Key Concepts and Complications: Managing Cancer-Associated Thrombosis

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Disclosures

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Objectives:

- Define deep vein thrombosis (DVT) or pulmonary embolism (PE) based on location, acuity, and severity.
- Implement an appropriate intervention for treatment.
- Identify risk factors for venous thromboembolism (VTE) and recurrence and understand rationale for duration of anticoagulation.
Defining the Clot - Location

- A venous clot can be superficial (superficial thrombophlebitis) or deep.
- A DVT can be proximal (popliteal vein and above) or distal (below the popliteal vein).
- In general, treatment duration and/or dosing is different depending on these factors. There is somewhat less variation in the case of cancer-associated thromboembolism, as we will discuss.

This and other helpful material can be found at clotconnect.org

Defining the Clot - Acute vs Chronic

- Venous Doppler can usually differentiate between acute and chronic features for DVT.
- It is less straightforward to determine the chronicity of PE, particularly if incidentally found.
- In general, the appearance on imaging should be considered in conjunction with the patient history.
- If questions arise, call radiology for clarification!

Pulmonary Embolism - Definitions

- Lethal: no evidence of right heart strain.
- Catastrophic: evidence of right heart strain, without hemodynamic instability.
- Hemodynamic instability, generally without shock.
- To categorize, obtain troponin value and/or echocardiogram. Resting troponin >50 x C0 indicates. Radiation is an indication of RHH strain. Can also see RHH strain on CT scan.

Illustrations courtesy of Dr. Stephan Moll, UNC Hematology
Case:

- 45 yo female with metastatic breast cancer and new left lower extremity swelling and pain.
- Sent for lower extremity Doppler ultrasound:
  - Acute obstruction of the left lower extremity femoral vein at mid thigh, distal thigh, popliteal vein, posterior tibial vein 1/2, and peroneal vein.
  - No evidence of DVT in the Iliac.

Step 1: Define the clot.

- Is this a proximal DVT or a distal DVT?
- Is it acute or chronic?

Step 2: Assess Risk Factors

There are many risk factors with variable relevance.

Cancer patients are more likely to be impacted by some of these risks due to illness and treatment - i.e. infections, blood transfusions, trauma (surgery), etc.

Additionally, cancer itself is a risk factor for VTE.¹
Step 2: Assess Risk Factors

- This patient is receiving chemotherapy.
- She was recently admitted (3 weeks ago) for neutropenic fever, no source identified.
- She has not had a recent blood transfusion and she has not had surgery in 6 months.

Risk factors for VTE:
1. Active malignancy (metastatic breast cancer)
2. Recent hospitalization/immobility
3. Recent infection
4. Receiving Chemotherapy

Step 3: Treatment
Do they have contraindications to anticoagulation?

- Active bleeding (e.g., active bleeding, occult bleeding, non-occlusive arterial thrombosis)
- Unwillingness to accept anticoagulation
- Recent cerebrovascular accident
- Recent orthopedic surgery
- Thrombocytopenia (platelet count <30,000-50,000/μL or clinical judgment)
- Unwillingness to accept anticoagulation
- Recent operation (e.g., major abdominal surgery, percutaneous vascular or GI intervention, major biopsy, lumbar puncture)
- recent oral anticoagulant
- Severe organ dysfunction
- Recent major operation at high risk for bleeding
- High risk for falls (head trauma)
- CMS recommendations
- Long-term anticoagulation therapy

Step 3: Treatment - Drug Choice

- LMWH:
  - Preferred for patients with prior unprovoked venous thromboembolism
  - Preferred for patients with prior provoked venous thromboembolism
  - Risk factors for bleeding

- Other options
  - Fondaparinux
  - Direct oral anticoagulants (DOACs)
Considerations for specific anticoagulants:

**DOACs:**
- Stage IV/V CKD: CrCl <30 ml/min
- Active/clinically significant liver disease
- Drugs, vitamin K inhibitors, inducers of CYP3A4, P-gp

**LMWH:**
- CKD: Consider alternative for CrCl <30 ml/min
- History of HIT
- Fondaparinux
  - CAB: CrCl <30, caution with CrCl 30-50

**Warfarin:**
- Contraindicated inhibitors and inducers of CYP2C9, 1A2, 3A4

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Step 4: Treatment Duration

For most DVT/PE:
- At least 3 months
- OR
  - As long as active cancer
- Specifically for non-catheter-associated, recommendation is indefinite anticoagulation while cancer is active, undergoing treatment, or risk factors persist.

