CLINICAL AND LABORATORY BIOMARKERS OF VTE RISK IN CANCER PATIENTS

HOWARD A. LIEBMAN MA. MD
JANE ANNE NOHLH DIVISION OF HEMATOLOGY
KECK SCHOOL OF MEDICINE
UNIVERSITY OF SOUTHERN CALIFORNIA
DISCLOSURES

• CONSULTING: PFIZER, BMS, JANSSEN, RIGEL, AMGEN, NOVARTIS, SANOFI, GENZYME

• RESEARCH SUPPORT: JANSSEN, PROTOLEX, SYNTIMMUNE
Incidence of Thrombosis in Carcinoma of Various Organs

<table>
<thead>
<tr>
<th>Organ in which tumor arose</th>
<th>Total No. Cases</th>
<th>Cases With Thrombosis</th>
<th>Cases With Multiple Thromboses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No. Cases</td>
<td>Per cent of Total</td>
</tr>
<tr>
<td>Anywhere in pancreas</td>
<td>47</td>
<td>14</td>
<td>29.7</td>
</tr>
<tr>
<td>Head of pancreas</td>
<td>31</td>
<td>5</td>
<td>16.1</td>
</tr>
<tr>
<td>Body or tail of pancreas</td>
<td>16</td>
<td>9</td>
<td>56.2</td>
</tr>
<tr>
<td>Lung</td>
<td>81</td>
<td>12</td>
<td>14.8</td>
</tr>
<tr>
<td>Liver</td>
<td>22</td>
<td>6</td>
<td>27.2</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>30</td>
<td>5</td>
<td>16.6</td>
</tr>
<tr>
<td>Stomach</td>
<td>147</td>
<td>32</td>
<td>21.8</td>
</tr>
<tr>
<td>Duodenum</td>
<td>16</td>
<td>3</td>
<td>18.7</td>
</tr>
<tr>
<td>Colon</td>
<td>94</td>
<td>15</td>
<td>15.9</td>
</tr>
<tr>
<td>Kidney</td>
<td>27</td>
<td>7</td>
<td>25.9</td>
</tr>
<tr>
<td>Prostate</td>
<td>43</td>
<td>7</td>
<td>16.3</td>
</tr>
<tr>
<td>Uterus</td>
<td>27</td>
<td>6</td>
<td>22.2</td>
</tr>
<tr>
<td>Ovary</td>
<td>17</td>
<td>4</td>
<td>23.5</td>
</tr>
</tbody>
</table>

Where do incidental VTE occur in cancer patients?

Retrospective single institution cohort study: solid tumour and chemotherapy (N = 1,921)

Incidental VTE
n = 62

- PE alone: 26%
- PE with lower limbs DVT: 13%
- Lower limbs DVT alone: 31%
- Lower limbs DVT + SVT: 6%
- Portal or splanchnic veins: 10%
- Renal veins: 2%
- Iliac-cava vein: 4%
- DVT upper extremities: 8%

Symptomatic VTE
n = 39

- DVT lower extremities: 74%
- DVT upper extremities: 8%
- PE: 5%
- PE + DVT extremities: 5%
- DVT + superficial vein thrombosis: 8%

Incidental VTE n = 62
Symptomatic VTE n = 39

SVT = superficial vein thrombosis.

Laboratory abnormalities of hemostasis are common in 431 cancer patients

<table>
<thead>
<tr>
<th>Test (patients studied)</th>
<th>Abnormal (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>aPTT (275)</td>
<td>10/275 (3.6)</td>
</tr>
<tr>
<td>FDPs* (264)</td>
<td>21/264 (7.6)</td>
</tr>
<tr>
<td>PT† (403)</td>
<td>57/403 (14.4)</td>
</tr>
<tr>
<td>Increased platelet count (412)</td>
<td>148/412 (35.9)</td>
</tr>
<tr>
<td>Increased fibrinogen (262)</td>
<td>125/262 (47.7)</td>
</tr>
<tr>
<td>FPA‡ (72)</td>
<td>48/72 (66.7)</td>
</tr>
</tbody>
</table>

