Thrombosis and Clot Management

Lymphoma Tumor Board

October 13, 2017
Venous thromboembolism (VTE)

• Venous thromboembolism (VTE) is a leading cause of death in patients with cancer, regardless of cancer stage.
• Cancer is associated with a hypercoagulable state and a four-fold increase in thrombosis risk
• Types of thromboembolism include:
  • Deep vein thrombosis (DVT) – most common
  • Pulmonary embolism (PE)
  • Splanchnic veins and upper extremity venous system – less common
  • Catheter-related thrombosis – less common
• Advances in the management of VTE since the induction of low-molecular-weight-heparin (LMWH) have been modest
• Used for long-term therapy
• High risk for bleeding in cancer patients can limit therapeutic options
• “TF of tumor origin is a key molecule that initiates blood clotting and also supports tumor growth and metastasis by coagulation-independent mechanisms, such as up-regulation of VEGF and activation of PAR-2.”

Mechanisms of hemostatic system activation by tumor cells involves different hemostatic pathways. Tumor cells produce procoagulant, fibrinolytic, and platelet-aggregating activities and release proinflammatory and proangiogenic cytokines and procoagulant microparticles. Tumor cells interact with host vascular and blood cells (i.e., platelets, leukocytes, and endothelial cells) by means of direct adhesion, which activates the prothrombotic properties of these cells. Tumor cell-derived TF plays a central role in the generation of thrombin, but TF can also contribute to tumor growth and metastasis by coagulation-independent mechanisms, including influencing the expression of VEGF by the malignant cells and vascular cells and activating the PAR-2 signaling.

The generation of activated coagulation proteases (FVila, FXa, thrombin) and the formation of fibrin represent coagulation-dependent mechanisms of tumor progression, as they promote neo-angiogenesis and tumor proliferation. Fibrin coats also protect circulating cancer cells from attack by the host immune system.
Coagulation System

Blood coagulation \textit{in vivo}

- **Initiation Phase**
  - TF (tissue factor) → TF-VIIa → VII
  - IX
  - X
  - Xa

- **Amplification Phase**
  - (αTHR)
  - Xla → XIa
  - XI
  - VIIIa → VIII
  - Va
  - V
  - (αTHR)

- Stabilised, cross-linked fibrin clot

- Prothrombin → Thrombin → Fibrinogen → Fibrin → XIIIa → XIII
Why should we care?

- 47-fold increased risk of mortality from VTE
- 2\textsuperscript{nd} leading cause of death in cancer patients

Causes of Death in Patients with Cancer

- Cancer progression 71%
- Thromboembolism 9%
- Infection 9%
- Respiratory Failure 4%
- Bleeding 1%
- Aspiration 1%
- Other 6%
- Unknown 4%

VTE associated with early mortality during chemotherapy (HR=6.98)

## Risk Factors for Cancer-Associated VTE

<table>
<thead>
<tr>
<th>Patient-related factors</th>
<th>Treatment-related factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased age</td>
<td>Chemotherapy, antiangiogenesis agents, hormonal therapy</td>
</tr>
<tr>
<td>Ethnicity (risk increased in African Americans)</td>
<td>Radiation therapy</td>
</tr>
<tr>
<td>Co-morbidities (infection, renal and pulmonary disease, arterial thromboembolism, VTE history, inherited prothrombotic mutations)</td>
<td>Surgery ≥ 60 mins</td>
</tr>
<tr>
<td>Obesity</td>
<td>ESAs, transfusions</td>
</tr>
<tr>
<td>Performance status</td>
<td>Indwelling venous access</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cancer-related factors</th>
<th>Biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary site of cancer</td>
<td>Platelet count ≥ 350 x 10⁹/L</td>
</tr>
<tr>
<td>Stage (risk increases with higher stage)</td>
<td>Leukocyte count &gt; 11 x 10⁹/L</td>
</tr>
<tr>
<td>Histology</td>
<td>Hemoglobin &lt; 100g/L</td>
</tr>
</tbody>
</table>
| Time since diagnosis (risk increases during first 3-6 months) | }
Probability of DVT

- Clinical prediction rule called the Wells Score is used in suspected cases of DVT in patients.

