apixaban (Caravaggio) have all been compared to LMWH for CAT in separate randomized clinical trials. The primary outcome was recurrent VTE in the SELECT-D and Caravaggio trials, whereas the primary outcome was a composite of recurrent VTE or major bleeding in HOKUSAI-VTE cancer. The assigned treatment periods were either 6 months (SELECT-D and Caravaggio) or at least 6 months and up to 12 months (HOKUSAI-VTE Cancer). SELECT-D was designed as a pilot study and included 406 patients while the HOKUSAI-VTE Cancer and Caravaggio studies had over 1,000 patients each. No similar such randomized trials assessing the use of dabigatran in CAT that have been published.

Recurrent VTE:

Generally, the anti-Xa inhibitors were found to have similar and potentially lower rates of recurrent VTE when compared with LMWH, with rates between 4%-8% with the anti-Xa inhibitors.

Bleeding:

The rates of major bleeding with the anti-Xa inhibitors varied from 4% to 7%. There was more major bleeding with edoxaban compared with LMWH (HR 1.77), whereas there was no significant difference in major bleeding when rivaroxaban or apixaban were individually compared with LMWH. In addition, there were more gastrointestinal (GI) bleeds in patients with upper GI cancers in those who were on edoxaban or rivaroxaban, suggesting physicians should be cautious when prescribing these anti-Xa inhibitors in patients with GI malignancies and those at increased risk of GI bleeding. Apixaban had similar rates of GI bleeding compared with LMWH. Risks of intracranial and fatal bleeding were low and similar with the individual anti-Xa inhibitors and LMWH.

The rates of clinically relevant nonmajor bleeding (CRNMB – bleeding that requires medical attention or impairs quality of life) varied from 9% to 15% with the anti-Xa inhibitors. Apixaban and edoxaban had non-significantly higher rates of CRNMB compared with LMWH, whereas there was more CRNMB with rivaroxaban compared with LMWH (HR 3.76).

Important study exclusion criteria that may impact bleeding risk included thrombocytopenia (either below 75×10^9/L [apixaban]) or 50×10^9/L [edoxaban]), concomitant ASA use, and the presence of an intracranial malignancy or leukemia.

Other outcomes:

Similar to the trials that compared LMWH with warfarin in CAT, there was no overall survival benefit seen with the use of any anti-Xa inhibitor compared with LMWH. The COSIMO study demonstrated that patients

with CAT who changed their anticoagulant from LMWH, fondaparinux or VKA to rivaroxaban experienced an improvement in treatment satisfaction.

Dosing:

Apixaban: Initial LMWH is not required. Dosing is as usual at 10 mg twice daily for 1 week followed by 5 mg twice daily. For further information on dosing and drug interactions, see **Clinical Guide: Apixaban (Eliquis®)**. A small randomized trial (EVE) demonstrated that dose reduction to 2.5 mg twice daily in patients with cancer after 6 months of full dose initial therapy was associated with no significant difference in major bleeding or recurrent VTE, although there continues to be equipoise on the safety of dose reduction for extended secondary prevention of CAT. Results from EVE trial showed similar rates of bleeding with 2.5 mg twice daily compared to 5 mg twice daily without an increased risk of thrombosis.

Edoxaban: After an initial 5-day treatment with therapeutic LMWH, edoxaban 60 mg once daily is given. The dose is reduced to 30 mg once daily in those who have creatinine clearance between 30- and 50 mL/min, weigh 60 kg or less, or are taking potent P-glycoprotein inhibitors (such as erythromycin, cyclosporine, dronedarone, quinidine, or ketoconazole). For further information on dosing and drug interactions, see **Clinical Guide: Edoxaban (Lixiana®)**.

Rivaroxaban: Initial LMWH is not required. Dosing is as usual at 15 mg twice daily for 3 weeks followed by a daily dose of 20 mg. For further information on dosing and drug interactions, see **Clinical Guide: Rivaroxaban (Xarelto®)**. Dose reduction to 10 mg once daily after initial therapy has not been studied in this patient population.

Duration of therapy:

Optimal duration has not been studied. Patients should receive anticoagulation for a minimum of 3 to 6 months. At that time, continued anticoagulation is recommended if the patient: 1) is receiving systemic chemotherapy; 2) has metastatic disease; 3) has progressive or relapsed disease; or 4) has other ongoing risk factors that increase the risk of recurrent thrombosis (e.g. central venous catheter), and 5) bleeding risk remains low. Thereafter, reassessment should be done every 3 to 6 months.

Anticoagulation treatment decisions must also be considered alongside patient preference, quality of life, and life expectancy. Many patients near the end of life may benefit from anticoagulation discontinuation as bleeding risk approaches 10% in this population.

Monitoring:

Patient weight, CBC, and renal function should be checked every 3 months. Drug-drug interactions should be reviewed with any change in medication for patients receiving a DOAC. Drugs that are potent inhibitors or inducers of P-glycoprotein 1 and CYP3A4 pathways can increase or reduce the serum levels of DOACs.

Laboratory monitoring with anti-Xa levels is not routinely required. Heparin-induced thrombocytopenia is uncommon, occurring in <0.5% of patients who are receiving long-term, full-dose LMWH.