*FDPs = fibrin degradation products; †PT = prothrombin time; ‡FPA = fibrinopeptide A
Candidate Biomarkers

- **Blood counts**
  - Platelet count
  - Leukocyte count
  - Hemoglobin

- **D-dimer**
- **Tissue factor**
- **Soluble P-selectin**
- **C-reactive protein**
- **Factor VIII**
- **Neutrophil nets**

## The Khorana Clinical Risk Model

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of Cancer</td>
<td></td>
</tr>
<tr>
<td>Very high risk (stomach, pancreas)</td>
<td>2</td>
</tr>
<tr>
<td>High risk (lung, lymphoma, gynecologic, GU excluding prostate)</td>
<td>1</td>
</tr>
<tr>
<td>Platelet count $\geq 350,000$/mm$^3$</td>
<td>1</td>
</tr>
<tr>
<td>Hb $&lt; 10$g/dL or use of ESA</td>
<td>1</td>
</tr>
<tr>
<td>Leukocyte count $&gt; 11,000$/mm$^3$</td>
<td>1</td>
</tr>
<tr>
<td>BMI $\geq 35$ kg/m$^2$</td>
<td>1</td>
</tr>
</tbody>
</table>

*Risk for patients receiving systemic chemotherapy

Rates of VTE according to scores from the risk model in the derivation and validation cohorts.

Khorana A A et al. Blood 2008;111:4902-4907
Vienna CATS validation

- Full data available in 839 patients
- Median observation time/follow-up: 643 days

<table>
<thead>
<tr>
<th>Score</th>
<th>Number of Patients</th>
<th>Number of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥3</td>
<td>96</td>
<td>16 (17%)</td>
</tr>
<tr>
<td>2</td>
<td>231</td>
<td>25 (11%)</td>
</tr>
<tr>
<td>1</td>
<td>233</td>
<td>14 (6%)</td>
</tr>
<tr>
<td>0</td>
<td>279</td>
<td>7 (3%)</td>
</tr>
</tbody>
</table>

Ay et al. ISTH 2009 Abs
KHORANA SCORE OF ≥2 IS PREDICTIVE OF HIGH RISK OF VTE IN PROSPECTIVE CLINICAL TRIALS

AVERT TRIAL

- Venous thromboembolism — no. (%) 28/275 (10.2)*
- Deep-vein thrombosis — no. (%) 12 (4.4)
- Pulmonary embolism — no. (%) 16 (5.8)

* No pre-enrollment lower limb ultrasound performed.

CASSINI TRIAL

- Venous thromboembolism — no. (%) 37/421 (8.8)*
- Deep-vein thrombosis — no. (%) 22 (5.2)
- Pulmonary embolism — no. (%) 15 (3.6)

* Of 1080 enrolled patients, 49 (4.5%) excluded due to baseline DVT on screening ultrasound.

Candidate Biomarkers

- **Blood counts**
  - Platelet count
  - Leukocyte count
  - Hemoglobin
- **D-dimer**
- **PT F1.2**
- **Tissue factor**
- **Soluble P-selectin**
- **C-reactive protein**
- **Factor VIII**
- **Neutrophil nets**

BIOMARKERS FROM THE VIENNA CAT STUDY

• D-Dimer (> 1.44 μg/ml): HR 1.8 (95% CI: 1.0 to 3.2; P = .048)

• PT F 1.2 (>358 pmol/L): HR 2.0 (95% CI: 1.2 to 3.6; P = .015)

