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) has been the treatment of choice in patients with CAT because it offers superior efficacy over warfarin. Other non-anticoagulant effects of LMWH (e.g. anti-inflammatory properties) may also make it more effective than warfarin in CAT. The major barriers for LMWH use are drug cost and discomfort of daily injections; however, studies have shown that LMWH is well accepted by patients, while warfarin is associated with a reduced quality of life. LMWH is also recommended over unfractionated heparin (UFH) and fondaparinux. Recently, trials comparing anti-factor Xa direct oral anticoagulants (DOACs), including apixaban, edoxaban and rivaroxaban, with LMWH have shown that these agents are reasonable alternatives to LMWH in many cases of CAT.

Treatment of thrombosis in patients with primary or metastatic brain lesions, hematological malignancies, and at unusual sites, such as splanchnic vein thrombosis, is not well studied. A thorough review of the relative risks and benefits of available anticoagulant options, in addition to patient preference and values, is prudent prior to prescribing anticoagulant therapy in patients with CAT.

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 been used successfully for this indication. Baseline CBC and renal function should be checked prior to starting LMWH. In patients with active bleeding or severe thrombocytopenia (platelet count $<50 \times 10^9$/L) in whom anticoagulation can be dangerous, urgent referral to a hematologist or thrombosis expert for management is recommended. The following are the recommended doses for LMWHs:

- Dalteparin 200 U/kg daily for the first month then continue at ~150 U/kg daily. Alternatively, continuing at 200 U/kg for the duration of treatment can also be considered.
- Tinzaparin 175 IU/kg daily.
- Enoxaparin 1 mg/kg twice 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.

- In patients with severe renal insufficiency (creatinine clearance [CrCl] <30 mL/min), LMWH is generally avoided because of its dependence on renal clearance. However, the following options may be considered if appropriate in the specific case:
    1. It is possible to use LMWH if anti-Xa level measurement of is available to guide dose adjustment. Some experts suggest that a dose reduction should be considered if the trough anti-Xa level is >0.4 IU/mL; however, high quality data showing a correlation between these levels and poor clinical outcomes is lacking.
    2. For tinzaparin, available evidence demonstrates no accumulation in patients with CrCl levels down to 20 mL/min. There are limited data available in patients with an estimated CrCl < 20 mL/min.
    3. For some patients (for example, those who do not have a high risk of recurrent thrombosis or have an increased risk of bleeding), the dose of LMWH may be empirically reduced if this is consistent with the priorities of care.
    4. If none of the above criteria are satisfied, then warfarin can be considered. Consultation with a hematologist or thrombosis expert is recommended.
    5. One could consider apixaban, edoxaban or rivaroxaban as per clinical trials below (see product monographs for dosing)

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 1000 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 to and potentially lower rates of recurrent VTE when compared with LMWH, with rates between 4% - 8% with the anti-Xa inhibitors. Hazard ratios (HR) varied from 0.43 to 0.72 with statistical significance being found only with rivaroxaban (3.9% versus 8.9%, HR, 0.43 [0.19-0.99]).

Bleeding:
The rates of major bleeding with the anti-Xa inhibitors varied from 4% to 7%. There was more major bleeding with edoxaban as 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 nonsignificantly 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 x 10^9/L [apixaban]) or 50 x 10^9/L [edoxaban]), concomitant ASA use (above 75 mg daily with rivaroxaban or above 165 mg daily with apixaban), and presence of intracranial malignancy or leukemia (apixaban).

Other outcomes:
Similar to the trials that compared LMWH with warfarin in CAT, there was no survival benefit seen with the use of any anti-Xa inhibitor compared with LMWH. Event-free survival (absence of recurrent VTE, major bleeding, or death) was found to be higher with apixaban compared to LMWH (73.3% vs 68.6%; HR 1.36). There was no statistical difference in this outcome with edoxaban compared with LMWH, and this outcome was not reported with rivaroxaban.

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®)**. Dose reduction to 2.5 mg twice daily after initial therapy has not been studied in this population.

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). Thereafter, reassessment should be done every 3 – 6 months.

Even after 6 months of treatment, the risk of recurrent thrombosis remains high at ~0.5 - 0.7%/month while on LMWH therapy (so the risk is expected to be much higher if no anticoagulation was used). Bleeding risk also remains increased throughout anticoagulation. These risks must be considered

along with patient preference, quality of life, and life expectancy when making a decision about continuation of anticoagulation. 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 at least every 3 months. Drug-drug interactions should be reviewed with any change in medication if patient is receiving a DOAC. Whether drug-drug interactions are clinically significant is difficult to determine in some cases. Drugs that are potent inhibitors or inducers of P-glycoprotein 1 and CYP3A4 pathways can increase or reduce the serum levels of DOACs, respectively, and are absolutely contraindicated when relevant DOACs are used.

