SHARED CARE GUIDELINES

VTE TREATMENT AND SECONDARY PROPHYLAXIS IN ONCOLOGY OUTPATIENTS

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Venous thromboembolism (VTE), which includes pulmonary embolism (PE) and deep vein thrombosis (DVT), represents one of the most important causes of morbidity and mortality in cancer patients. Thromboembolism is the 2nd most common cause of death in ambulatory cancer patients (tied with infections).

Factors that may affect Risk for Cancer-Associated VTE

Cancer patients are at a significantly greater risk for developing a blood clot (PE or DVT) compared with patients without cancer.

**Key Facts in Cancer Patients:**
- Incidence of VTE ranges from 4-20%
- 4- to 6-fold increased risk for VTE vs. non-cancer patients
- 3-fold increased risk for recurrence of VTE vs. non-cancer patients
- 4 to 13 times higher rate of VTE in those with metastatic disease as compared with those with localized disease
- Clinical rates may underrepresent burden; at autopsy, VTE rates are as high as 50%

The underlying mechanisms are not completely understood. However, we know that cancer is a prothrombotic state, with the activation of the coagulation cascade integrally linked to the processes of tumor growth, metastasis and angiogenesis. Further, chemotherapy can result in activation of coagulation within a few hours of administration through the induction of tissue factor (TF) in tumour cells and monocytes, the downregulation of anticoagulant proteins, damage to vascular endothelium, and platelet activation. Anti-angiogenic agents also contribute to thrombosis, perhaps through endothelial cell and platelet activation. The pathophysiology of cancer-associated thrombosis is likely multifactorial with different factors assuming lesser or greater degrees of importance depending on the patient, the type of cancer and the clinical setting.

The following factors can impact a patient’s risk for cancer-associated VTE.

**Patient-related factors**
- Increased age
- Ethnicity (risk increased in African Americans)
- Co-morbidities (infection, renal and pulmonary disease, arterial thromboembolism, VTE history, inherited prothrombotic mutations
- Obesity
- Performance status

**Cancer-related factors**
- Primary site of cancer
- Stage (risk increases with higher stage)
- Comorbid conditions
- Histology
- Time since diagnosis (risk increases during first 3-6 months)

**Treatment-related factors**
- Chemotherapy, antiangiogenesis agents, hormonal therapy
- Radiation therapy
- Surgery ≥ 60 mins
- Erythropoiesis-stimulating agents (ESAs), transfusions
- Indwelling venous access

**Biomarkers**
- Platelets ≥ 350 x 10^9/L
- Leukocyte count >11 x 10^9/L
- Hemoglobin <100g/L
Symptoms of VTE

Symptoms are the same for cancer patients as they are for people without cancer.

Symptoms of Possible DVT
- Recent swelling of one leg or arm
- Unexplained pain or tenderness of one leg or arm
- Skin may be warm to the touch or is discoloured (red, purple or blue)

Symptoms of Possible PE
- Recent or sudden shortness of breath or breathlessness
- Sharp chest pain or upper back pain, especially when inhaling
- Light-headedness or coughing up blood

Which VTE to Treat

Consider anticoagulation therapy in patients with:
- Lower extremity DVT
- PE
- Upper extremity DVT (brachial, axillary, or more proximal vein involvement)
- Unusual site thrombosis (brachial vein, splanchnic vein, cerebral vein, etc.)
- Incidental PE and DVT should be treated the same as symptomatic VTE

Indication for VTE Treatment & Secondary Prophylaxis within Guidelines

Current International Guidelines provide recommendations for the treatment of VTE in oncology patients with a focus on preventing recurrent VTE.

