VTE 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).

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.

Factors that may affect Risk for Cancer-Associated VTE

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

Assessing Risk for VTE

All cancer patients have an increased risk of VTE. However, routine pharmacological thromboprophylaxis is not indicated in cancer outpatients. Evidence suggests that certain patients have a higher risk than others. With this knowledge, Dr. Alok Khorana and colleagues developed a risk assessment tool to assist with identifying cancer patients at the greatest risk of VTE. This tool was developed from a database of neutropenic patients and has been validated in almost 10,000 patients* including a post-hoc analysis within the SAVE-ONCO study.¹¹,¹²

<table>
<thead>
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RISK OF VTE based on score:

- Score 0 = 0.5%
- Score 1 – 2 = 2%
- Score ≥ 3 = 7%

Beyond the risk factors identified in the Khorana risk assessment model, other potential risk factors that should be considered include: (from ACCP Guidelines 2008)

- Previous venous thrombosis
- Immobilization
- Hormonal therapy
- Angiogenesis inhibitors (i.e. Avastin, thalidomide, lenalidomide)

* Patient groups included in the risk analysis had cancers of: lung, stomach, pancreas, lymphoma, gynecological, and GU excluding prostate

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Indication for VTE Prophylaxis within Guidelines

Current International Guidelines do provide some recommendations for thromboprophylaxis in oncology patients some using the Khorana Risk score. However, while there is some consensus on thromboprophylaxis of inpatients, there is no consensus on thromboprophylaxis in oncology outpatients despite the fact that the risk of VTE remains increased in some cancer patients, even when ambulatory.

**ASCO 2013**/**ESMO 2011**
- Routine pharmacologic thromboprophylaxis is not recommended in cancer outpatients
- Clinicians may consider LMWH prophylaxis on a case-by-case basis in highly selected outpatients with solid tumours receiving chemotherapy
- Patients with multiple myeloma receiving lenalidomide- or thalidomide-based regimens with chemotherapy and/or dexamethasone should receive thromboprophylaxis with either aspirin or LMWH for lower-risk patients and LMWH for higher-risk patients

**ACCP 2012**
- No routine anticoagulation UNLESS
  - Solid tumor
  - Presence of risk factors including: previous VTE, hormone therapy, immobilization, angiogenesis inhibitors, lenalidomide, thalidomide
- If above present, then consider LMWH or unfractionated heparin

**NCCN 2013**
- Thalidomide/lenalidomide patients, otherwise no routine thromboprophylaxis
- Utilizing Khorana predictive risk model: patients with high risk (≥3) COULD BE considered for prophylaxis on an individual basis evaluating risk/benefit ratio

Canadian Prophylaxis Recommendations

All cancer patients should be assessed for VTE risk at the time of chemotherapy initiation and periodically thereafter. In the outpatient setting, risk is best assessed using a validated risk assessment tool like the Khorana tool. Consideration should also be given to other potential VTE risk factors.

### Step 1: Calculate Risk Score

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### Step 2

**Consider other VTE Risk Factors**
- Previous venous thrombosis
- Immobilization
- Angiogenesis inhibitors (e.g. thalidomide, lenalidomide)

**Determine Risk**
- High Risk: score ≥3 &/or other VTE risk factors
- Non-High Risk: risk score <3
**Canadian Prophylaxis Recommendations**

**If patient is High Risk (score ≥3 &/or other risk factors)**
- Consider prophylaxis with a LMWH at prophylactic dose\(^\text{^}\)
- Decision should be guided by contraindications as well as risk:benefit ratio

Patients should be reassessed periodically, at least every 3 months, after initiation of prophylactic treatment.

**If patient is Non-High Risk (score <3)**
- Reassess as appropriate
  
  \(\text{OR}\)
  
  - Consider thromboprophylaxis if other VTE risk factors exist

\(^\text{^}\)enoxaparin dose adjustment recommended in patients with impaired renal function\(^\text{17}\)

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

**Contraindications to Anticoagulation**

It is important to review and understand the patient’s risks and possible contraindications to anticoagulation.