It can be difficult to determine when “active cancer” ends during early survivorship/surveillance. Shared decision making is helpful in determining plans for this interval.

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Case 2:

- 60 year old male with rectal cancer and new erythematous, tender area with palpable cord along the medial thigh
- Sent for Doppler which demonstrate:
  - Acute superficial vein thrombosis involving the great saphenous vein, 4 cm from the saphenofemoral junction.
Step 1: Define the clot

- Is the clot superficial or deep?
- Is it acute or chronic?

Illustrations courtesy of Dr. Stephan Moll, UNC Hematology

Step 2: Assess risk factors

- This patient is receiving chemotherapy, has not recently been hospitalized, has not had recent surgery, but has a BMI of 40. He has a family history of PE in his father.
- His risk factors:
  1) Active malignancy (rectal cancer)
  2) Obesity (BMI 40)
  3) Family history of VTE
  4) Receiving chemotherapy

Step 2: Assess Risk Factors - Bleeding

- This patient has rectal cancer and has a history of GI bleeding.
- He is not on any antiplatelet medications.
- He has normal platelets.
- He has normal renal function, CrCl 65ml/min
- Risks for bleeding:
  1) GI malignancy with history of GI bleeding
Step 3: Treatment - Choice of Drug

- Recall: NCCN Guidelines caution against use of DOACs with GI malignancies.
- However, Caravaggio Trial demonstrates similar bleeding risks for apixaban and dalteparin, including in GI malignancies.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Recurrent VTE</th>
<th>Major Bleeding</th>
<th>Recurrent &amp; GI Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>48/579 (8.8%)</td>
<td>22/579 (3.8%)</td>
<td>10/579 (1.7%)</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>30/576 (5.2%)</td>
<td>11/576 (1.9%)</td>
<td>46/579 (7.9%)</td>
</tr>
</tbody>
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Recall these findings may extend the proportion of patients with both cancer and venous thromboembolism who would be eligible for treatment with apixaban, including patients with gastrointestinal cancer. On the basis of these

Step 4: Treatment Duration

- **NCCN Guideline**
  - Anticoagulation at least 4 weeks or if SVT > 5 cm or if SVT < 5 cm and below SVT < 5 cm.
  - SVT within 60% of DVT: Anticoagulation for at least 3 mo.
  - Consider repeat ultrasound in 7–10 days if SVT < 5 cm or below SVT < 5 cm.

- The duration of treatment in this patient should be at least 4 weeks because his SVT extends above the knee but is <5 cm from the SFJ.
- While the NCCN guidelines do not mandate longer-term anticoagulation for this patient, his risk of recurrence and/or VTE is likely significant while he continues to have active malignancy.
- This situation warrants discussion regarding risks and benefits of anticoagulation considering both his episode of VTE/recurrence risk and his bleeding risk.

Case 3:

- 67 yo female with diffuse large B-cell lymphoma receiving chemotherapy who presents with shortness of breath and pleuritic pain.
- Troponin negative, D-dimer 4.98D
- Chest CT:
  - Acute pulmonary emboli involving bilateral lower lobe segmental and subsegmental pulmonary arteries. No CT evidence of right heart strain.
Step 1: Define the clot

- Acute pulmonary embolism, Low-Risk
  - This episode was acute, with new sudden-onset symptoms.
  - Her PE would be considered low-risk because:
    - No evidence of right heart strain on CTA
    - Negative troponin

Step 2: Assess Risk Factors

- This patient has DLBCL but is not obese (BMI 24), has no personal or family history of VTE, is not on hormone therapy.
- Her risks:
  1) Active malignancy (DLBCL)
  2) Receiving chemotherapy
- Risk factors for bleeding:
  1) Thrombocytopenia associated with chemotherapy cycles

Step 3: Treatment - Choice of Drug

- Treatment for this episode would be the same as with proximal DVT, as discussed above.
- However -
  - This patient is receiving cytotoxic chemotherapy.
  - On review of records, her platelets decline to 20-70 range with each cycle of chemotherapy.