ASCO 2013⁹ / NCCN 2013¹¹ / ACCP 2012¹² / ESMO 2011¹³
- For long-term anticoagulation, LMWH preferred for at least 6 months as monotherapy due to improved efficacy over warfarin
- Warfarin daily is an option in some patients (particularly if LMWH is not available), for long-term use; however, regular monitoring and dose adjustment is essential to ensure a target INR of 2-3. Cancer patients treated with warfarin have an increased risk of bleeding compared to non-cancer patients due to a number of factors including chemotherapy, frequent use of antibiotics, liver disease/impairment due to cancer, decreased clotting factor synthesis, reduced vitamin K intake
- Anticoagulation with LMWH or warfarin beyond the initial 6 months may be considered for select patients with active cancer, such as those with metastatic disease, those receiving chemotherapy and those with persistent major risk factors
- The insertion of a vena cava filter is only indicated for patients with contraindications to anticoagulant therapy. It may be considered as an adjunct to anticoagulation in patients with progression of thrombosis (recurrent VTE or extension of existing thrombus) despite optimal therapy with LMWH
- For patients with primary CNS malignancies, anticoagulation is recommended for established VTE as described for other patients with cancer. Careful monitoring is necessary to limit the risk of hemorrhagic complications
- Use of novel oral anticoagulants for either prevention or treatment of VTE in cancer patients is not recommended at this time
Once a DVT or PE has been confirmed, anticoagulant treatment should be initiated with a LMWH.

1. Renal function
   - eGFR >30 mL/min: tinzaparin, enoxaparin, dalteparin
   - eGFR 20-30 mL/min: Dose adjustment may be required for tinzaparin; tinzaparin clearance was not shown to be correlated with CrCl, even when the CrCl was as low as 20 mL/min\textsuperscript{18} Dose adjustment will be required for dalteparin and enoxaparin\textsuperscript{15,16}
   - eGFR <20 mL/min: no LMWH; use unfractionated heparin in combination with warfarin

2. Dose
   - Weight-based dosing

3. Dose adjustment
   - Generally not needed after 1 month, check local protocols/procedures

4. Duration
   - Minimum 6 months, may be extended if clinically warranted

Initiating Anticoagulation

Prior to initiating any anticoagulant, the following assessments should be done:

- Assess for additional medical conditions or patient parameters (e.g. renal function, body weight, known coagulopathy)
- Baseline blood work, including serum creatinine and CBC
- Identification of current antiplatelet use (e.g. ASA)
- Identification of current anticoagulant use with reassessment of agent (i.e. warfarin, dabigatran, rivaroxaban, apixaban). Note there is no clinical data to support the efficacy or safety of the new oral anticoagulant agents (apixaban, dabigatran, rivaroxaban) for VTE treatment in oncology patients

Choosing the Appropriate Anticoagulant

Choice of anticoagulant should be guided by best practices with consideration of the following criteria:

- Clinical trial data
- Kidney function
- Provincial reimbursement/cost\textsuperscript{^}
- Hospital formulary coverage
- Frequency of administration (OD vs. BID)
- Monitoring

\textsuperscript{^}Note: Outpatient choice may have fewer restrictions as all LMWHs have similar coverage on the majority of provincial formularies.
Dosage and Administration

LMWH is the treatment of choice except in the case of severe kidney failure for VTE treatment, for both inpatients and outpatients.

LMWH†:

Dalteparin
- 200 IU/kg subcutaneously once a day OR 100 IU/kg subcutaneously BID
  - Dose adjustment to 150 IU/kg recommended after 1st month of treatment15
  - Dose adjustment will be required if CrCl<30 mL/min

Enoxaparin
- 1 mg/kg subcutaneously BID OR 1.5 mg/kg subcutaneously once daily
  - Note there is no consensus on the dosage of enoxaparin for the treatment of cancer-associated thrombosis
  - Dose adjustment will be required if CrCl<30 mL/min16

Tinzaparin
- 175 IU/kg subcutaneously once a day
  - Dose adjustment may be required if CrCl<30 mL/min, tinzaparin clearance was not shown to be correlated with CrCl, even when the CrCl was as low as 20 mL/min18

Note: There is insufficient clinical data to support the efficacy or safety of the new oral anticoagulant agents (apixaban, dabigatran, rivaroxaban) in oncology patients.