  - **Wells score criteria**: (possible score −2 to 9)
    - Active cancer (treatment within last 6 months or palliative): +1 point
    - Calf swelling ≥ 3 cm compared to asymptomatic calf (measured 10 cm below tibial tuberosity): +1 point
    - Swollen unilateral superficial veins (non-varicose, in symptomatic leg): +1 point
    - Unilateral pitting edema (in symptomatic leg): +1 point
    - Previous documented DVT: +1 point
    - Swelling of entire leg: +1 point
    - Localized tenderness along the deep venous system: +1 point
    - Paralysis, paresis, or recent cast immobilization of lower extremities: +1 point
    - Recently bedridden ≥ 3 days, or major surgery requiring regional or general anesthetic in the past 12 weeks: +1 point
    - Alternative diagnosis at least as likely: −2 points

- Those with Wells scores of +2 or more have a 28% chance of having DVT, those with a lower score have 6% odds
Imaging of VTE

An ultrasound with a blood clot visible in the left common femoral vein

An abdominal CT scan with a clot in the right common iliac vein

Venograms of DVT
Pooled incidence rates (per 1000 person-years) of venous thrombosis per type of cancer

Cancer site

- breast (n=4 studies)
- prostate (n=6)
- bone (n=2)
- colorectal (n=5)
- haematologic (n=9)
- lung (n=7)
- brain (n=5)
- pancreas (n=7)

Incidence rate per 1000 p-ys


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Incidence rates of venous thrombosis (VT) per type of cancer plotted against the 1-year relative mortality for each cancer type.

Two-year cumulative incidence (%) of venous thrombosis per type and stage of cancer

Table 2. Guidelines for Managing VTE in Cancer Patients

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial therapy</td>
<td>LMWH preferred</td>
<td>LMWH recommended</td>
<td>LMWH recommended</td>
</tr>
<tr>
<td>Chronic therapy</td>
<td>LMWH preferred over warfarin for 1st 6 mo</td>
<td>LMWH preferred for ≥6 mo</td>
<td>LMWH preferred Extended therapy &gt;3 mo recommended. In patients not treated with LMWH, VKA suggested over rivaroxaban or dabigatran</td>
</tr>
<tr>
<td>Chronic outpatient</td>
<td>Novel oral anticoagulants not currently recommended for VTE thromboprophylaxis or treatment owing to insufficient clinical data in cancer patients</td>
<td>Novel oral anticoagulants not currently recommended for patients with cancer and VTE owing to limited data in cancer patients</td>
<td>LMWH and VKA recommended over rivaroxaban or dabigatran</td>
</tr>
<tr>
<td>treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: References 15, 19, 20.
### Table 3. Pharmacokinetics of Oral Anticoagulants

