Challenges of Hemostasis in Cancer Patients

VTE Risk Assessment

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## Faculty Disclosure

<table>
<thead>
<tr>
<th>Company Name</th>
<th>Honoraria/Expenses</th>
<th>Consulting/Advisory Board</th>
<th>Funded Research</th>
<th>Royalties/Patent</th>
<th>Stock Options</th>
<th>Ownership/Equity Position</th>
<th>Employee</th>
<th>Other (please specify)</th>
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<tbody>
<tr>
<td>Example: company XYZ</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Thrombosis and Cancer

1 of 5 VTE events are related to cancer

Prevalence of VTE According to Cancer Types

- Patients with active cancer and a first VTE (N=6592)

Thrombosis and Cancer

1 of 5 VTE events is related to cancer

Cancer and Thrombosis

1 in 5 patients with cancer will develop VTE*

*High rates of „incidental“ (unsuspected) pulmonary embolism (PE)

Rates of VTE in Patients With Cancer

- Vienna Cancer and Thrombosis Study (CATS)

![VTE-incidence (%)](chart)

VTE-incidence (%) during a median follow-up of 501 days [IQR, 255-731] in 825 patients with different types of cancer.
Cancer and Thrombosis - Burden of Disease

Case-fatality at 30 days: 25%

Urgently needed

(Improving) risk assessment → Identification of patients at high risk → (Primary) prevention of VTE

Cancer and Thrombosis - Burden of Disease

- VTE in patients with cancer increases the risk of morbidity and mortality
  - VTE is a leading cause of death in cancer
  - Risk of mortality 3.7-fold [95% CI: 1.3-14.4] higher in cancer patient with VTE (adjusted for tumor stage, age and ethnicity)
  - Case-fatality rate at 30-days: 25%

- High risk of VTE recurrence in patients with cancer (3-fold)
- High risk of bleeding during anticoagulation (2-fold)

Risk Factors for VTE in Cancer Patients

**Patient-related**
- Medical comorbidities (CCI ≥3)
- Presence of varicose veins
- Prior VTE
- Hereditary risk factors (eg, factor V Leiden)

**Biomarkers**
- Hematologic biomarkers (eg, platelet, haemoglobin, leukocyte counts)
- D-dimer
- P-selectin
- Prothrombin fragment 1 + 2
- Thrombin generation potential
- MP-tissue factor activity
- C-reactive protein, VEGF, MPV, etc.

**Treatment-related**
- Platinum-based and other chemotherapy
- Anti-angiogenesis agents
- Hormonal therapy
- Surgery
- Radiotherapy
- Blood transfusion
- Central venous catheters
- Hospitalization and immobility

**Tumor-Related**
- Site of cancer
  - Very High: stomach, pancreas, brain
  - High: lung, hematologic, gynaecologic, renal, bladder
- Histological grade of a tumour
- Stage of cancer/metastases
- Time since cancer diagnosis

**Cancer-Associated VTE Risk**

Risk Factors for Cancer-associated VTE

**Tumor characteristics**
- Site: high risk = pancreatic, brain, lung, ovarian, lymphoma, myeloma, kidney, stomach, bone
  - low risk = breast, prostate
- Stage: localized, metastatic

**Blood cells**
- Platelet count
- Leukocyte count

**Hemostatic System**
- Prothrombotic variants
- Anticoagulant deficiencies

**Patient characteristics**
- History of VTE
- Age
- Immobilization
- Obesity

**Treatment**
- Chemotherapy
- Radiotherapy
- Surgery
- CVC
- Hormone therapy
- Erythropoiesis stimulating agents
- Anti-angiogenic agents
Risk Assessment of VTE in Patients With Cancer

- Prediction of cancer-associated VTE during chemotherapy with the „Khorana-Score“ (follow-up 2.4 months)

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Risk score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Site of cancer</strong></td>
<td></td>
</tr>
<tr>
<td>Very high risk (stomach, pancreas)</td>
<td>2</td>
</tr>
<tr>
<td>High risk (lung, lymphoma, gynecologic, bladder, testicular)</td>
<td>1</td>
</tr>
<tr>
<td>Prechemotherapy platelet count ≥ 350 × 10^9/L or more</td>
<td>1</td>
</tr>
<tr>
<td>Hemoglobin level less than 100 g/L or use of red cell growth factors</td>
<td>1</td>
</tr>
<tr>
<td>Prechemotherapy leukocyte count more than 11 × 10^9/L</td>
<td>1</td>
</tr>
<tr>
<td>BMI ≥ 35 kg/m² or more</td>
<td>1</td>
</tr>
</tbody>
</table>