† Generally, round UP to nearest pre-filled syringe dose. No dose capping for patients with high body weight. Dosing is done based on clinical judgement (impacted by person weight/size and size and location of clot). Volume of dose is a consideration with daily administration – high-volume subcutaneous injections are not well tolerated.

Monitoring / Follow-Up

Anticoagulation monitoring is not needed with LMWHs. However follow-up at specific stages is recommended to reassess the balance of thrombosis, bleeding and anticoagulation, as well as reassessing anticoagulant dose and duration. Patient weight and renal function should also be reassessed at follow-up.

Follow-up recommendations:

- Bring patient back, if possible, in the first week to ensure self-injections are properly administered, and to assess for bleeding complications
- Follow at one week and six months; alternatively follow-up at one month and after six months
  - Patients with metastatic disease should generally continue with anticoagulation beyond 6 months
- Review injection technique at each visit. Provide patients with tips to maximize injection success

Information to the patient

Provide the patient with information about VTE in oncology and their treatment.
Patients/carers need to be educated about VTE as well as about their new treatment. Review benefits/requirement for treatment as well as restrictions/risks. Have patient or carer do the first injection in the clinic with the assistance of clinic nurse.

**Items that should be reviewed with the patient/carer:**

- Patient’s VTE risk and options to lower their risk
  - Explain why injection vs. oral medication (note currently no indication or data for new oral agents in oncology). Patients should be reassessed as appropriate, and at a minimum of 3 months after initiation of treatment

- Symptoms of a blood clot, particularly PE

- What to do if symptoms are suspected
  - Seek medical attention → provide clear direction including phone numbers etc.

- Purpose of anticoagulation medication
  - Anticoagulants don’t break up an existing clot but prevent it from growing bigger and stop new clots from forming
  - Therapy will need to continue for weeks to months to allow time for body to clear clot

- Restrictions when on anticoagulation medication
  - No dietary restrictions with LMWHs
  - Alcohol in moderation only

- Risks of using/taking anticoagulation medication
  - Increased risk of bleeding – exercise caution with sharp objects, avoid contact and high-risk sports, and avoid using ASA & NSAIDs without your doctor’s permission
  - Inform other Healthcare Professionals/providers, including dentists, that they are using anticoagulation. There may be a concern with dental extractions, but really only if there is 4 or more extractions

  - **Bleeding on an anticoagulant/blood thinner is a medical emergency**

- Post-thrombotic syndrome

- Blood clot prevention
  - Stay active
  - Don’t smoke or stop smoking if you do
  - Maintain a normal body weight, if possible
  - Drink plenty of liquids
  - When travelling, wear compression stockings and/or get up and walk frequently


Date: 
Time: 

**VTE Outpatient Assessment Form and Treatment Recommendations**

<table>
<thead>
<tr>
<th>Investigations:</th>
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<tbody>
<tr>
<td>☐ Baseline CBC</td>
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Patient Weight: (kg) __________ Site of Cancer _______________________

Current Cancer Therapy
- ☐ Angiogenesis inhibitors (e.g. Avastin, thalidomide, lenalidomide)
- ☐ Biological response modifiers (e.g. interferon, Rituxan, Herceptin)
- ☐ Nonspecific immunomodulating agents (e.g. 5-fluorouracil)

**Confirmation of DVT / PE:**
- ☐ Lower extremity DVT
- ☐ PE
- ☐ Upper extremity DVT (brachial, axillary, or more proximal vein involvement)
- ☐ Unusual site thrombosis (brachial vein, splanchnic vein, cerebral vein, etc.)

