Venous Thromboembolism Risk and Management in Patients with Hematologic Malignancies

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Objectives

• Identify risk factors for venous thromboembolism (VTE) in patients with hematologic malignancies
• Discuss prevention and treatment options for VTE in this population
• Evaluate the role of direct oral anticoagulants (DOACs) in the management of patients with hematologic malignancies
Significance of VTE

• 2\textsuperscript{nd} leading cause of death in patients with malignancy
• Recurrent VTE and bleeding rates are higher in cancer patients, when compared to non-cancer patients
• Associated with 3-fold increase in hospitalizations and higher total healthcare costs

Risk Factors for VTE

• Can generally be divided into 3 broad categories:
  • Intrinsic and extrinsic patient-related factors
  • Cancer-related factors
  • Treatment-related factors
Risk Factors for VTE

• Can generally be divided into 3 broad categories:
  • Intrinsic and extrinsic patient-related factors
    • Advanced age
    • Obesity
    • Pre-chemotherapy thrombocytosis, leukocytosis, hemoglobin < 10 g/dL
      • Anemia may be complicated by use of erythropoietin-stimulating agents
    • History of VTE
    • Hypercoaguable conditions (i.e. pregnancy)
    • Hospitalization
    • Other medical comorbidities
    • Poor performance status
    • Prolonged immobilization
  • Cancer-related factors
  • Treatment-related factors

Risk Factors for VTE

- Can generally be divided into 3 broad categories:
  - Intrinsic and extrinsic patient-related factors
  - Cancer-related factors
    - Presence of malignancy
      - Increases risk 4-7 fold
    - Type of cancer (pancreatic, brain tumors, stomach, kidney, uterine, lung, ovarian, bladder, testicular, lymphoma, acute leukemia, multiple myeloma)
    - Histology (adenocarcinomas > squamous cell tumors)
    - Extent of disease (localized vs. metastatic)
  - Chemotherapy
  - Extrinsic vascular compression (from cancer-associated regional bulky lymphadenopathy)
  - Treatment-related factors

Risk Factors for VTE

• Can generally be divided into 3 broad categories:
  • Intrinsic and extrinsic patient-related factors
  • Cancer-related factors
  • Treatment-related factors
    • Surgery
    • Presence of central venous catheter
    • Administration of chemotherapy
      • Cytotoxic chemotherapy agents
      • Hormone therapy with estrogenic compounds
      • Anti-angiogenic agents
## Risk Score Calculator – Khorana Predictive Model for Chemotherapy-Associated VTE

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Risk Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of Primary Cancer</td>
<td></td>
</tr>
<tr>
<td>• Very high risk (stomach, pancreas)</td>
<td>2</td>
</tr>
<tr>
<td>• High risk (lung, lymphoma, gynecologic, breast, testicular)</td>
<td>1</td>
</tr>
<tr>
<td>Pre-chemotherapy platelet count ≥ 350 x 10⁹/L</td>
<td>1</td>
</tr>
<tr>
<td>Hemoglobin &lt; 10 g/dL or use of red cell growth factors</td>
<td>1</td>
</tr>
<tr>
<td>Pre-chemotherapy leukocyte count ≥ 11 x 10⁹/L</td>
<td>1</td>
</tr>
<tr>
<td>BMI 35 kg/m² or higher</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total Score</th>
<th>Risk Category</th>
<th>Risk of Symptomatic VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low</td>
<td>0.8-3%</td>
</tr>
<tr>
<td>1, 2</td>
<td>Intermediate</td>
<td>1.8-8.4%</td>
</tr>
<tr>
<td>3 or higher</td>
<td>High</td>
<td>7.1-41%</td>
</tr>
</tbody>
</table>