Khorana et al, Blood 2008
Vienna Cancer and Thrombosis Study (CATS)

Total number of patients included in this analysis: 819

Score 0 (n=276)
Score 1 (n=229)
Score 2 (n=221)
Score ≥3 (n=93)

At 6 months:
- Score 0: 1.5%
- Score 1: 3.8%
- Score 2: 9.6%
- Score ≥3: 17.7%
External Validation of the Khorana Risk Score

Table 5. Multivariable Analysis of Baseline and Treatment Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>Adjusted P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1</td>
<td></td>
<td>.15</td>
</tr>
<tr>
<td>Female</td>
<td>1.31</td>
<td>0.91 to 1.88</td>
<td>.00</td>
</tr>
<tr>
<td>Age (per 10-year increase)</td>
<td>1.19</td>
<td>1.02 to 1.39</td>
<td>.03</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1</td>
<td></td>
<td>.11</td>
</tr>
<tr>
<td>Asian</td>
<td>0.87</td>
<td>0.41 to 1.85</td>
<td>.61</td>
</tr>
<tr>
<td>African American</td>
<td>1.43</td>
<td>0.74 to 2.76</td>
<td>.26</td>
</tr>
<tr>
<td>KPS (per 10-unit increase)</td>
<td>0.92</td>
<td>0.68 to 1.26</td>
<td>.02</td>
</tr>
<tr>
<td>Central venous catheter/pacemaker</td>
<td>1.51</td>
<td>1.10 to 2.36</td>
<td>.01</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td>.57</td>
</tr>
<tr>
<td>Early</td>
<td>1</td>
<td></td>
<td>.84</td>
</tr>
<tr>
<td>Locally advanced</td>
<td>0.84</td>
<td>0.41 to 1.72</td>
<td>.44</td>
</tr>
<tr>
<td>Metastatic</td>
<td>1.02</td>
<td>0.50 to 2.12</td>
<td>.64</td>
</tr>
<tr>
<td>Khorana risk group</td>
<td></td>
<td></td>
<td>.04</td>
</tr>
<tr>
<td>Low</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>1.33</td>
<td>0.81 to 2.16</td>
<td>.56</td>
</tr>
<tr>
<td>High</td>
<td>2.08</td>
<td>1.16 to 3.66</td>
<td>.04</td>
</tr>
</tbody>
</table>

Abbreviation: KPS, Karnofsky performance status.

Table 4. Venous thromboembolism according to age, time from first tumor diagnosis, Khorana score and the use of antiangiogenic agents: multivariate analysis

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Chi-square</th>
<th>P-value</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>2.3749</td>
<td>0.1233</td>
<td>1.019 (0.995–1.044)</td>
</tr>
<tr>
<td>Time from first tumor diagnosis</td>
<td>2.1908</td>
<td>0.1388</td>
<td>0.921 (0.825–1.027)</td>
</tr>
<tr>
<td>Khorana score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High (≥3)</td>
<td>15.9257</td>
<td>&lt;0.0001</td>
<td>7.876 (2.858–21.704)</td>
</tr>
<tr>
<td>Intermediate (1–2)</td>
<td>6.6582</td>
<td>0.0099</td>
<td>2.747 (1.275–5.919)</td>
</tr>
<tr>
<td>Low (0)</td>
<td></td>
<td></td>
<td>1*</td>
</tr>
<tr>
<td>Antiangiogenic with cytotoxic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.6730</td>
<td>0.1959</td>
<td>1.617 (0.781–3.352)</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td>1*</td>
</tr>
</tbody>
</table>

*Reference class.

