Management of Anticoagulants in Cancer

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Disclosure Statement

- Nothing to disclose

Objectives

- Review the incidence and risk factors for VTE (venous thromboembolism) in cancer patients
- Describe the role for VTE prophylaxis and appropriate medications to use in cancer patients
- Discuss the recommended length of VTE treatment in cancer patients
- Evaluate the available medication options for VTE treatment in cancer patients
**Background**

- Association between VTE and cancer first reported by Armand Trousseau in 1865
- Pathophysiology
  - Hypercoagulability
  - Vessel wall damage
  - Vessel stasis

**VTE Incidence**

- Cancer patients: 4-7 fold greater risk of VTE
  - Increased risk of death
  - Increased rates of recurrence
- Idiopathic VTE: 2-4 fold increased risk of malignancy
  - Especially first year
  - No recommendations for extensive malignancy screening

**VTE Risk Factors**

- Patient Related
- Cancer Related
- Treatment Related
### Patient Related Risk Factors
- Advanced age
- Obesity
- Prechemotherapy thrombocytosis, leukocytosis, hemoglobin < 10 g/dL
- History of VTE
- Hypercoagulable conditions
- Hospitalization
- Poor performance status
- Medical comorbidities
- Prolonged immobilization

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### Cancer Related Risk Factors
- Presence of malignancy
  - Very high: brain, pancreas, stomach
  - High: bladder, gynecologic, lung, lymphoma, testicular, renal
  - Low: breast, prostate
- Metastatic disease
- Extrinsic vascular compression due to regional lymphadenopathy

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### Treatment Related Risk Factors
- Surgery
- Central venous access device
- Cytotoxic chemotherapy
- Hormone therapy
- Antiangiogenic agents
- Erythropoiesis stimulating agents (ESAs)
- Red blood cell and platelet transfusions
VTE Predictive Model

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Score</th>
<th>Risk</th>
<th>VTE Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very high risk: stomach, pancreas</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>High risk: lung, lymphoma, gynecologic, bladder, testicular</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Platelets &gt; 350,000/mm³</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Hemoglobin &lt; 10 g/dL or use of ESA</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Pre-chemotherapy WBC &gt; 11,000/mm³</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>BMI ≥ 35 kg/m²</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Score: Risk

0 Low 0.8-3%
1-2 Intermediate 1.8-8.4%
≥ 3 High 7.1-41%

Khorana, 2008
NCCN, 2015

Prophylaxis

Agents for Prophylaxis

<table>
<thead>
<tr>
<th>Agent</th>
<th>Standard Dosing</th>
<th>Obese Dosing (BMI ≥ 40 kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalteparin</td>
<td>5,000 units SC daily</td>
<td>7,500 units SC daily (limited dose)</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>40 mg SC daily</td>
<td>40 mg SC q 12 hours</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>2.5 mg SC daily</td>
<td>5 mg SC (limited dose)</td>
</tr>
<tr>
<td>UFH (unfractioned heparin)</td>
<td>5,000 units SC q 8-12 hours</td>
<td>7,500 units SC q 8 hours</td>
</tr>
<tr>
<td>Aspirin</td>
<td>81-325 mg daily [low risk Multiple Myeloma outpatients]</td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>Target INR 2-3 [selected high risk, Multiple Myeloma outpatients]</td>
<td></td>
</tr>
</tbody>
</table>
Ambulatory Patients Receiving Chemotherapy

**PROTECHT**
- Metastatic or locally advanced lung, gastrointestinal, pancreatic, breast, ovarian, or head and neck cancer patients on chemotherapy
- Randomized, double blind trial
- Nadroparin 3800 IU anti-Xa SC once daily (n=779) vs placebo (n=387)
- Reduced thrombotic events: 2.0% vs 3.0% (single-sided p=0.02)
- No significant difference in major bleeding: 0.7% vs 0.3% (two-sided p=0.18)

**Cochrane Review**
- Randomized controlled trials (RCTs) (n=3538)
- LMWH (low molecular weight heparin) compared to inactive control
  - Reduced symptomatic VTE: RR 0.62; CI 0.41-0.93; NNT 60
  - 60% increase in major bleeding: RR 1.57; CI 0.69-3.60
- Multiple myeloma
  - LMWH significantly decreased symptomatic VTE compared to warfarin
  - RR 0.33; CI 0.14-0.83
  - No difference in major bleeding