## Risk Assessment in Multiple Myeloma

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Recommended Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Individual Risk Factors</strong></td>
<td>No risk factor or only one individual/myeloma risk factor:</td>
</tr>
<tr>
<td>• Obesity (BMI ≥ 30 kg/m²)</td>
<td>• Aspirin 81-325 mg once daily</td>
</tr>
<tr>
<td>• Prior VTE</td>
<td>≥ 2 individual/myeloma risk factors:</td>
</tr>
<tr>
<td>• CVAD or pacemaker</td>
<td>• LMWH (enoxaparin 40 mg once daily) OR</td>
</tr>
<tr>
<td>• Associated disease:</td>
<td>• Full dose warfarin (target INR 2-3)</td>
</tr>
<tr>
<td>- Cardiac</td>
<td></td>
</tr>
<tr>
<td>- Chronic renal</td>
<td></td>
</tr>
<tr>
<td>- Diabetes</td>
<td></td>
</tr>
<tr>
<td>- Acute infection</td>
<td></td>
</tr>
<tr>
<td>- Immobilization</td>
<td></td>
</tr>
<tr>
<td>• Surgery:</td>
<td></td>
</tr>
<tr>
<td>- General surgery</td>
<td></td>
</tr>
<tr>
<td>- Any anesthesia</td>
<td></td>
</tr>
<tr>
<td>- Trauma</td>
<td></td>
</tr>
<tr>
<td>• Use of erythropoietin</td>
<td></td>
</tr>
<tr>
<td>• Blood clotting disorders</td>
<td></td>
</tr>
<tr>
<td><strong>Myeloma related risk factors</strong></td>
<td></td>
</tr>
<tr>
<td>• Diagnosis of myeloma, per se</td>
<td></td>
</tr>
<tr>
<td>• Hyperviscosity</td>
<td></td>
</tr>
<tr>
<td><strong>Myeloma therapy</strong></td>
<td></td>
</tr>
<tr>
<td>• Immunomodulating agent in combination with:</td>
<td></td>
</tr>
<tr>
<td>- High dose dexamethasone (≥ 480 mg/month)</td>
<td></td>
</tr>
<tr>
<td>- Doxorubicin</td>
<td></td>
</tr>
<tr>
<td>- Multi-agent chemotherapy</td>
<td></td>
</tr>
<tr>
<td>• LMWH (enoxaparin 40 mg once daily) OR</td>
<td></td>
</tr>
<tr>
<td>• Full dose warfarin (target INR 2-3)</td>
<td></td>
</tr>
</tbody>
</table>

Anticoagulation Contraindications and Risks

Contraindications

- **Absolute:**
  - Recent CNS bleed
  - Presence of intracranial or spinal lesions at high risk of bleeding
  - Major active bleeding (>2 units of blood transfused in 24 hours)

- **Relative:**
  - Chronic, clinically significant bleeding
  - High risk for falls/head trauma
  - Thrombocytopenia
  - Severe platelet dysfunction
  - Underlying hemorrhagic coagulopathy
  - Neuraxial anesthesia/lumbar puncture

Risks

- Bleeding
- Osteoporosis
- Heparin-induced thrombocytopenia
- Drug interactions
- Food interactions
Mechanism of Action of Anticoagulant Agents

Available Agents

<table>
<thead>
<tr>
<th>Generic Name (Brand)</th>
<th>Dosing</th>
<th>DVT Prophylaxis</th>
<th>DVT Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INJECTABLE AGENTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dalteparin (Fragmin®)</td>
<td>Ppx: 2500-5000 units daily Tx: 200 units/kg daily x 30 days, then 150 units/kg</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Enoxaparin (Lovenox®)</td>
<td>Ppx: 30-40 mg daily-BID Tx: 1 mg/kg BID or 1.5 mg/kg daily</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Fondaparinux (Arixtra)</td>
<td>Ppx: 2.5 mg once daily (≥50kg) Tx: Fixed dosing based on weight</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Unfractionated Heparin</td>
<td>Ppx: 5000 units every 8-12 hours Tx: 80 units/kg IV bolus, then CI 18 units/kg/hr</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>ORAL AGENTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban (Eliquis®)</td>
<td>10 mg BID x 7 days, then 5 mg BID</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Dabigatran (Pradaxa®)</td>
<td>150 mg BID (after 5-10 parenteral therapy)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Edoxaban (Savaysa®)</td>
<td>60 mg once daily (after 5-10 parenteral therapy)</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Rivaroxaban (Xarelto®)</td>
<td>15 mg BID x 21 days, then 20 mg daily</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Warfarin (Coumadin®)</td>
<td>Individualized dosing</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
Recommendations for VTE Prophylaxis

