Cancer Associated Thrombosis
Review and Update

Family Practice Oncology CME Day
November 21st 2015
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Disclosures

- No conflicts of interest to declare
Objectives

To review evidence in cancer-associated VTE

- Epidemiology
- VTE risk factors/Risk stratification
- Primary prophylaxis
- Treatment of cancer-associated VTE
  - VTE and thrombocytopenia
  - VTE and bleeding
  - Incidental VTE
Case 1: Ms. P.E.

- 65 year old female
- PMHx hypertension, hypothyroidism and obesity
- Recently diagnosed with unresectable locally advanced **pancreatic** cancer
- ECOG 2
- Plan to place **port-a-cath** and start multi-agent chemotherapy

What is this patient’s risk of VTE? Is the risk high enough to need primary prophylaxis?
Cancer-Associated VTE (CAT)

- ~20% of all VTE cases are associated with cancer
- VTE is associated with higher mortality
  - 2nd leading cause of death in cancer patients
- Significant burden on the health care community
  - Increased hospitalization
  - Health care costs and resource utilization
- Can cause treatment discontinuation/delays

Pathogenesis of CAT

- Multifactorial etiology
  - Venous stasis
  - Endothelial Dysfunction
  - Hypercoagulability
Pathogenesis of CAT

- Multifactorial etiology
  - Venous stasis
  - Endothelial Dysfunction
  - Hypercoagulability
    - Genetic mutations in cancer cells
    - Cytokines
    - Adhesion molecules
    - Tissue factor microparticles
Risk Factors for VTE in Cancer

- Divided into 3 main categories
  - Patient-related risk factors
  - Treatment-related risk factors
  - Cancer-related risk factors

- Overall risk is not static and varies over time
  - Acquisition of new risk factors
  - Disease progression
  - Initiation of new therapies
## Risk Factors for VTE in Cancer

<table>
<thead>
<tr>
<th>Patient-related</th>
<th>Cancer-related</th>
<th>Treatment-related</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Older age</td>
<td>• Primary site</td>
<td>• Surgery</td>
</tr>
<tr>
<td>• Race</td>
<td>• Histology</td>
<td>• Chemotherapy</td>
</tr>
<tr>
<td>• Prior VTE</td>
<td>• Stage</td>
<td>• Hormonal therapy</td>
</tr>
<tr>
<td>• Platelet count</td>
<td>• Grade</td>
<td>• Anti-angiogenic agents</td>
</tr>
<tr>
<td>• Obesity</td>
<td>• Time interval since diagnosis</td>
<td>• ESA</td>
</tr>
<tr>
<td>• Comorbid conditions</td>
<td></td>
<td>• Hospitalization</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Catheters</td>
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Tumour Type and VTE Risk

RR of VTE ranges from 1.02 to 4.34

CAT is Increasing Over Time

Risk of VTE with Age

- Annual incidence of VTE varies with age
  - Overall $\rightarrow 1/1000$
  - $< 30 \text{ y} \rightarrow 1/10,000$
  - $\sim 80 \text{ y} \rightarrow 1/100$

- After age 50
  - Risk doubles with each decade
  - Men have higher risk than women

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Silverstein M.D. Arch Intern Med 1998
Who Are At Risk for CAT?

- Highest VTE risk in:
  - Older patients
  - Pancreatic, brain, upper GI tumours and lymphoma
  - Metastatic disease
  - First 3 months after cancer diagnosis
  - First month after surgery
  - Systemic chemotherapy (especially cisplatin, anthracyclines, thal/lenalidomide, bevacizumab)

How do we identify individual patient risk?
## Risk Stratification in CAT

### Khorana risk model
- 5-independent risk factors identified

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<th>Score</th>
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<tr>
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<td>2</td>
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<td>High risk (lung, lymphoma, gyne and GU)</td>
<td>1</td>
</tr>
<tr>
<td>Pre-chemo platelet count ≥ 350</td>
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<tr>
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</tr>
<tr>
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<tr>
<td>BMI ≥ 35</td>
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Low risk = 0  
Moderate Risk = 1-2  
High Risk ≥ 3

Khorana A. et al Blood 2008
Risk Stratification in CAT

**Khorana risk model**

- 5-independent risk factors identified

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Low risk 0.3%
Moderate Risk 2.0%
High Risk 6.7%

Khorana A. et al Blood 2008
Risk Stratification in CAT

- **Khorana risk model**
  - 5-independent risk factors identified

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For Ms. P.E
Score=3/6
HIGH RISK

Khorana A. et al Blood 2008
Who Should Get Primary Prophylaxis

- ASCO 2013 Guideline
  - Routine primary prophylaxis not indicated in outpatients
  - LMWH should be considered “case-by-case basis in highly selected outpatients” with solid tumours receiving chemo
  - ASA or LMWH should be given to those with myeloma receiving thalidomide or lenalidomide regimens with chemo/dex
  - Educate patient regarding signs and symptoms of VTE, particularly in high risk patients
Case 1: Ms. P.E.

