CANCER RELATED VENOUS THROMBOEMBOLISM
PROPHYLAXIS AND TREATMENT
LEARNING OBJECTIVES

• Discuss indications for anticoagulation prophylaxis in cancer patients

• Discuss role of direct oral anticoagulants and low molecular weight heparin in treatment of cancer associated venous thromboembolism

• Challenging scenarios – management of bleeding and thrombocytopenic patients
CANCER AND THROMBOSIS

• 20% of venous thromboembolism cases are associated with cancer
• 20% of cancer patients develop venous thrombosis
• 4-7 x higher risk of Venous Thromboembolism (VTE)
• 3 x higher risk of recurrent VTE
• 2 x higher risk of bleeding with Anticoagulation
• 10 x higher risk of death compared to patients without cancer
RISK FACTORS

• Cancer type
• Cancer genetics (i.e. Jak2 V617F)
• Cancer stage and grade
• Type of treatment
• Underlying comorbidities (i.e. prior history of VTE, thrombophilia carrier)

MECHANISM OF THROMBOSIS IN CANCER

- Extracellular vesicles may contain Tissue Factor
- Neutrophil extracellular traps
- Inflammatory cytokines - TNFα, IL-1β, IL6, VEGF
- Extracellular microRNAs

Image from Girardi et al. ATVB. Volume: 43, Issue: 6, Pages: 824-831, DOI: (10.1161/ATVBAHA.123.318779)
THROMBOSIS PROPHYLAXIS IN HOSPITALIZED PATIENTS

• For hospitalized medical patients with cancer:

  thromboprophylaxis recommended during hospitalization

  LWWH over UFH

  no need in transplant admissions or with short procedures
THROMBOSIS PROPHYLAXIS IN HOSPITALIZED PATIENTS

• For patients with cancer undergoing surgery:
  low bleeding risk – pharmacologic prophylaxis
  high bleeding risk – mechanical prophylaxis
  high thrombosis risk but without high bleeding risk – both mechanical and pharmacologic prophylaxis

• Extended prophylaxis up to 4 weeks with major abdominal/pelvic cancer surgery
# Ambulatory Patients

## Khorana Risk Score

### Patient Characteristics

<table>
<thead>
<tr>
<th>Site of cancer</th>
<th>Risk score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very high risk (stomach, pancreas)</td>
<td>2</td>
</tr>
<tr>
<td>High risk (lung, lymphoma, gyn, GU)</td>
<td>1</td>
</tr>
<tr>
<td>Prechemotherapy plt count ≥ 350 x10⁹/L</td>
<td>1</td>
</tr>
<tr>
<td>Prechemotherapy Hgb &lt; 10 g/dL or use of Red Cell growth factors</td>
<td>1</td>
</tr>
<tr>
<td>Prechemo WBC count &gt;11 x10⁹/L</td>
<td>1</td>
</tr>
<tr>
<td>BMI ≥ 35 kg/m²</td>
<td>1</td>
</tr>
</tbody>
</table>

0 = low risk
1-2 = intermediate risk
>2 = high risk

Khorana et al. Blood. 2008 May;111(10):4902-7
OTHER PREDICTION MODELS

• **PROTECHT** score = Khorana + chemotherapeutic agents (cisplatin, carboplatin and gemcitabine)

• Vienna Cancer and Thrombosis Study (**CATS**) score = Khorana + D-dimer and soluble P-selectin

• **CONKO** score = Khorana – BMI + PS
**MORE PREDICTION MODELS**

- **COMPASS-CAT**

<table>
<thead>
<tr>
<th>VTE predictors</th>
<th>score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cancer-related risk factors</strong></td>
<td></td>
</tr>
<tr>
<td>Endocrine therapy or Anthracycline</td>
<td>6</td>
</tr>
<tr>
<td>Time since dg &lt;6 mo</td>
<td>4</td>
</tr>
<tr>
<td>CVC</td>
<td>3</td>
</tr>
<tr>
<td>Advanced stage</td>
<td>2</td>
</tr>
<tr>
<td><strong>Predisposing risk factors</strong></td>
<td></td>
</tr>
<tr>
<td>CV risk factors (at least 2 of: Hx of PAD, ischemic stroke, CAD, Htn, hyperlipidemia, DM, obesity)</td>
<td>5</td>
</tr>
<tr>
<td>Recent hospitalization for acute illness</td>
<td>5</td>
</tr>
<tr>
<td>Personal VTE history</td>
<td>1</td>
</tr>
<tr>
<td><strong>Biomarkers</strong></td>
<td></td>
</tr>
<tr>
<td>Plt count &gt; 350 10^9/L</td>
<td>2</td>
</tr>
</tbody>
</table>

Low/Intermediate risk: 0–6 (1.7% had VTE); high risk: > 7 (13.3%)

- **New VIENNA model**

- **ONKOTEV** = Khorana score > 2 + metastatic disease + vascular or lymphatic compression + previous VTE event.
# Prevention of VTE in Ambulatory Cancer Patients - LMWH

<table>
<thead>
<tr>
<th>Study (LMWH in pts with advanced cancers)</th>
<th>VTE in LMWH vs no prophy</th>
<th>Major bleed in LMWH vs no prophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kakkar et al 2004</td>
<td>2.4% vs 3.3%</td>
<td>0.5% vs 0</td>
</tr>
<tr>
<td>Agnelli et al 2009</td>
<td>2% vs 3.9%</td>
<td>0.7% vs 0</td>
</tr>
<tr>
<td>Khorana et al 2015</td>
<td>12% vs 21%</td>
<td>2% vs 2%</td>
</tr>
<tr>
<td>Sideras et al 2005</td>
<td>6% vs 7%</td>
<td>3% vs 7%</td>
</tr>
<tr>
<td>Doormaal et al 2011</td>
<td>6.5% vs. 5.8%</td>
<td>4.1% vs 3.5%</td>
</tr>
</tbody>
</table>
PREVENTION OF VTE IN AMBULATORY CANCER PATIENTS - DOACS