- **Inpatients**
  - All patients without contraindication to therapy should receive VTE prophylaxis
  - Assumption that ambulation not enough to prevent VTE
  - LMWHs, fondaparinux, subcutaneous UFH

- **Outpatients**
  - High risk patients continue to be at risk post-discharge
    - Abdominal or pelvic surgery patients, multiple myeloma patients
  - Risk-benefit assessment in other high risk patients
Treatment of VTE – What Should We Use?
Immediate Treatment of VTE

• Meta-analysis comparing outcomes with UFH, LMWH, and fondaparinux as initial treatment
• LMWH associated with a significant reduction in mortality at 3 months (RR 0.71, 95% CI 0.52-0.98)
• No significant difference in VTE recurrence between LMWH and UFH
• No statistically significant differences between heparin and fondaparinux in mortality, VTE recurrence or bleeding events
• Establishes role of LMWH for acute management (no hospitalization or monitoring required, preferred option for long term therapy)

CANTHANOX trial

- Included 147 adult patients with any cancer and diagnosis of DVT/PE
- Randomized to subcutaneous enoxaparin 1.5 mg/kg daily vs. warfarin (titrated to achieve INR 2-3) given for 3 months
- Outcomes:
  - Recurrent VTE and/or major bleeding: 10.5% vs. 21.1% (p=0.09)
  - 3 month mortality: 11.3 vs 22.7% (p=0.07)
  - Major hemorrhage: 7 vs. 16% (p=0.09)

CLOT trial

- Included 676 adult patients with active cancer with newly diagnosed, symptomatic proximal DVT, PE or both
- Dalteparin alone (200 IU/kg daily x 1 month, 150 IU/kg daily x 5 months) vs. dalteparin 200 IU/kg daily x 5-7 days with warfarin titrated to INR 2-3
- Outcomes:
  - Recurrent DVT/PE during study period: 27 vs. 53 events (HR 0.48, p=0.002)
  - Clinically overt bleeding: 6% vs. 4% (p=0.27)
  - Death: 39% vs. 41% (p=0.53)
- Establishes role of LMWH as chronic therapy in patients with metastatic disease diagnosed with VTE

Summary – Risk of Recurrent VTE with LMWH alone vs. VKA

Summary – Major Bleeding Risk with LMWH alone vs. VKA


<table>
<thead>
<tr>
<th></th>
<th>No patients with event/No. of patients</th>
<th>Relative Risk (65% CI)</th>
<th>Weight</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMWH</td>
<td>Meyer 5/71</td>
<td></td>
<td>22.3%</td>
<td>0.4 (0.13, 1.19)</td>
</tr>
<tr>
<td>VKA</td>
<td>Lee 12/75</td>
<td></td>
<td></td>
<td>1.6 (0.77, 3.36)</td>
</tr>
<tr>
<td></td>
<td>Hull 7/100</td>
<td></td>
<td>22.8%</td>
<td>1 (0.34, 2.96)</td>
</tr>
<tr>
<td></td>
<td>Delitcher 6/67</td>
<td></td>
<td>5.8%</td>
<td>3.25 (0.37, 28.12)</td>
</tr>
<tr>
<td></td>
<td>Pooled Random-effects 37/576</td>
<td></td>
<td>100%</td>
<td>1.06 (0.5, 2.23)</td>
</tr>
</tbody>
</table>
Recommendations for VTE Treatment

• Immediate treatment with LMWH for initial and long-term treatment of cancer-related thrombosis
• VKAs for long-term management is acceptable in LMWH is not an option
• Duration of therapy:
  • Minimum 3 months of therapy for patients with DVT/PE with either LMWH or warfarin
  • LMWH as monotherapy for first 6 months in patients with proximal DVT or PE and for prevention of recurrent VTE in those with advanced or metastatic disease
  • Indefinite therapy should be considered in patients with active cancer or persistent risk factors
But What About the DOACs?