<table>
<thead>
<tr>
<th>Factor</th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>~100%</td>
<td>3%-7%</td>
<td>10-mg dose: 80%-100%</td>
<td>50%; prolonged absorption</td>
<td>62%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>20-mg dose: 66% (fasting)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to max concentration</td>
<td>4 h (peak anticoagulant effect delayed 72-96 h)</td>
<td>1-2 h</td>
<td>2-4 h</td>
<td>3-4 h</td>
<td>1-2 h</td>
</tr>
<tr>
<td>Protein binding</td>
<td>35%</td>
<td>92%-95%</td>
<td>87%</td>
<td>99%</td>
<td>55%</td>
</tr>
<tr>
<td>Metabolism</td>
<td>CYP2C9, 2C19, 2C8, 2C18, 1A2, 3A4</td>
<td>Conjugation, prodrug is Pgp substrate</td>
<td>CYP3A4/5, CYP2J2, hydrolysis, Pgp substrate</td>
<td>CYP3A4 (major), CYP1A2, 2C8, 2C19, 2J2 (all minor), Pgp substrate</td>
<td>Conjugation, hydrolysis, CYP3A4 (all minor), Pgp substrate</td>
</tr>
<tr>
<td>Elimination</td>
<td>Hepatic metabolism</td>
<td>Renal (80%); renal (66%; 36% unchanged)</td>
<td>Renal (27%), fecal</td>
<td>Renal (50%), metabolism and biliary/intestinal excretion (50%)</td>
<td></td>
</tr>
<tr>
<td>Half-life</td>
<td>~40 h</td>
<td>12-17 h</td>
<td>5-9 h; longer in elderly</td>
<td>12 h</td>
<td>10-14 h</td>
</tr>
</tbody>
</table>

*max: maximum; Pgp: P-glycoprotein.
Source: References 27-31.*
# Treatment for VTE

## Table 4. Common Agents for the Treatment of VTE

<table>
<thead>
<tr>
<th>Agent</th>
<th>Usual Dosage</th>
<th>Dosage Adjustment</th>
<th>Food Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enoxaparin</strong></td>
<td>1 mg/kg SC q12h or 1.5 mg/kg SC once daily</td>
<td>CrCl &lt;30 mL/min: 1 mg/kg once daily. Not approved for use in dialysis patients.</td>
<td>None</td>
</tr>
</tbody>
</table>
| **Dalteparin** | Initial: 200 U/kg SC once daily × 30 days (max 18,000 U)  
Maintenance: ~150 U/kg once daily (max 18,000 U) | Caution in renal impairment. If CrCl <30 mL/min, manufacturer recommends monitoring anti-Xa levels. | None                                               |
| **Warfarin** | Dosage adjusted to maintain INR 2-3               | Based on INR results                                                              | Vitamin K–containing foods may decrease effectiveness |
| **Dabigatran** | 5-10 days with parenteral agent, then 150 mg po bid | CrCl <30 mL/min: no manufacturer recommendation                                  | None                                               |
| **Rivaroxaban** | 15 mg po bid × 21 days, then 20 mg po once daily | CrCl <30 mL/min: avoid use                                                        | Take doses >10 mg/day with food to increase bioavailability |
| **Apixaban** | 10 mg po bid × 7 days, then 5 mg po bid. After ≥6 mo, 2.5 mg bid | No adjustment necessary, but in Hokusai VTE trial, patients excluded if CrCl <30 mL/min | None                                               |
| **Edoxaban** | 5-10 days with parenteral agent, then 60 mg po once daily | CrCl 15-50 mL/min: 30 mg once daily; CrCl <15 mL/min: avoid use. Moderate-to-severe hepatic impairment (Child-Pugh B-C): avoid use. Weight ≤60 kg: 30 mg once daily | None                                               |

*Dalteparin is FDA-approved only for VTE treatment in cancer patients; it is used off-label in VTE patients without cancer. CrCl: creatinine clearance; INR: international normalized ratio; max: maximum; VTE: venous thromboembolism.*

*Source: References 33-38.*
Management algorithm of VTE in patients with cancer and thrombocytopenia

A

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 $\geq 50 \times 10^9/L$
    - Hold anticoagulation

B

Subacute/Chronic VTE event

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

- Platelet count 20-50 $\times 10^9/L$
  - Half-dose LMWH

- Platelet count $< 20 \times 10^9/L$
  - Hold anticoagulation

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Agnes Y. Y. Lee, and Erica A. Peterson Blood 2013; 122:2310-2317
Patients with VTE who should be treated for 3 months and who should be treated indefinitely