- Returns to clinic for assessment prior to cycle 2
- Complains of a 1 week history of worsening calf pain and swelling
- Worsening SOB on exertion
- On exam left leg, swollen, tender to palpation and erythematous
- US confirms a left leg DVT

What do you do now?
Treatment of CAT

- All major consensus guidelines recommend LMWH monotherapy as the preferred treatment for CAT
- Recommendations based on results of 3 open-label RCTs
  - **CANTHANOX** study: enoxaparin vs. warfarin
  - **CLOT** study: dalteparin vs. warfarin/acenocoumarol
  - **LITE** study: tinzaparin vs. warfarin

Risk of Recurrent VTE with LMWH

Recurrent VTE

Cochrane Review

<table>
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<th>Outcome</th>
<th>HR (95% CI)</th>
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<td>Recurrent VTE</td>
<td>0.47 (0.32 – 0.71)</td>
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<tr>
<td>Major bleeding</td>
<td>1.07 (0.52 – 2.19)</td>
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<tr>
<td>Survival</td>
<td>0.96 (0.81 – 1.14)</td>
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- Dalteparin 200 u/kg x 1 mo then 150 u/kg x 5 mo
- Tinzaparin 175 u/kg (3 mo LITE; 6 mo CATCH)
- Enoxaparin 1.5 mg/kg x 3 mo
- Warfarin to target INR 2.0 to 3.0

Akl E. et al Cochrane Database Syst Rev 2014
Risk of Bleeding with LMWH

Major Bleeding

CLOT  |  LITE  |  CATCH  |  CANTHANOX
---|---|---|---
p=0.27  |  p=NS  |  p=0.77  |  p=0.09

Dalteparin
Tinzaparin
Enoxaparin
Warfarin to target INR 2.0 to 3.0

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Bleeding rates decrease over time
3.6% in the first month
1.1% for months 2-6
0.7% for months 7-12

Francis C.W. et al J Thromb Haemost 2015
Tolerability of LMWH in Cancer

- Qualitative studies indicate that cancer patients
  - Are usually accepting of daily injections
  - Find LMWH convenient and empowering
  - Prefer efficacy and safety over the route of administration
  - Do not want the anticoagulant to interfere with their cancer treatment

Case 1: Ms. P.E.

1 month follow-up
- Significant bruising and subcutaneous hematomas at injection sites
- Wants to know if it is possible to switch to the “new oral pill” she saw advertised on CNN

Are the new oral anticoagulants a suitable option in cancer patients?
Anticoagulant Sites of Action

Direct Thrombin (IIa) Inhibitors
- Bivalirudin
- Lepirudin
- Argatroban
- Dabigatran

Direct Factor Xa Inhibitors
- Rivaroxaban
- Apixaban
- Edoxaban
- Betrixaban
- Darexaban

Unfractionated Heparin

Low Molecular Weight Heparin

Fondaparinux

Courtesy of Dr. J Ansell.
## DOAC Pharmacology

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>Thrombin</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
<td>Vit K dependent factors</td>
</tr>
<tr>
<td><strong>Action onset</strong></td>
<td>1 – 2 h</td>
<td>2 – 4 h</td>
<td>1 – 3 h</td>
<td>4-5 days</td>
</tr>
<tr>
<td><strong>Half life</strong></td>
<td>12-17 h</td>
<td>5-13 h</td>
<td>12-15 h</td>
<td>40 h</td>
</tr>
<tr>
<td><strong>Renal clearance</strong></td>
<td>80%</td>
<td>33%</td>
<td>25%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>BID</td>
<td>OD (BID)</td>
<td>BID</td>
<td>OD</td>
</tr>
<tr>
<td><strong>Lab monitoring</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>YES</td>
</tr>
<tr>
<td><strong>Antidote</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>YES</td>
</tr>
<tr>
<td><strong>Drug interactions</strong></td>
<td>P-gp</td>
<td>P-gp/CYP3A4</td>
<td>P-gp/CYP3A4</td>
<td>MANY</td>
</tr>
</tbody>
</table>
DOAC Drug Interactions