ELEVATED D-DIMER IS A MAJOR RISK FACTOR FOR VTE IN CHINESE CANCER PATIENTS

<table>
<thead>
<tr>
<th>Univariate analysis</th>
<th>$t/\chi^2$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>2.70</td>
<td>.007</td>
</tr>
<tr>
<td>PLT</td>
<td>2.93</td>
<td>.004</td>
</tr>
<tr>
<td>Tumor diameter</td>
<td>1.97</td>
<td>.048</td>
</tr>
<tr>
<td>Tumor diameter $&gt;10\text{cm}$</td>
<td>4.259</td>
<td>.039</td>
</tr>
<tr>
<td>Cardiovascular complications</td>
<td>6.264</td>
<td>.012</td>
</tr>
<tr>
<td>D-dimer $&gt;0.5\text{ \mu g/mL}$</td>
<td>41.84</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age $&gt;55\text{y}$</td>
<td>11.30</td>
<td>.001</td>
</tr>
<tr>
<td>PLT $&gt;300 \times 10^9/\text{L}$</td>
<td>4.727</td>
<td>.030</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Multivariate analysis</th>
<th>$P$</th>
<th>OR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age $&gt;55\text{y}$</td>
<td>.003</td>
<td>13.110</td>
<td>2.451–70.133</td>
</tr>
<tr>
<td>PLT $&gt;300 \times 10^9/\text{L}$</td>
<td>.037</td>
<td>3.987</td>
<td>1.085–14.657</td>
</tr>
<tr>
<td>D-dimer $&gt;0.5\text{ \mu g/mL}$</td>
<td>&lt;.001</td>
<td>17.317</td>
<td>3.485–86.057</td>
</tr>
<tr>
<td>Tumor diameter $&gt;10\text{cm}$</td>
<td>.015</td>
<td>4.930</td>
<td>1.364–17.819</td>
</tr>
</tbody>
</table>

CI = confidence interval, OR = odds ratio, VTE = venous thromboembolism.

Zhang W et al. Medicine 2018; 97: 31 (e11758)
Elevated levels of D-dimer are predictive of survival in lung cancer

- Pre-treatment plasma levels of D-dimer predicted survival independent of stage, tumour size, performance status or histology

- Pre-treatment levels of D-dimer predicted survival on multivariate analysis

Candidate Biomarkers

- **Blood counts** ¹
  - Platelet count
  - Leukocyte count
  - Hemoglobin

- **D-dimer** ²

- **PT F1.2** ²

- **Tissue factor** ³,⁴

- **Soluble P-selectin** ⁵

- **C-reactive protein** ⁶

- **Factor VIII** ⁷,⁸

- **Neutrophil nets** ⁹

Tissue Factor (TF) in Cancer: Lack of standardized assays

- Immunohistochemistry of tumor specimens
- TF ELISA
- TF MP procoagulant activity assay
- Impedance-based flow cytometry
Tissue Factor Expression and VTE in Patients with Pancreatic Cancer

Plasma Tissue Factor Antigen and VTE

Cumulative incidence of VTE for cancer patients according to TF–bearing microparticles

Log Rank P=0.002

 Patients at risk
TFMP+ | 16 | 7 | 3 | 2 | 1 | 1
TFMP- | 44 | 28 | 21 | 8 | 5 | 2

MICROTEC OUTCOME

Competing-risks regression

Cumulative Incidence

analysis time

- High TFMP (enoxaparin)
- High TFMP (observation)
- Low TFMP

P=0.06

27.3%

7.2%

5.6%

Tissue Factor As a Predictor of Recurrent Venous Thromboembolism in Malignancy: Biomarker Analyses of the CATCH Trial

Subdistributional hazard ratios (SHRs; and 95% CIs) in the combined competing risk regression model. Competing risk regression analysis of time to recurrent VTE that accounts for study design variables and significant predictors identified in individual analyses.

CRP, C-reactive protein; TF, tissue factor.

