



CANCER AND THROMBOSIS

TARGET AUDIENCE: All Canadian health care professionals: medical oncologists, hematologists, internists, family physicians, nurse practitioners, pharmacists - all health professionals providing care to cancer patients.

OBJECTIVE:

To assist health care professionals in the recognition and management of cancer-associated thrombosis.

ABBREVIATIONS:

CAT	cancer-associated thrombosis
CrCl	creatinine clearance
LMWH	low-molecular-weight heparin
VTE	venous thromboembolism

BACKGROUND:

Low-molecular-weight heparin (LMWH) is the treatment of choice in patients with cancer-associated thrombosis (CAT) because it offers superior efficacy over warfarin.

MECHANISM OF ACTION:

LMWH accelerates the inhibition of thrombin and activated factor X by antithrombin. Given in adequate doses, it will shut down thrombin activity and clot formation. In contrast, warfarin only reduces the plasma levels of carboxylated vitamin-K dependent coagulant proteins (factors II, VII, IX and X). Consequently, thrombin generation and clot formation are still possible in warfarin-treated patients with hypercoagulable states such as malignancy. Other non-anticoagulant effects of LMWH (e.g. anti-inflammatory or anti-angiogenic properties) may also make it more effective than warfarin in CAT.

INDICATION:

For initial and long-term (extended) treatment of CAT.

DOSING:

- a) Dalteparin 200 U/kg daily, rounding up to the nearest prefilled syringe (available in doses of 10,000 U, 12,500 U, 15,000 U, 18,000 U) for the first month, and then continue at ~150 U/kg

daily. Tinzaparin (175 IU/kg daily) and enoxaparin (1 mg/kg twice daily) are given at full doses for the duration of treatment.

- b) In patients weighing more than 90 kg, use multi-dose vials of dalteparin (25,000 U/mL concentration). No weight-based capping of the dose is necessary.
- c) In patients with severe renal insufficiency (creatinine clearance [CrCl] < 30 mL/min), LMWH is generally avoided because of its dependence on renal clearance. However, it is possible to use LMWH if measurement of anti-Xa levels is available to guide dose adjustment so as to ensure no bioaccumulation of the anticoagulant effect. Dose reduction is necessary if the trough anti-Xa level is > 0.4 IU/mL. If anti-Xa levels are not readily available with a rapid (i.e. same day) turnaround time, then warfarin is a better option.

MONITORING:

Laboratory monitoring of the anticoagulant effect of LMWH with anti-Xa levels is not routinely required in patients receiving such treatment for CAT.

ADVERSE EFFECTS:

Major or serious bleeding occurs in approximately 5% of patients over 6 months. Some patients have injection site bruising or hematomas, but this can be minimized by applying firm pressure to the injection site for 2-5 minutes after an injection. Heparin-induced thrombocytopenia is uncommon, occurring in < 0.5% of patients who are receiving LMWH.

PERI-PROCEDURAL MANAGEMENT:

Cancer patients not infrequently undergo surgery for both malignancy and non-malignancy associated conditions and are at higher risk for developing post-operative venous thromboembolism (VTE). Stopping LMWH is not necessary for procedures associated with a low risk of bleeding, such as skin biopsy, dental extraction or cataract surgery. For patients having major surgery or other procedures associated with an increased bleeding risk, the last injection of therapeutic-dose LMWH should be given 24 hours before an elective invasive procedure (but not earlier). After the procedure, provided that hemostasis is achieved, a prophylactic dose of LMWH (e.g. dalteparin 5,000 U daily) can be restarted 12-24 hours post-procedure. If there is no bleeding, then the dose can be escalated towards the therapeutic dose (e.g. dalteparin 200 U/kg daily) 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 LMWH to avoid causing serious bleeding that will lead to prolonged withholding of anticoagulation.

SPECIAL CONSIDERATIONS:

Thrombocytopenia: In patients who develop thrombocytopenia, typically as a consequence of chemotherapy, full-dose LMWH (e.g. dalteparin 200 U/kg daily) can be continued unless the platelet count is < 50,000. Half-dose LMWH (e.g. dalteparin 100 U/kg daily) is recommended for patients with a platelet count between 20,000 and 50,000. For patients with a platelet count < 20,000, anticoagulants are usually considered contraindicated and should be withheld until the platelet count increases.

Active bleeding: Hold LMWH 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 consider reintroducing LMWH once bleeding stops.

Catheter-related thrombosis: Anticoagulant therapy involves the same regimen as for deep vein thrombosis/pulmonary embolism using LMWH alone or transition to warfarin for long-term treatment. Treatment should continue for a minimum of 3 months and as long as the catheter remains in place (see Central Venous Catheter-Related DVT guide).

Asymptomatic thrombosis: Not infrequently, an incidental finding is detected, typically during imaging of the chest or abdomen, when such imaging is done to determine response to cancer treatment or to assess for cancer recurrence. Referral to a specialist is recommended in such cases to help guide whether anticoagulation is warranted.

- **Pulmonary embolism:** If detected, asymptomatic pulmonary embolism warrants anticoagulant therapy with the same treatment regimen as for symptomatic thrombosis. There may be exceptions when anticoagulation is not warranted (e.g. isolated subsegmental pulmonary embolism).
- **Portal vein thrombosis:** If detected, asymptomatic portal vein thrombosis may not require treatment, especially if there are signs that it is chronic (e.g. cavernous transformation).
- **Splanchnic (mesenteric, splenic) vein thrombosis:** If detected, such thrombi warrant anticoagulant therapy with the same treatment regimen as for symptomatic thrombosis.

PEDIATRICS:

In children with cancer, venous thromboembolism (VTE) management should follow the guidelines for VTE (see Pediatrics section in Duration of Anticoagulant Therapy guide). Treatment should continue for a minimum of 3 months until the precipitating factor has resolved (e.g. use of asparaginase). 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 hematologist, supported by consultation with an experienced pediatric hematologist, is recommended.

REFERENCES:

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