**Considerations:**

Current Anticoagulant Therapy
- • Antiplatelet therapy
  - ☐ Yes Type and dose: ___________________ ☐ No
- • Oral Anticoagulant therapy (e.g. warfarin, dabigatran, rivaroxaban, apixaban):
  - ☐ Yes Type and dose: ___________________ ☐ No

**Antithrombotic Therapy for Treatment of VTE:**

Low Molecular Weight Heparin:
- eGFR >30 mL/min
  - ☐ Tinzaparin Dose: __________ ☐ Enoxaparin Dose: __________
  - ☐ Dalteparin Dose 1st month: __________ Dose 2-6 months: __________
- eGFR 20-30 mL/min
  - ☐ Tinzaparin Dose: __________

Other therapy*: (e.g. UFH, warfarin)
- ☐ Yes
- ☐ No State reason: ____________________________________________
- ☐ No therapy – State Reason ______________________________________

*There is no clinical data to support the efficacy or safety of the new oral anticoagulant agents (apixaban, dabigatran, rivaroxaban) in oncology patients.

If eGFR >30 mL/min

<table>
<thead>
<tr>
<th>Dalteparin Dose</th>
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<th>Tinzaparin Dose</th>
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<tbody>
<tr>
<td>200 IU/kg SC once daily</td>
<td>1 mg/kg SC BID OR 1.5 mg/kg SC once daily</td>
<td>175 IU/kg SC once daily</td>
</tr>
<tr>
<td>OR 100 IU/kg SC BID</td>
<td>After 1st month: 150 IU/kg recommended</td>
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</tr>
</tbody>
</table>

Generally round UP to nearest pre-filled syringe dose. No dose capping for patients with high body weight.

If eGFR <30 mL/min:
- • Dose adjustment will be required for dalteparin and enoxaparin
- • Dose adjustment may be required for tinzaparin; tinzaparin clearance was not shown to be correlated with CrCl, even when the CrCl was as low as 20 mL/min

HCP Name (print): __________________________ Signature: __________________________
**Recurrence**
Recurrence, despite standard doses of anticoagulant therapy, should be assessed for treatment compliance, HIT or any evidence of mechanical compression resulting from malignancy.

**Management options:**
- Increase dose of LMWH by ~25% of current dose or increase it back up to the therapeutic weight-adjusted dose if receiving non-therapeutic dosing
- Switch to warfarin for long-term therapy with patient choice considerations
- In palliative care, allow patient to drive treatment decisions based on risk:benefit

**Incidental VTE**
Incidental findings of PE and/or DVT during routine staging can occur, with up to 50% of DVT and >35% of PEs being incidentally discovered.

Rates of VTE recurrence, bleeding, and mortality seem to be similar in cancer patients whether VTE was symptomatic or incidental.

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**Contraindications to LMWHs:**

<table>
<thead>
<tr>
<th>Absolute Contraindications to LMWHs</th>
<th>Relative Contraindications to LMWHs</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Heparin induced thrombocytopenia</td>
<td>• Severe thrombocytopenia</td>
</tr>
<tr>
<td>• Active bleeding</td>
<td>• Severe coagulopathy</td>
</tr>
<tr>
<td>• Stop LMWH at least 12 hours before spinal invasion; Next dose should be held at least 2 hours after spinal invasion</td>
<td>• High bleeding risk</td>
</tr>
</tbody>
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**eGFR <30 mL/min:**
- Dose adjustment may be required for tinzaparin; tinzaparin clearance was not shown to be correlated with CrCl, even when the CrCl was as low as 20 mL/min
- Dose adjustment will be required for dalteparin and enoxaparin.

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**Kidney function:**
- eGFR: > 30 mL/min tinzaparin, dalteparin or enoxaparin; 20-30 mL/min tinzaparin (dose adjustment may be required); dalteparin and enoxaparin (dose adjustment required).
- < 20 mL/min no LMWH; UFH in combination with warfarin

**Dose adjustment:** generally not needed after 1st month, check local protocols

**Duration:** Minimum 6 months, may be extended