How do you manage her anticoagulation in the setting of recurrent thrombocytopenia?
Management of Anticoagulation with Chemotherapy-Induced Thrombocytopenia:

- If high risk (i.e., within 1 month of VTE event or history of recurrent VTE), consider transfusing to 30,000 or in rare cases, IVC filter.
- For patients lower risk for recurrence, consider dose-reduction/holding anticoagulation.

| Treatment | Description | Duration | Consistency | Certainty | Evidence | Recommendation
|-----------|-------------|----------|-------------|-----------|----------|----------------|
| LMWH      | Low molecular weight heparin | 6 months | Moderate | Strong | Low to intermediate | 25
| DOACs     | Direct oral anticoagulants (apixaban, edoxaban, or rivaroxaban) | 6 months | Moderate | Strong | Low to intermediate | 26
| UFH        | Unfractionated heparin | 6 months | Moderate | Strong | Low to intermediate | 27
| Fondaparinux | | 6 months | Moderate | Strong | Low to intermediate | 28

Note: NCCN currently does not recommend use of DOACs below a platelet count of 50,000/µL as there is limited published experience using DOACs in this indication.

Step 4: Duration of Treatment

- Same as Case 4.
- Review here the ASH and ASCO Guidelines.

Case 5:

- 75 year old male with metastatic lung cancer who presents with newly diagnosed left upper lobe and left lower lobe segmental pulmonary emboli incidentally found on monitoring CT.
- Last prior CT was 3 months ago and no emboli were present.
- He is asymptomatic.

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Step 1: Define the clot
- CTA with PE, no evidence of right heart strain
- Troponin was not performed
- No echo
Given no symptoms, incidental finding, and no CT evidence of right heart strain, this would be considered a new VTE.

Step 2: Assess Risk Factors
- Patient is 72 years old with a BMI of 23. Non-smoker. No family history of DVT. Has been receiving chemotherapy. Has a port which has been present for 1 year without issues. No recent travel. Last hospitalization for pneumonia 6 mos ago.
- Risk factors:
  1. Active malignancy (metastatic lung cancer)
  2. Receiving chemotherapy
Risk factors for bleeding: 1) Age

Step 3: Treatment - Choice of Drug and Step 4: Duration of Therapy
- We have reviewed drug options - DOAC, LMWH, but...
- For incidentally found VTE, do you treat at all? Yes

Recommendation 4.2: For patients with cancer and incidentally found VTE, the American Society of Hematology guideline panel suggests short-term anticoagulation treatment rather than observation (conditional recommendation, very low certainty in the evidence of effects).
Case 6:

- 55 year old female with uterine cancer presents with three days of worsening left upper arm swelling, pain, and tenderness. She has a PICC line in the left arm.

Step 1: Define the clot

- Venous Dopplers are obtained and confirm thrombosis:
  - Acute obstruction in the left brachial vein, axillary vein. Other veins fully compressible.

Is this a deep or superficial vein thrombosis?
Choice of drug – as reviewed, recommended. DOAC or LMWH would be appropriate. 

Take-home points: 

1. Define the clot 
2. Re-evaluate for other causes if initial testing is unrevealing and clinical suspicion remains high 
3. Consider further diagnostic imaging/testing 
4. Anticoagulation to be managed without removing the PICC line. 
5. PICC line for bleeding: None.
UNC DVT Walk-In Program

- Rapid follow-up for patients with newly diagnosed DVT
- Ensure anticoagulation is started, appropriate, affordable, and that patient receives education.
- Located at UNC Eastowne
  - 100 Eastowne Drive, Chapel Hill, NC
- Can place referral within the UNC system.
- Hope to expand to accept referrals outside UNC in 2022.

Citations