**SAVE-ONCO**
- Metastatic or locally advanced solid tumors
- Double-blind, multicenter trial
- Semuloparin 20 mg SC once daily (n=1608) vs placebo (n=1604)
- Decreased risk of symptomatic VTE or VTE-related death
  - 1.2% vs 3.4% for placebo (HR 0.36; CI 0.21-0.60; p<0.001)
  - No difference in major bleeding
  - 1.2% vs 1.1% (HR 1.05; CI 0.55-1.99)
  - No difference in rate of death
  - 43.4% vs 44.5% (HR 0.96; CI 0.86-1.06; p=0.40)
Apixaban: Pilot Study

- Advanced or metastatic lung, breast, gastrointestinal, bladder, ovarian, or prostate cancer, or cancers of unknown or primary site
- Myeloma, or selected lymphomas
- Receiving first or second line chemotherapy
- Randomized, multicenter trial

Apixaban 5 mg (n=32), 10 mg (n=30), or 20 mg (n=33) PO once daily vs placebo (n=30)

- Major bleeding
  - 0%, 0%, 6.3%, 3.4%

- Clinically relevant non-major bleeding
  - 3.1%, 3.4%, 6.3%, 0%

Lower rates of VTE (excluding am DVT [deep vein thrombosis])
- Apixaban 0% vs placebo 10.3%

Levine, 2012

Patients Undergoing Surgery

- ENOXACAN
  - Elective, curative abdominal or pelvic surgery for gastrointestinal, gynecological, or urological cancer
  - Double-blind, randomized, international, multicenter trial
  - Intravenous 40 mg (n=312) vs UFH 5,000 I U SC TID (n=319)
  - VTE incidence (including death): 14.7% vs 18.2%; CI 9.2-2.3
  - No significant difference in bleeding: 18.7% vs 17.1%

Cochrane Review
- 16 RCTs (n=11,847)

Preoperative prophylactic anticoagulation
- No difference in VTE risk or mortality for LMWH or UFH

Extended duration VTE prophylaxis
- Planned double-blind surgery for abdominal or pelvic cancer
- Double-blind, multicenter trial (n=30)
  - Enoxaparin 40 mg SC daily x 6-10 days followed by enoxaparin for 21 more days or placebo
  - Extended duration enoxaparin reduced rate of VTE 4.8% vs 12.0% (p=0.02)
  - Benefit continued at 3 months 5.5% vs 13.8% (p=0.01)
  - No significant difference in rates of bleeding or other complications

Major abdominal surgery
- Multicenter prospective, randomized, open-label study
  - Enoxaparin, 40 mg SC daily x 6-10 days followed by enoxaparin for 21 more days
  - Enoxaparin 4.8% vs 12.0% (p=0.02)
  - No increase in major or minor bleeding

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Bergqvist, 1997

Rasmussen, 2006
hospitalized non-surgical patients

- MEDDENOX
  - Double-blind, randomized study
  - Enoxaparin: 20 mg (n=364; 15.4% cancer), 40 mg (n=367; 12.3% cancer), or placebo (n=371; 15.1% cancer) SC once daily x 6-14 days
  - Significantly decreased VTE incidence by day 14 with enoxaparin: 5.5% vs 14.9%; RR 0.37; CI 0.22-0.63; p<0.001
    - Cancer subgroup: nonsignificant reduction in VTE with enoxaparin vs placebo
      - ARR (absolute risk reduction) 9.8%; RR 0.50; CI 0.14-1.72; p=0.4
  
- PREVENT
  - Double-blind, randomized, placebo-controlled, multicenter, multinational trial
  - Dalteparin: 5000 units SC daily (n=1848; 4.6% cancer) vs placebo (n=1833; 5.7% cancer) x 14 days
  - Significant reduction in VTE by day 21: 2.77% vs 4.96%; RR 0.55; CI 0.38-0.80; p=0.0015
  - Cancer subgroup: 3.08% vs 8.33%; RR 0.37

- ARTEMIS
  - Double-blind, randomized, placebo-controlled trial
  - Fondaparinux: 2.5 mg SC daily (n=429; 14.5% cancer) vs placebo (n=420; 16.4% cancer) x 6-14 days
  - Decreased VTE by day 15: 5.6% vs 10.5%; RRR (relative risk reduction) 46.7%; CI 7.7-69.3; p=0.029
  - No significant difference in incidence of major bleeding

patients with CVCs (central venous catheters)