**Isolated distal DVT**
- Stop at 3 Months

**Reversible provoking factor**
- Stop at 3 Months

**Unprovoked proximal DVT or PE**

- **Cancer**
  - Indefinite therapy or until cancer inactive

**High Bleeding Risk OR prefers to stop even if D-dimer was positive**
- Stop at 3 Months

**Others**
- Stop and measure D-dimer after 1 month

**Not High Bleeding Risk AND prefers to stay on even if D-dimer was negative**
- Indefinite therapy

**Second VTE**
- Indefinite therapy

**Negative D-dimer**
- Stay off therapy (Stop at 3 Months)

**Positive D-dimer**
- Restart therapy (Indefinite therapy)

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1: Male would stop even if recurrence risk 16% in first year
Female would stop even if recurrence risk 10% in first year

2: Male would stay on if recurrence risk 8% in first year
Female would stay on even if recurrence risk 5% in first year

Clive Kearon, and Elie A. Akl *Blood* 2014; 123:1794-1801
Comparison of randomized controlled trials of different preparations of LMWH vs VKA for the long-term management of cancer-associated thrombosis

Agnes Y. Y. Lee, and Erica A. Peterson Blood 2013; 122:2310-2317
Risks of recurrent VTE after stopping anticoagulant therapy

Table 1

<table>
<thead>
<tr>
<th>Effect of 5 y of anticoagulation on mortality*</th>
<th>Recommendation</th>
<th>Risk of recurrent VTE without anticoagulation† (%)</th>
<th>Low bleeding risk‡</th>
<th>Intermediate bleeding risk§</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>5 y</td>
<td>First y</td>
</tr>
<tr>
<td>Any increase</td>
<td>Strong for 3 mo</td>
<td>&lt;9</td>
<td>&lt;9</td>
<td>&lt;3</td>
</tr>
<tr>
<td>0%–0.5% decrease</td>
<td>Weak for 3 mo</td>
<td>9–24</td>
<td>3–8</td>
<td>18–33</td>
</tr>
<tr>
<td>0.5%–1% decrease</td>
<td>Weak for indefinite</td>
<td>24–39</td>
<td>8–13</td>
<td>18–33</td>
</tr>
<tr>
<td>&gt;1% decrease</td>
<td>Strong for indefinite</td>
<td>&gt;39</td>
<td>&gt;13</td>
<td>&gt;39</td>
</tr>
</tbody>
</table>

Assumptions as described in text and in the ACCP guidelines† for: case fatality of recurrent VTE (3.6%) and major bleeding (11.3%); proportion of major bleeds attributable to anticoagulation (62%); risk reduction for VTE with anticoagulation (88%).

* Net effect of decrease in recurrent VTE and increase in bleeding.

† Calculations based on a 5–year period, with one-third of recurrences in the first year and two-thirds in the next 4 years.

‡ Risk of major bleeding of 0.8% for each of the 5 years.

§ Risk of major bleeding of 1.6% for each of the 5 years.
Survival of patients with cancer-related thrombosis following initial diagnosis of cancer
Survival of patients with cancer-related thrombosis according to site of thrombosis

The graph displays the cumulative proportion surviving (Kaplan-Meier) for patients following thrombosis. The survival times are differentiated by site of thrombosis:
- Lower limbs (median: 23.9 months)
- Others (median: 16.4 months)
- Upper limbs (median: 13.5 months)
- Multiple (median: 3.4 months)

The p-value for the comparison among these groups is 0.21158.
Time elapsed from diagnosis of cancer to onset of thrombosis and impact on survival

- Before Ca Dx (median: 13.4 months)
- 0–3 m at Ca Dx (median: 13.5 months)
- >3 m after Ca Dx (median: 18.5 months)
- History of clots (median 21.4 months)

Cumulative proportion surviving (Kaplan-Meier)

Survival following thrombosis (months)

P = 0.08171

P* < 0.0001
References

• den Exter, Paul, The Newer Anticoagulants in Thrombosis Control in Cancer Patients. https://doi.org/10.1053/j.seminoncol.2014.04.014