Special Considerations:

Medication Absorption: A potential benefit of LMWH is parenteral administration. This would be the preferred anticoagulant in those with significant nausea and vomiting as it may affect oral medication absorption. In addition, DOACs should be avoided in those who do not have an intact upper GI tract, as absorption is unpredictable and may be subtherapeutic. This may be relevant to patients who have undergone abdominal cancer surgery involving the bowel.

Recurrent thrombosis despite anticoagulation: Insertion of a vena cava filter is not recommended for recurrent thrombosis in patients receiving therapeutic anticoagulation, as this has been shown to increase the risk of DVT while offering no reduction in PE or survival benefit. Based largely on expert opinion, those who develop clot recurrence while on warfarin or a DOAC should switch to therapeutic dosing of LMWH. For patients who have a recurrent thrombosis despite adherence to therapeutic LMWH, the dose of LMWH can be increased by approximately 25% once heparin-induced thrombocytopenia has been excluded. Consultation with a hematologist or thrombosis expert is recommended.

Thrombocytopenia: In patients with acute cancer-associated VTE who develop thrombocytopenia, full-dose anticoagulation can be continued until the platelet count is $<50 \times 10^9$/L. Half-dose LMWH is recommended for patients with a platelet count between 25 and 50×10^9/L. For patients with a platelet count $<20 \times 10^9$/L, anticoagulants are usually withheld until the platelet count increases. For acute proximal VTE, platelet transfusions can be used to maintain the platelet count above 50×10^9/L to allow full-dose administration of anticoagulation. Consultation with a hematologist or thrombosis expert is recommended.

Catheter-related thrombosis: Anticoagulant therapy generally involves the same regimen as for lower extremity DVT/PE. LMWH and DOACs can be considered, although there is limited direct evidence for DOACs in this setting. Treatment should continue for a minimum of 3 months and for as long as the catheter remains in place. The catheter can be kept in place if it is functional, well positioned, not infected, and symptoms improve on anticoagulation therapy. If no longer indicated, the catheter can be removed as per standard practice. [see the **Clinical Guide:** **Central Venous Catheter-Related Deep Vein Thrombosis**].

Incidental thrombosis: Incidental thrombosis is common during imaging of the chest or abdomen to assess for cancer recurrence or response to cancer treatment. Patients may or may not have symptoms consistent with thrombosis.

- **Pulmonary embolism:** Involvement of segmental or more proximal pulmonary arteries warrants anticoagulant therapy with the same treatment regimen as for symptomatic thrombosis. For incidental cancer-associated subsegmental PE, a preference to treat is supported by a meta-analysis showing that patients with cancer and subsegmental PE have a risk of recurrent venous thromboembolism comparable to that of patients with more proximal clots.
- **Portal or splenic vein thrombosis:** Anticoagulant therapy for asymptomatic cancer-associated portal or splenic vein thrombosis is suggested for most patients. Anticoagulation may not be required when the thrombus is localized or there are signs that it is chronic (e.g. cavernous transformation).
- **Mesenteric, renal, cerebral vein thrombosis:** Full dose anticoagulation is suggested for patients with mesenteric, renal, or cerebral vein thrombosis. [see **Clinical Guide:** **Cerebral Venous Thrombosis]**

Primary prevention of thrombosis in ambulatory cancer patients: Patients at high risk for thrombosis may benefit from prophylaxis with a DOAC using apixaban (2.5 mg po BID) or rivaroxaban (10 mg po daily). This approach has been studied most notably in patients with locally advanced/metastatic pancreatic cancer and in patients with Khorana score > 2. Randomized trials and meta-analyses have also shown that daily LMWH prophylaxis reduces the occurrence of symptomatic venous thromboembolism (VTE) in ambulatory cancer

patients. The ultimate decision to start prophylactic anticoagulation in an ambulatory setting should be based on VTE risk, bleeding risk, as well as patient values and preferences.

Cancer-associated thrombosis in children: Pediatricians with expertise in thromboembolism should manage, where possible, pediatric patients with thromboembolism. When this is not possible, a combination of a neonatologist/pediatrician and an adult or pediatric hematologist is recommended.

Primary prevention of thrombosis in surgically treated patients: Patients undergoing cancer surgery should be started on prophylactic doses of LMWH (if creatinine clearance >30mL/min), starting approximately 12 hours post-operatively (assuring that adequate hemostasis has been achieved). LMWH should be continued for at least 7-10 days in total or until discharge from hospital [see the **Clinical Guide: Thromboprophylaxis: Non-Orthopedic Surgery**]. Some patient groups such as those undergoing major cancer abdominal or pelvic surgery may benefit from extended thromboprophylaxis to 4 weeks duration. There is insufficient data to support the use of a direct oral anticoagulant in this setting.

Other Relevant Thrombosis Canada Clinical Guides:

- Apixaban (Eliquis®)
- Cerebral Vein Thrombosis
- Central Venous Catheter-Related Deep Vein Thrombosis
- Deep Vein Thrombosis: Treatment
- DOACs: Perioperative Management
- Edoxaban (Lixiana®)
- Pulmonary Embolism: Treatment
- Rivaroxaban (Xarelto®)
- Unfractionated Heparin, Low-molecular-weight Heparin and Fondaparinux
- Vena Cava Filter

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Date of Version: 10September2024