DOAC = direct oral anticoagulant
EINSTEIN trial

- Pooled analysis of EINSTEIN-DVT and EINSTEIN-PE trials, which included 8282 patients
  - Pre-specified subgroup analysis of cancer patients
  - Cancer defined as active cancer at study entry or cancer diagnosed during tx
- Treatment consisted of rivaroxaban 15 mg BID x 21 days, then 20 mg QDay or enoxaparin 1 mg/kg SQ BID followed by warfarin (INR 2-3)
  - Treatment duration 3, 6, or 12 months (determined locally)
- Outcomes:
  - 430 patients with active cancer at baseline (5.2%), 167 diagnosed during study (2%)
  - Symptomatic recurrent VTE:
    - All patients: 2.1 vs. 2.3% (HR 0.89, 95% CI 0.66-1.19, p<0.001 for non-inferiority)
    - Cancer patients: 5.1 vs. 7.1% (HR 0.69, 95% CI 0.36-1.33)
  - Clinically relevant bleeding:
    - All patients: 9.4 vs. 10.0% (HR 0.93, 95% CI 0.81-1.06)
    - Cancer patients: 2.8 vs 5% (HR 0.53, 95% CI 0.23-1.23)

HOKUSAI-VTE trial

• Randomized, double-blind, non-inferiority trial comparing edoxaban with warfarin for long-term treatment of symptomatic proximal DVT and/or PE in 8292 patients
  • Excluded patients with active cancer for whom long-term LMWH tx was anticipated
  • Patients with hx of cancer were eligible if long-term tx was not planned

• Edoxaban 60 mg po once daily vs. warfarin (titrated to INR 2-3)

• Outcomes:
  • 771 cancer patients enrolled (9.3%, 208 with active cancer, 563 with hx)
  • Recurrent symptomatic VTE:
    • Active cancer: 3.7 vs. 7.1% (HR 0.55, 95% CI 0.16-1.85)
    • All cancer patients at study entry: 3.7 vs. 7.1% (HR 0.53, 95% CI 0.28-1.00)
    • Non-cancer patients: 2.8 vs. 2.7% (HR 1.03, 95% CI 0.78-1.36, p=0.004)
  • Major or clinically relevant non-major bleeding
    • Active cancer: 18.3 vs. 25.3% (HR 0.72, 95% CI 0.40-1.30)
    • All cancer patients at study entry: 12.4 vs. 18.8% (HR 0.64, 95% CI 0.45-0.92)
    • Non-cancer patients: 7.7 vs. 9.1% (HR 0.83, 95% CI 0.71-0.97, p=0.022)

RE-COVER and RE-COVER II trials

• Pre-specified subgroup analysis of RE-COVER and RE-COVER II to investigate safety and efficacy of dabigatran vs. warfarin in patients with and without active cancer
  • Active cancer: diagnosis of cancer (other than BCC or SCC of skin) within 5 years before enrollment, any treatment for cancer within 5 years before enrollment, or recurrent/metastatic cancer

• Intervention: Parenteral treatment + warfarin or warfarin + placebo for at least 5 days until INR ≥ 2, followed by warfarin or dabigatran 150 mg po BID

• Outcomes:
  • 5107 total patients, 335 with cancer (6.6%)
  • Recurrent VTE or VTE-related death:
    • Cancer patients: 7.4 vs. 5.8%
    • Non-cancer patients: 2.4 vs 2.7% (HR 1.09, 95% CI 0.77-1.54)
  • Major bleeding events: overall incidence lower with dabigatran (HR 0.60)

AMPLIFY trial

• Randomized, double blind phase III study comparing apixaban with conventional therapy for acute VTE
  • Patients with active cancer and long term tx with LMWH planned were excluded
  • Active cancer = diagnosed or treated within last 6 months
• Apixaban 10 mg BID x 7, then 5 mg BID x 6 months vs. conventional therapy with enoxaparin SQ, followed by warfarin
• Outcomes
  • Cancer patients represent 3.1% of patients randomized (N=5395)
  • Recurrent symptomatic VTE or death: 3.7 vs. 6.4% (RR 0.56, 95% CI 0.13-2.37)
  • Major bleeding: 2.3 vs. 5% (RR 0.45, 95% CI 0.08-2.46)