- Cochrane Review
  - 12 RCTs (n=2823) assessing efficacy and safety of VTE prophylaxis with UH, LMWH, vitamin K antagonists, or placebo in patients with CVCs
  - Prophylactic heparin (UH and LMWH) and low-dose VKAs
    - Significant reduction in symptomatic DVT for prophylactic heparin compared to no intervention (RR 0.48; CI 0.27-0.86)
      - No significant impact on mortality, major bleeding, infection, bleeding symptoms, or minor bleeding
    - Significant reduction in symptomatic DVT for low-dose VKAs compared to no VKAs (RR 0.43; CI 0.30-0.62)
      - No significant impact on mortality, symptomatic DVT, major bleeding, or minor bleeding
    - Patients compared to UH showed higher rates of symptomatic DVT (RR 3.75; CI 2.85-4.41; one RCT)
Patient Case

- 63 yo female presents to the GYN-ONC clinic for a pre-op visit prior to admission for debulking surgery for stage III ovarian cancer
- Should she be on prophylactic anticoagulation in the ambulatory setting?
- Should she receive post-op VTE prophylaxis?
- How long?

Prophylaxis Summary

- Routine prophylaxis not recommended in ambulatory patients
- Offer to patients receiving highly thrombogenic adjuvant/winding-based combination chemotherapy
- Consider VTE prophylaxis with UHLMWH, direct thrombin inhibitor during hospitalization for all patients undergoing major surgical intervention for malignant disease
- Consider prolonged prophylaxis (up to 4 weeks) in patients undergoing major abdominal or pelvic surgery with high risk factors
- Residual malignant disease, death prior VTE
- Consider VTE prophylaxis in all hospitalized nongynecologic cancer patients unless contraindicated
- Routine prophylaxis not recommended for patients with CVI

Treatment
### Agents for Acute Treatment

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalteparin (preferred)</td>
<td>200 units/kg SC daily x 4 weeks, then 150 units/kg SC daily</td>
<td>Anti-Xa assay (LMWH) Once daily 1.2 U/mL, IDO, 0.51 U/mL</td>
</tr>
<tr>
<td>Enoxaparin (preferred)</td>
<td>1 mg/kg SC q 12 hour; 1.5 mg/kg SC daily</td>
<td>Anti-Xa assay (LMWH) Once daily 1.2 U/mL</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>50 mg if &lt; 50 kg; 75 mg if 50-100 kg; 100 mg if &gt; 100 kg</td>
<td>Anti-Xa assay (heparin)</td>
</tr>
<tr>
<td>UFH (IV)</td>
<td>80 units/kg load, then 18 units/kg/hr; target APTT of 2.5 x control, super hospital standard</td>
<td>Anti-Xa assay (heparin)</td>
</tr>
<tr>
<td>UFH (SC)</td>
<td>333 units/kg load, then 250 units/kg q 12 hour</td>
<td>Anti-Xa assay (heparin)</td>
</tr>
</tbody>
</table>

### Agents for Chronic Management

- **LMWH**
  - Preferred for 6 months as monotherapy
  - Initiate concurrently with parenteral agent used for acute therapy
  - Continue ≥ 5 days and until INR ≥ 2 for 24 hour
- **NOACs**
  - Not recommended

### Initial Treatment of Acute VTE

- **Cochrane Review**
  - 16 RCTs assessing acute treatment of VTE with LMWH, UFH, fondaparinux
  - 11 trials of LMWH vs UFH included in metaanalysis
    - Anti-Xa activity, measured mean RR: 0.71 (0.52-0.98)
    - 3 trials included in metaanalysis comparing LMWH vs UFH
      - No statistically significant reduction in VTE recurrence RR 0.69 (0.34-1.39)
      - No significant difference in death, recurrent VTE or major or minor bleeding with UFH vs fondaparinux
      - No significant difference in mortality comparing dalteparin to unfractionated heparin
Department of Medicine

**Long-term Treatment of VTE**

- **CLOT**: Active cancer and newly diagnosed symptomatic VTE
  - Internationale multicenter randomized study
  - Dalteparin 300 units/kg SC x 1 month, then 150 units/kg SC x 6 months (n=338)
  - Dalteparin 300 units/kg SC x 3.57 days, then warfarin 70 units/kg SC x 6 months (n=338)
  - Dalteparin significantly decreased recurrent VTE: 8% vs 16%, HR 0.48; CI 0.30-0.77; p=0.002
  - No significant differences in major bleeding or mortality

- **Cochrane Review**: Assessing long-term treatment of LMWHs in anticoagulant-dependent patients with symptomatic objectively confirmed VTE
  - Meta-analysis of 7 RCTs with LMWH compared to VKA