**Inhibitors**
- antifungals
- ritonavir
- amiodarone
- verapamil
- clarithromycin
- quinidine
- **tamoxifen**
- TKIs
- cyclosporin
- tacrolimus

**Inducers**
- rifampicin
- phenytoin
- carbamazepine
- phenobarbitone
- dexamethasone
- doxorubicin
- vinblastine
- St. John’s wort

Increase Drug Levels

Decrease Drug Levels
DOAC trials for VTE treatment

Dabigatran: RE-COVER and RE-COVER II
- UFH/LMWH + Warfarin
- Dabigatran 150 mg BID

Rivaroxaban: EINSTEIN DVT AND EINSTEIN PE
- Rivaroxaban 15 mg BID x 21 days then 20 mg OD
- Enoxaparin + Warfarin

Apixaban: AMPLIFY
- Apixaban 10 mg BID x 1 week then 5 mg BID
- Enoxaparin + Warfarin

DOAC trials for VTE treatment

Dabigatran: RE-COVER and RE-COVER II

- UFH/LMWH
- Dabigatran 150 mg BID
- UFH/LMWH + Warfarin
- Warfarin

9.5% active cancer

Rivaroxaban: EINSTEIN DVT AND EINSTEIN PE

- Rivaroxaban 15 mg BID x 21 days then 20 mg OD
- Enoxaparin + Warfarin
- Warfarin

9.2% active cancer

Apixaban: AMPLIFY

- Apixaban 10mg BID x 1 week then 5 mg BID
- Enoxaparin + Warfarin
- Warfarin

5.3% active cancer

All cancer patients were highly selected
- Well
- No bleeding
- No significant renal/hepatic dysfunction

DOAC trials for VTE treatment

DOACs = Warfarin
But...LMWH > Warfarin in cancer patients

DOAC Limitations in Cancer Patients

- Unreliable administration and absorption in patients with n/v, diarrhea and mucosal erosion
- Higher risk of GI bleed for dabigatran
- Liver and renal dysfunction is common in cancer
- Drug interactions may be clinically important
- Lack of measurement (therapeutic range) and antidote
- Lack of experience on management for procedures and thrombocytopenia
- No comparison against long-term LMWH for treatment
- Paucity of clinical trial data
Practical Pearls about LMWH ...

- Get over YOUR fear/reluctance of injections
- Have patient do his/her first injection in clinic
- Allow alcohol to dry before injection
- Inject SLOWLY (over 5-10 seconds)
- **Firm pressure for 2 – 5 min after injection**
  - Reduces bruising, hematomas and pain
- **DO NOT RUB**
- Insulin syringe offers greater comfort than prefilled syringes
Practical Pearls about LMWH ...

- Rotate sites and use "love handles"
- **Round UP** on dose to nearest prefilled syringe
- Dose based on body weight
- **No capping for weight**
Case 1: Ms. P.E.

- 2 months later
  - Patient presents to ER with UGIB
    - Hb 90
    - Platelets 42

What do you do with her anticoagulation?
Does she require an IVC filter?
VTE and Bleeding

- Multiple reasons for bleeding in cancer patients
- In patients with bleeding who also require anticoagulation, need to consider:
  - Severity and source of bleed (e.g. epistaxis vs ICH)
  - Whether source can be treated or eliminated
  - How long is the bleeding event likely to last
  - Likelihood of recurrence of bleeding event
  - Indication for anticoagulation
VTE and Bleeding

- No evidence-based guidance on management
- Treat bleeding source whenever possible
- Active, serious bleeding:
  - Hospitalize and withhold anticoagulation
  - Insert retrievable filter only if risk of recurrent VTE is very high (within first 4 weeks after VTE diagnosis)
  - Start anticoagulation and remove filter when bleeding stops
- When restarting anticoagulation restart prophylactic doses and uptitrate as tolerated
IVC Filters

- Efficacy and safety remain ill-defined after 40 years of use
- Long-term data shows no reduction in total VTE or mortality
- Short and long-term complications are common
  - Thrombosis (6 – 36%)
  - Filter tilt, fracture, migration or embolization (3 – 69%)
  - IVC perforation (3 – 86%)
  - Post-thrombotic syndrome (5 – 70%)