Alok A. Khorana; Pieter W. Kamphuisen; Guy Meyer; Rupert Bauersachs; Mette S. Janas; Mikala F. Jarner; Agnes Y.Y. Lee; Journal of Clinical Oncology 2017 351078-1085. DOI: 10.1200/JCO.2016.67.4564
Candidate Biomarkers

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- **D-dimer**
- **PT F1.2**
- **Tissue factor**
- **Soluble P-selectin**
- **C-reactive protein**
- **Factor VIII**

BIOMARKERS FROM THE VIENNA CAT STUDY

- sP-selectin ($\geq 53.1$ ng/ml)$^1$: HR 2.6 (95% CI: 1.4 to 4.9; $P = .003$)

- Factor VIII ($\geq 232\%$)$^2$: HR 2.8 (95% CI: 1.7 to 4.6; $P = .001$)

Association between Laboratory Characteristics and Thromboembolic Events.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Positive</th>
<th></th>
<th></th>
<th></th>
<th>Negative</th>
<th></th>
<th></th>
<th></th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean</td>
<td>SD</td>
<td></td>
<td>n</td>
<td>Mean</td>
<td>SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>58</td>
<td>10.29</td>
<td>1.92</td>
<td></td>
<td>112</td>
<td>11.05</td>
<td>2.07</td>
<td></td>
<td>0.007</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>58</td>
<td>31.38</td>
<td>5.22</td>
<td></td>
<td>112</td>
<td>33.51</td>
<td>5.80</td>
<td></td>
<td>0.007</td>
</tr>
<tr>
<td>Platelets (k/mm³)</td>
<td>58</td>
<td>220.14</td>
<td>97.61</td>
<td></td>
<td>112</td>
<td>258.83</td>
<td>302.99</td>
<td></td>
<td>0.645</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>59</td>
<td>1.19</td>
<td>1.40</td>
<td></td>
<td>100</td>
<td>1.01</td>
<td>1.12</td>
<td></td>
<td>0.136</td>
</tr>
<tr>
<td>FBN (mg/dl)</td>
<td>52</td>
<td>411.46</td>
<td>149.96</td>
<td></td>
<td>94</td>
<td>435.81</td>
<td>143.01</td>
<td></td>
<td>0.240</td>
</tr>
<tr>
<td>TNF-α (pg/ml)</td>
<td>48</td>
<td>14.76</td>
<td>6.48</td>
<td></td>
<td>88</td>
<td>17.85</td>
<td>19.57</td>
<td></td>
<td>0.215</td>
</tr>
<tr>
<td>AFXa (%)</td>
<td>52</td>
<td>102.94</td>
<td>25.72</td>
<td></td>
<td>94</td>
<td>106.81</td>
<td>30.35</td>
<td></td>
<td>0.439</td>
</tr>
<tr>
<td>hsCRP (mg/l)</td>
<td>49</td>
<td>68.42</td>
<td>73.39</td>
<td></td>
<td>89</td>
<td>43.92</td>
<td>61.70</td>
<td></td>
<td>0.056</td>
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<tr>
<td>IL-6 (pg/ml)</td>
<td>44</td>
<td>24.83</td>
<td>27.02</td>
<td></td>
<td>76</td>
<td>21.72</td>
<td>48.40</td>
<td></td>
<td>0.032</td>
</tr>
<tr>
<td>Dimer-D (ng/ml)</td>
<td>45</td>
<td>4.615.38</td>
<td>6.460.54</td>
<td></td>
<td>91</td>
<td>977.52</td>
<td>2.145.50</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P-selectin (ng/ml)</td>
<td>44</td>
<td>33.60</td>
<td>23.35</td>
<td></td>
<td>73</td>
<td>20.40</td>
<td>6.92</td>
<td></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

SD, standard deviation; FBN, fibrinogen, TNF-α, tumor necrosis factor-α; AFXa, activated factor Xa; hsCRP, ultrasensitive C-reactive protein; IL-6, interleukin-6.

Barbour Fernandes LF et al. Molecular Clinical Oncology 2017; 8: 188
Cumulative Risk of Recurrent Venous Thromboembolism (VTE) in Patients with Cancer and Pulmonary Embolism (PE) According to Elevated Interleukin-6 (IL-6) Levels

$P = 0.010; \text{ log-rank test}$