**Avert** trial 2.5 mg bid Apixaban vs placebo
VTE rates Apixaban 4.2% vs 10.2% placebo
Major bleeding rates Apixaban 3.5% vs 1.8% placebo

**Cassini** trial 10 mg daily Rivaroxaban vs placebo
VTE rates Rivaroxaban 6% vs 8.8% placebo
Major bleeding rates Rivaroxaban 2% vs 1% placebo

THROMBOPROPHYLAXIS IN AMBULATORY CANCER PATIENTS

• No thromboprophylaxis in low risk patients

• In high risk patients
  ASH suggests
  ISTH suggests
  ASCO may be offered
  NCCN consider
LMWH BETTER THAN WARFARIN

CLOT trial
Recurrent VTE: 15.7 % warfarin vs 7.9 % dalteparin
Major Bleeding: 6% warfarin vs 4% dalteparin

CATCH trial
Recurrent VTE: 10% warfarin vs 6.9% tinzaparin
Major Bleeding: 2.7% warfarin vs 2.4% tinzaparin

Lee et al. JAMA. 2015 Aug 18;314(7):677-86
DIRECT ORAL ANTICOAGULANTS VS LMWH

Edoxaban
  Recurrent VTE: 7.9% vs 11.3%
  Major bleeding: 6.9% vs 4.0%

Rivaroxaban
  Recurrent VTE: 4% vs 11%
  Major bleeding: 6% vs 4%

Apixaban
  Recurrent VTE: 5.6% vs 7.9%
  0.7% vs 6.3%
  Major bleeding: 3.8% vs 4.0%
  0 vs 1.4%

COMPARISON OF DOACS AND LMWH
TREATMENT OF CANCER-ASSOCIATED VENOUS THROMBOEMBOLISM

Initial treatment 1st week

Primary Treatment 3-6 months

Long term treatment (secondary prophylaxis) beyond 6 months
INITIAL TREATMENT

• Direct oral anticoagulant: Apixaban, Rivaroxaban or LMWH
• LMWH favored over unfractionated heparin (except in severe renal failure)
• Caution with DOACs in patients with gastrointestinal cancers and GU cancers with bleeding risk
SHORT AND LONG TERM TREATMENT

• Direct oral anticoagulant such as Apixaban, Edoxaban or Rivaroxaban preferred over LMWH

• Continue treatment beyond 6 months in patients with active cancer

• Unclear if DOAC dose can be reduced with long term treatment
CANCER VTE SCENARIOS

• In patients with cancer should you treat with anticoagulation:
  - Incidental PE  **YES**
  - Subsegmental PE  **YES** (case by case ASCO 2019 guidelines)
  - Visceral/splanchnic vein thrombosis  **YES** though observation is also an option

Can you keep CVC in patients with cancer and CVC-related clot  **YES**

• For patients with cancer and recurrent VTE despite receiving therapeutic LMWH consider increasing the LMWH dose to a supratherapeutic level

• IVC filter is not recommended for prevention in recurrent VTE (may be offered per ASCO 2019 guideline)
ANTICOAGULATION IN THROMBOCYTOPENIC PATIENT

• Cut off 50 k/uL for therapeutic anticoagulation
• Consider intermediate or prophylactic anticoagulation with plt count 20-50 k/uL
• Consider timing of acute clot (< 3 months vs >3 months), type of tumor and treatment
ANTICOAGULATION IN BRAIN CANCER

• Is not contraindicated but caution advised
• Does not significantly increase risk of ICH in patients with brain mets
• Significantly increased ICH risk in primary brain cancer
• DOACS do not increase bleeding risk over LMWH (may decrease)
• IVC filters not very effective
BLEEDING IN CANCER PATIENTS REQUIRING ANTICOAGULATION
TO ANTICOAGULATE OR NOT TO ANTICOAGULATE?

<table>
<thead>
<tr>
<th>Absolute contraindications to AC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active major, serious, or potentially life-threatening bleeding</td>
</tr>
<tr>
<td>Severe, uncontrolled malignant hypertension</td>
</tr>
<tr>
<td>Severe, uncompensated coagulopathy, Severe platelet dysfunction or inherited bleeding disorder</td>
</tr>
<tr>
<td>Persistent, severe thrombocytopenia (&lt; 20,000/uL)</td>
</tr>
<tr>
<td>High-risk invasive procedure in a critical site</td>
</tr>
<tr>
<td>DOAC only - concomitant use of potent P-glycoprotein or CYP3A4 inhibitors or inducers</td>
</tr>
</tbody>
</table>

Location: PE >> distal DVT or CVC- associated DVT
Timing: < 3 months vs >3 months
Type of tumor and stage
Mutational status of tumor
Treatment
IN SUMMARY

• Cancer patients are at high risk of thrombotic as well as bleeding complications

• Consider prophylactic anticoagulation in patients with cancer and high risk of thrombosis

• DOACs or LMWH are recommended for initial treatment of thrombosis in cancer patients with DOACs preferred for short as well as long term therapy

• Long term anticoagulation is recommended as long as patient is at high thrombotic risk

• Anticoagulation can be continued with thrombocytopenia, especially if plt count >50k, use clinical judgment
THANK YOU