IVC Filter Complications
VTE and thrombocytopenia

- If platelet count less than $50 \times 10^9$/L:
  - Transfuse platelets if VTE recent ($< 30$ days)
  - Reduce dose of LMWH if VTE established ($> 30$ days)
VTE and thrombocytopenia

Acute VTE event

- Platelet count $\geq 50 \times 10^9$/L
  - Weight-based full dose LMWH

- Platelet count $< 50 \times 10^9$/L
  - Transfuse to maintain platelet count $\geq 50 \times 10^9$/L
  - Platelet count 20-50 $\times 10^9$/mL
    - Weight-based full dose LMWH
  - Platelet count $< 20 \times 10^9$/mL
    - Half-dose LMWH
  - Unable to maintain platelet count $\geq 50 \times 10^9$/L
    - Platelet count $< 20 \times 10^9$/mL
      - Hold anticoagulation

$\rightarrow$ VTE within last 4 weeks

Lee AY Blood 2013;122:2310
VTE and thrombocytopenia

- Subacute/Chronic VTE event
  - Platelet count ≥50 x 10^9/L → Weight-based full dose LMWH
  - Platelet count 20-50 x 10^9/L → Half-dose LMWH
  - Platelet count <20 x 10^9/L → Hold anticoagulation

→ VTE >4 weeks

Lee AY Blood 2013;122:2310
Case 2: Mr. D.v.T.

- 71 y.o. male with metastatic colon cancer
- Recent surgery and hospitalization for intestinal obstruction
- Large saddle embolus seen on CT scan performed for complete cancer staging
- Clinically and hemodynamically stable
- Currently asymptomatic according to his oncologist

Should we initiate anticoagulation? Does this affect the patient’s overall prognosis?
Incidental VTE

- Indirect evidence suggests that incidental and symptomatic VTE share the same risk factors:
  - older age
  - hospitalization
  - previous VTE
  - elevated WBC
  - cancer
  - recent chemotherapy
  - metastatic disease
  - first 3-6 months after cancer diagnosis

Incidental VTE

- Retrospective studies in oncology patients
  - Douma et al: incidental VTE 2.5%, PE/DVT 1.3% and abdominal vein thrombosis 1.1%
  - Cronin et al: incidental VTE 6%, DVT 6.8% and PE 3.3%

- Prospective studies
  - Shah et al: incidental VTE 2%

- Observed rates are increasing over time due
  - Improved imaging techniques
  - More scans

Incidental VTE

Symptomatic VTE
- PE: 74%
- PE + DVT: 5%
- DVT: 8%
- DVT + phlebitis: 8%
- UE DVT: 5%

Incidental VTE
- PE: 26%
- PE + DVT: 13%
- DVT: 35%
- DVT + phlebitis: 10%
- UE DVT: 8%
- Splanchnic/portal: 2%
- Renal: 6%

Di Nisio M. et al Thromb Haemost 2010
Incidental PE: Clinically Significant?

- Thrombus burden/location of emboli are similar to symptomatic PE
- When compared to matched controls incidental PE patients were more likely to have:
  - Fatigue (54% vs. 20% p=0.0002)
  - SOB (22% vs. 8% p=0.02)
- Incidental and symptomatic PE are both associated with increased mortality
- Patients with incidental PE have similar rates of recurrent VTE, bleeding and mortality compared to those with symptomatic PE

Management Strategy for Incidental PE

- **Incidental PE**
  - **Segmental or larger PE**
    - Consider risk for bleeding
    - Anticoagulation if no contraindication
  - **Subsegmental PE**
    - Review with chest radiologist or do CTPA
    - If uncertain do US of pelvis and legs
      - Positive for PE
        - Positive for DVT
        - Consider serial imaging
      - Negative for DVT
        - Withhold anticoagulation
    - Positive for DVT
      - Withhold anticoagulation
Incidental VTE in Cancer

- Prevalence increasing due to improved imaging, greater awareness and likely true rise in incidence
- **Must confirm diagnosis**
- Prognosis appears to be similar to symptomatic VTE in terms of VTE recurrence and mortality
- Role of anticoagulation is unclear
  - Currently recommended by ACCP guideline (2B) and 2013 ASCO guideline

Conclusions

- CAT is a **common**, costly and **potentially fatal**
- VTE risk assessment and patients education should be done routinely prior to starting chemotherapy
- Primary prophylaxis is not routinely indicated but should be discussed with patients at high risk
- Incidental VTE should be treated with standard therapy
- LMWH is still the treatment of choice but we need to encourage research using DOACs
Questions?