- **ONCENOX**: Patients with active cancer and acute VTE
  - Pilot feasibility study randomized, open-label, multicenter, active comparator, parallel-design trial
  - Enoxaparin 1 mg/kg SC BID x 5 days, then enoxaparin 1 mg/kg SC daily x 175 days (n=31)
  - Enoxaparin 1 mg/kg SC BID x 5 days, then 1.5 mg/kg SC daily x 175 days (n=36)
  - Enoxaparin 1 mg/kg SC BID x ≥5 days until INR 2-3.5, warfarin started on day 2 x 180 days total period

- **Occurrence of VTE**
  - Overall 7.5%, 4.7%, 6.3%, 10.0%

  - No significant difference in major common bleeding

**Patient Case**

- 74 y/o male with stage IV prostate cancer is newly diagnosed with a VTE

  - How should he be treated?

  - For how long?
Treatment of VTE Recurrence

- Treatment of VTE Recurrence
  - Recurrence on VKA, switch to LMWH
  - Superior efficacy of LMWH
  - Potential increased bleeding risk with INR fluctuation or higher target
  - Recurrence on LMWH
    - Retrospective cohort study of patients with recurrent VTE despite anticoagulation (LMWH vs. VKA; n=200 vs. n=380)
    - Initial therapy on LMWH, dose escalation 20%-25% x ≥ 4 weeks or increase to therapeutic dose x 6-12 weeks
    - In patients on VKA, switched to therapeutic LMWH x 1 month
    - 8.6% of patients experienced 2nd VTE recurrence during 3 months follow-up
    - No further thrombotic events after increased LMWH dose

Novel Oral Anticoagulants

- Novel Oral Anticoagulants
  - Direct Thrombin (IIa) Inhibitor
    - Dabigatran
  - Factor Xa Inhibitor
    - Rivaroxaban
    - Apixaban
    - Edoxaban

- RE-COVER
  - Acute symptomatic VTE
  - Randomized, double-blind, noninferiority, multicenter, international trial
  - rivaroxaban (10 mg PO BID vs. 2.5-5.0 mg/kg SC)
  - No difference in recurrent VTE: 2.4% vs. 2.1%; HR 1.10; CI: 0.65-1.84
  - Subgroup analysis of cancer patients: 2.5% vs. 3.9%

- EINSTEIN-DVT
  - Acute symptomatic DVT
  - Open-label, randomized, extravascular noninferiority study
  - rivaroxaban (15 mg PO BID vs. enoxaparin 1 mg/kg SC)
  - No difference in recurrent VTE: 2.1% vs. 3.2%; HR 0.66; CI: 0.40-1.04
  - Subgroup analysis of cancer patients: 4.2% vs. 8.5%
Meta analysis of RCT assessing safety and efficacy of NOACs in patients with VTE and cancer
- 4 studies: 2 dabigatran, 2 rivaroxaban, 1 edoxaban, 1 apixaban
- VTE Recurrence
  - 3.9% NOACs vs 6% comparator; OR 0.63; CI 0.37-1.10
- Major Bleeding
  - 3.2% NOACs vs 4.2% comparator; OR 0.77; CI 0.41-1.44
- Clinically Relevant Bleeding (CRB)
  - 14.5% NOACs vs 16.5% comparator; OR 0.85; CI 0.62-1.18

Vedovati, 2015

Patient Case
- 45 yo male with metastatic prostate cancer develops a recurrent VTE on treatment with warfarin. He refuses to inject himself.
- Would you switch him to a NOAC?

Treatment Summary
- LMWH preferred for initial VTE treatment x 6 months
- Treat patients for 3-6 months if VTE occurred during adjuvant chemotherapy and are without active cancer and not on treatment
- Indefinite anticoagulation for patients with active cancer
- IVC filter for patients with acute VTE who cannot receive anticoagulation due to bleeding diathesis, prolonged thrombocytopenia, or recurrent VTE despite adequate anticoagulation
- Dose escalate LMWH 20-25% if a patient develops a recurrent VTE or initiate LMWH in a patient on a VKA
- NOACs not recommended at this time

Connolly, 2013
Lyman, 2015
NCCN, 2015
Objectives

- Review the incidence and risk factors for VTE (venous thromboembolism) in cancer patients
- Describe the role for VTE prophylaxis and appropriate medications to use in cancer patients
- Discuss the recommended length of VTE treatment in cancer patients
- Evaluate the available medication options for VTE treatment in cancer patients

References