- Current anticoagulation therapy
- Recent bleeding events – increases risk for further bleeds
- HIT
- Bleeding disorder

**Initiating Anticoagulation**

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

- Assess for additional medical conditions
- Determine renal function, body weight, know coagulopathy
- Baseline blood work performed, including serum creatinine and CBC
- Identification of current antiplatelet or anticoagulant use (e.g. ASA, Warfarin)
Choosing the Appropriate Anticoagulant

Always weigh the benefits vs. risks of anticoagulation.

Risk for bleeding is increased in patients with:

- Thrombocytopenia
- Moderate-severe kidney dysfunction
  - almost 1/3 of cancer patients have renal insufficiency, with 1 in 5 having normal serum creatinine but low eGFR
- Current antiplatelet therapy

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

- Kidney function
  - eGFR <30 mL/min dose adjustment for enoxaparin recommended
  - eGFR 20-30 mL/min: tinzaparin*
  - eGFR < 20 mL/min: no dose adjustment needed for tinzaparin or dalteparin
  - Provincial reimbursement/cost^*Outpatient choice may have fewer restrictions as all LMWHs have similar coverage on the majority of provincial formularies. Tinzaparin clearance was not shown to be correlated with CrCl, even when the CrCl was as low as 20 mL/min.

LMWH is the therapy of choice except in the case of severe kidney failure for VTE prevention for inpatients and outpatients. Thromboprophylaxis should continue for a minimum of 3 months, it may be extended if clinically warranted.

LMWH:

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<tr>
<th>Weight</th>
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In patients with impaired renal function (<30 mL/min):

- Dalteparin: no dose adjustment is required
- Enoxaparin: a dosage adjustment is recommended since enoxaparin appears to accumulate in this patient group and may increase risk of bleeding.
- Tinzaparin: no dose adjustment of tinzaparin at prophylaxis doses is needed in patients with impaired renal function, renal failure or on hemodialysis.

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

Dosage and Administration

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 kidney 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
- Monitor as part of standard chemotherapy protocol
- Review injection technique at each visit. Provide patients with tips to maximize injection success

Patients should be reassessed as appropriate, and at a minimum of 3 months after initiation of prophylactic treatment.
Patient Education

Patients/carers need to be educated about VTE risk and the available options to lower the risk. If thromboprophylaxis is initiated then education about this new therapy must also be done. Review benefits/requirements for thromboprophylaxis as well as restrictions/risks. Have patient or carer do the first injection in the clinic with the assistance of clinic nurse or physician.

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 prophylactic treatment

- Symptoms of a blood clot, particularly DVT or PE

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

- Purpose of anticoagulation medication
  - Anticoagulants reduce the amount of clotting taking place in the blood allowing the blood to flow more freely. They also prevent the formation of blood clots or prevent existing blood clots from growing
  - Therapy will need to continue for several months to reduce the risk of developing a 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 physical activities, 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 are 4 or more extractions
  - **Bleeding on an anticoagulant/blood thinner is a medical emergency**

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

Information to the patient

Provide the patient with information about VTE in oncology and their treatment.
VTE Outpatient Assessment Form and Prophylaxis Recommendations

Investigations:

- □ Baseline CBC
- □ Serum creatinine
- eGFR _____ mL/min

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)

VTE RISK

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RISK SCORE

- □ High Risk (score ≥3 &/or other VTE risk factors)
- □ Non-High Risk (risk score <3)

Thromboprophylaxis Recommended

- □ Yes
- □ No – State Reason

Step 2: Other Risk Factors

- □ Previous venous thrombosis
- □ Immobilization
- □ Hormonal therapy
- □ Angiogenesis inhibitors (e.g. thalidomide, lenalidomide)

Considerations

Current Anticoagulant Therapy

- □ Anticoagulant therapy
  - Yes Type and dose: ____________________________ □ No
  - Oral Anticoagulant therapy (e.g. warfarin, dabigatran, rivaroxaban, apixaban):
    - Yes Type and dose: ____________________________ □ No

Thromboprophylaxis - Low Molecular Weight Heparin

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HCP Name (print): ____________________________ Signature: ____________________________
Contraindications to LMWHs

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<td>• Heparin induced thrombocytopenia</td>
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<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>
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• In the prophylaxis setting, mechanical thromboprophylaxis should be provided to all patients with a contraindication to LMWHs

*Use clinical judgment to weigh the risk of venous thromboembolism versus the risk of bleeding

^enoxaparin dose adjustment recommended in patients with impaired renal function