Summary – Risk of Recurrent VTE with DOACs

### Summary – Major Bleeding Risk with DOACs

<table>
<thead>
<tr>
<th>Study</th>
<th>No patients with event/No. of patients</th>
<th>Relative Risk (95% CI)</th>
<th>Weight</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EINSTEIN</td>
<td>DOAC: 6/232, VKA: 8/196</td>
<td></td>
<td>34.8%</td>
<td>0.63 (0.22, 1.79)</td>
</tr>
<tr>
<td>HOKUSAI</td>
<td>DOAC: 5/109, VKA: 3/99</td>
<td></td>
<td>19%</td>
<td>1.51 (0.37, 6.17)</td>
</tr>
<tr>
<td>RECOVER</td>
<td>DOAC: 6/159, VKA: 7/152</td>
<td></td>
<td>32.9%</td>
<td>0.82 (0.28, 2.38)</td>
</tr>
<tr>
<td>AMPLIFY</td>
<td>DOAC: 2/87, VKA: 4/80</td>
<td></td>
<td>13.5%</td>
<td>0.46 (0.09, 2.44)</td>
</tr>
<tr>
<td>Pooled, Random-effects model</td>
<td>DOAC: 19/587, VKA: 22/527</td>
<td></td>
<td>100%</td>
<td>0.78 (0.42, 1.44)</td>
</tr>
</tbody>
</table>

Take Home Points for the DOACs

• All data presented was subgroup analysis, rather than stand alone trial in cancer patients
  • Studies ongoing comparing edoxaban/apixaban/rivaroxaban vs. dalteparin/LMWH in cancer patients
• Definition of cancer highly variable from study to study
• Percentage of cancer patients included in each study small
  • May also be lower risk cancer patient vs. those included in studies with LMWH as treatment arm
• Comparator arm in all studies was VKA therapy, arguably an inferior comparator
# Clinical Characteristics of the DOACs

<table>
<thead>
<tr>
<th>Agent</th>
<th>Renal Adjustments</th>
<th>Hepatic Adjustments</th>
<th>Half-Life</th>
<th>Drug Interactions</th>
<th>Administration Instructions</th>
<th>Financial Assistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban (Eliquis®)</td>
<td>Yes, depends on indication</td>
<td>Yes, with severe impairment</td>
<td>~12 hours</td>
<td>PGP and CYP 3A4 substrate</td>
<td>Administer with or without food; may be crushed *grapefruit products may ↑ levels</td>
<td>Copay card and free 30 day trial offer</td>
</tr>
<tr>
<td>Dabigatran (Pradaxa®)</td>
<td>Pts with CrCl ≤ 30 were excluded from trials</td>
<td>None</td>
<td>12-17 hours</td>
<td>PGP substrate</td>
<td>Administer with or without food; do NOT open capsules (can ↑ absorption by 75%); Discard bottle 4 months after opening</td>
<td>Savings card and free 30 day trial offer</td>
</tr>
<tr>
<td>Edoxaban (Savaysa®)</td>
<td>Reduce if CrCl ≤ 50</td>
<td>Avoid in moderate-severe impairment</td>
<td>10-14 hours</td>
<td>PGP substrate</td>
<td>Administer with or without food</td>
<td>Savings card</td>
</tr>
<tr>
<td>Rivaroxaban (Xarelto®)</td>
<td>Yes, depends on indication</td>
<td>Avoid in moderate-severe impairment</td>
<td>5-9 hours, 11-13 in elderly</td>
<td>PGP and CYP 3A4 substrate</td>
<td>Administer doses ≥15 mg/day with food; dose of 10 mg/day may be administered without regard to meals; can be crushed</td>
<td>Copay card and free 30 day trial offer</td>
</tr>
</tbody>
</table>
Conclusions

• Prevention and management of VTE in hematologic malignancy is often a clinically challenging scenario.

• Current data continues to support LMWH as the mainstay of therapy, but newer data with the DOAC agents may change this recommendation in the future.
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