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

SPECIAL CONSIDERATIONS:

Injection site hematoma and bruising: Injection site bruising and hematomas can be minimized by applying firm pressure to the injection site for 2-5 minutes after an injection and injecting very slowly. Applying ice to the injection area before and/or after an injection may also reduce bruising and discomfort. Switching to smaller gauge needles (e.g., 30-gauge insulin syringes) and using multi-dose vials (instead of prefilled syringes) will help to reduce bruising.

Perioperative management: Cancer patients are at higher risk for developing post-operative VTE. Stopping anticoagulants is unnecessary for procedures associated with a very low risk of bleeding, such as skin biopsy. For major surgery or other procedures associated with an increased bleeding risk, the last injection of therapeutic-dose LMWH should NOT be given within 24 hours of the procedure. Provided that hemostasis is achieved, a prophylactic dose of LMWH can be restarted 12-24 hours after the procedure. If there is no bleeding, then the dose can be escalated towards the therapeutic dose over the next 24-72 hours. For procedures or surgeries associated with a very high risk of bleeding (e.g. transurethral resection of the prostate), it is important to be conservative when reintroducing full-dose anticoagulation to avoid causing serious bleeding that will lead to prolonged withholding of anticoagulation. For perioperative management of DOAC therapy, see the **Clinical Guide: NOACs/DOACs – Perioperative Management**.

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.

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. If heparin-induced thrombocytopenia has been excluded and adherence has been confirmed, increasing the dose of

LMWH by approximately 25% is suggested by experts. Those who develop recurrence on warfarin or DOAC should switch to LMWH. Consultation with a hematologist or thrombosis expert is recommended for further management guidance.

Thrombocytopenia: In patients who develop thrombocytopenia, full-dose anticoagulation can generally be continued unless the platelet count is <50 x 10^9/L. Data are available to support dose modification for more severe thrombocytopenia for LMWH but not for the DOACs. Half-dose LMWH is recommended for patients with a platelet count between 20 and 50 x 10^9/L. For patients with a platelet count <20 x10^9/L, anticoagulants are usually withheld until the platelet count increases. During the first month of therapy when the risk of recurrent thrombosis is highest, platelet transfusions can be considered to maintain the platelet count above 50 x 10^9/L to allow full-dose administration of LMWH if the thrombotic load is large or threatens hemodynamics. Consultation with a hematologist or thrombosis expert is recommended.

Active bleeding: Hold anticoagulant therapy until the bleeding source is treated or bleeding stops. If bleeding was not in a critical site or came from a local lesion that has been treated, then anticoagulant therapy can be reintroduced once bleeding stops. Avoid insertion of an IVC filter if bleeding is expected to be transient.

Catheter-related thrombosis: Anticoagulant therapy generally involves the same regimen as for lower extremity DVT/PE, and LMWH therapy is preferred. Warfarin is an option for patients who cannot tolerate long-term subcutaneous injections. In a pilot study using rivaroxaban for 12 weeks, there was one case of fatal PE and the risk of clinically relevant bleeding was a higher than anticipated at 12.9%. These results suggest that further studies are required prior to recommending routine use of rivaroxaban in this setting. Data for the other DOACs in this setting are lacking. Treatment should continue for a minimum of 3 months and as long as the catheter remains in place. The decision to maintain or remove a catheter should not be based on the presence of residual thrombosis. [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. This generally also applies to patients with cancer associated isolated subsegmental PE but there may be exceptions when anticoagulation may not be warranted. A preference to treat most cancer associated isolated subsegmental PE 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:** Differing from the recommendations in the non-cancer population, anticoagulant therapy for most asymptomatic cancer associated portal or splenic vein thrombosis is suggested. Anticoagulation may not be required when the thrombus is localized or there are signs that it is chronic (e.g. cavernous transformation). Acute symptomatic portal vein thrombosis warrants anticoagulant therapy using a standard treatment regimen.

- **Mesenteric, renal, cerebral vein thrombosis:** such thrombi warrant anticoagulant therapy with the same treatment regimen as for symptomatic thrombosis given the high risk of end organ damage.

Primary prevention of thrombosis in ambulatory cancer patients: Randomized trials and meta-analyses have shown that LMWH reduces the occurrence of symptomatic venous thromboembolism (VTE) in ambulatory cancer patients; however, this intervention is not routinely used or even recommended because of the cost and inconvenience associated with injections, as well as the difficulty in selecting patients most likely to benefit. A meta-analysis of two studies that utilized the Khorana score to select patients at higher risk of VTE who might benefit from prophylaxis with a DOAC (e.g., rivaroxaban and apixaban) showed that while low dose DOAC therapy reduces the overall risk of VTE, it may also increase the risk of major bleeding. Therefore, clinicians need to assess the risk-benefit ratio of prophylaxis on a case-by-case basis to select patients most likely to benefit from a low dose DOAC; this will depend on calculated VTE risk, whether or not the patient has a high risk lesion for bleeding (e.g., gastrointestinal, genitourinary or gynecologic), cost to the patient (and healthcare system), 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.

OTHER RELEVANT THROMBOSIS CANADA CLINICAL GUIDES:

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

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