"Expanded" Risk Prediction Scores for VTE in Cancer Patients

<table>
<thead>
<tr>
<th>Item</th>
<th>Khorana score (points)</th>
<th>Vienna CATS score (points)</th>
<th>PROTECHT score (points)</th>
<th>CONKO score (points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic or gastric cancer (very high-risk tumors)</td>
<td>+2</td>
<td>+2</td>
<td>+2</td>
<td>+2</td>
</tr>
<tr>
<td>Lung, gynecological, lymphoma, bladder, or testicular (high-risk tumors)</td>
<td>+1</td>
<td>+1</td>
<td>+1</td>
<td>+1</td>
</tr>
<tr>
<td>Pre-chemotherapy hemoglobin &lt;10 g/dL or use of erythropoietin stimulating agents</td>
<td>+1</td>
<td>+1</td>
<td>+1</td>
<td>+1</td>
</tr>
<tr>
<td>Pre-chemotherapy white blood cell count &gt;11 x 10^9/L</td>
<td>+1</td>
<td>+1</td>
<td>+1</td>
<td>+1</td>
</tr>
<tr>
<td>Pre-chemotherapy platelet count ≥350 x 10^9/L</td>
<td>+1</td>
<td>+1</td>
<td>+1</td>
<td>+1</td>
</tr>
<tr>
<td>Body Mass Index &gt;35 kg/m²</td>
<td>+1</td>
<td>+1</td>
<td>+1</td>
<td>–</td>
</tr>
<tr>
<td>D-dimer &gt;1.44 μg/L</td>
<td>–</td>
<td>+1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Soluble P-selectin &gt;53.1 ng/L</td>
<td>–</td>
<td>+1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Gemcitabine chemotherapy</td>
<td>–</td>
<td>–</td>
<td>+1</td>
<td>–</td>
</tr>
<tr>
<td>Platinum-based chemotherapy</td>
<td>–</td>
<td>–</td>
<td>+1</td>
<td>–</td>
</tr>
<tr>
<td>WHO performance status ≥2</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+1</td>
</tr>
</tbody>
</table>
Cumulative Incidence of Venous Thromboembolism in Low and High Risk Patients

A clinical prediction model for cancer-associated venous thromboembolism: a development and validation study in two independent prospective cohorts

Ingrid Pabinger, Nick van Es, Georg Heinze, Florian Posch, Julia Riedl, Eva-Maria Reitter, Marcello Di Nisio, Gabriela Cesarman-Maus, Noémie Kraaijpoel, Christoph Carl Zielinski, Harry Roger Büller, Cihan Ay
Development of the model (in CATS)

Penalized regression approach (LASSO, R library glmnet)\(^*\) with cause-specific VTE hazards over 12 months (in order to increase model stability) for selection of prognostic variables for the clinical prediction model from a large pool of clinical and laboratory candidate variables

Clinical Prediction Rule

- **Tumour site category**
  - “Low/intermediate”
    - Breast, prostate
  - “high”
    - Lung, colorectal, lymphoma, genitourinary excluding prostate, gynecologic excluding breast, esophageal, others
  - “Very high”
    - Stomach, pancreas

- **D-Dimer (μ g/mL)**
  - as continuous variable

*This model compared to Khorana score: Population-weighted net reclassification improvement (NRI)=0.31
Nomogram for predicting the 6-month risk of cancer-associated VTE

Points

D-Dimer

Tumor site risk

Low/Intermediate  High  Very High

Total points

Cumulative 6-months incidence (%)

For more on the risk calculator see: catscore.meduniwien.ac.at
Nomogram for predicting the 6-month risk of cancer-associated VTE

For more on the risk calculator see: catscore.meduniwien.ac.at
Risk Assessment for VTE
ASCO Guidelines Recommendation

**CLINICAL QUESTION 6**

What is known about risk prediction and awareness of VTE among patients with cancer?

**Recommendation 6.1**

Based on consensus, the Panel recommends that patients with cancer be assessed for VTE risk at the time of chemotherapy initiation and periodically thereafter. Individual risk factors, including biomarkers and cancer site, do not reliably identify patients with cancer at high risk of VTE. In the outpatient setting, risk assessment can be conducted based on a validated risk assessment tool (Table 5).

**Recommendation 6.2**

Based on consensus, the Panel recommends that oncologists educate patients regarding VTE, particularly in settings that increase risk such as major surgery, hospitalization, and while receiving systemic antineoplastic therapy.
Summary & Take Home Messages

• VTE is frequent in subgroups of patients with cancer
• Multiple risk factors contribute to occurrence of VTE in patients with cancer
• It is possible to identify high risk patients by clinical and laboratory parameters
• Risk assessment models seem to be promising

• Advances in risk assessment since the publication of the „Khorana Score“
  • A novel (externally validated) clinical prediction model includes two variables: tumour site category (“low/intermediate”, “high” and “very high” VTE-risk tumor site) and D-Dimer.

• Improving risk prediction might facilitate decision making on primary thromboprophylaxis
Thank you for your attention!