VENOUS THROMBOEMBOLISM AND CANCER: PREDICTION AND PREVENTION

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DISCLOSURES

• Consultant for Sanofi & Leo
Why You Should Care:
Prevalence, Consequences, Costs

Predicting VTE in Cancer

Preventing VTE in Cancer
Why You Should Care: Prevalence, Consequences, Costs

Predicting VTE in Cancer

Preventing VTE in Cancer
Why You Should Care: VTE AND MORTALITY

2nd leading cause of death in cancer patients
- Accounts for 9% of deaths
- Associated with early mortality during chemotherapy (HR=6.98)
- 47-fold increased risk of mortality from VTE

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

2. Kuderer NM et al *ASCO* 2008 # 9521
Why You Should Care: VTE and Mortality

HR=3.04* [95% CI: 1.31-7.15; P<0.01]

*Adjusted for major confounders: Age, gender, race, cancer type, stage, year of therapy, chemotherapy type and dose intensity, major laboratory abnormalities, PS, BMI, and comorbid conditions.
Why You Should Care: VTE and Public Health Burden

Patients with cancer: 19.8%

All DVT and PE

One-fifth of all VTE occurs in patients with cancer
Why You Should Care: Increasing Frequency of VTE In Malignancy

P<0.0001

Pts on chemotherapy—47% increase
All pts -28% increase

932 patients receiving cisplatin-based chemotherapy at MSKCC in 2008

- TEE occurred in 18.1%

Moore et al, JCO 2011
Cancer is *Omnicoagulable*

**Natural history following major surgery**

- Peptides may be released during surgery that can trigger coagulation.
- The body's response to surgery can lead to increased blood clotting.

**VTE in cancer with chemotherapy**

- Retrospective, single institution cohort study
- N = 1,921 medical records of cancer patients (solid T + chemotherapy)

**Statistics:**

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

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Kakkar VV et al. Lancet 1969, August 2: 230-33

Incidental VTE

- VTE detected on imaging studies conducted for other indications, typically staging\(^1\)
  - PE or DVT
  - Visceral vein thrombosis
- Term “asymptomatic” VTE discouraged; patients often have unrecognized symptoms\(^2\)
- Prevalence varies
  - 1.5-3.4% per scan in outpatient staging
  - 4-9% in hospitalized cancer patients

Proportion of Incidental VTE

- Symptomatic: 56%
- Incidental: 44%

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N=932 patients receiving cisplatin-based chemotherapy at MSKCC

N=1,151 scans of 135 pancreatic cancer patients at UR

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Incidental vs Symptomatic PE in Cancer

Recurrent VTE

Follow-up Time (days)

Cumulative Recurrence Rate

Incidental PE
Symptomatic PE

Survival

Follow-up Time (days)

Cumulative Survival Rate

Incidental PE
Symptomatic PE

$P=0.77$  Den Exter PL, et al. *J Clin Oncol* 2011  $P=0.70$
Incidental and symptomatic VTE are both associated with worsened 3-month mortality in pancreatic cancer.

Menapace et al Throm Haem 2011
Why You Should Care: Costs

- Cancer patients with VTE had 3 times
  - increase in all-cause hospitalizations (mean 1.38 versus 0.55 per patient)
  - days in hospital (10.19 versus 3.37) (all P < 0.0001).

- Cancer patients with VTE incurred
  - higher overall all-cause inpatient costs (mean $21,299 versus $7459 per patient),
  - outpatient costs ($53,660 versus $34,232 per patient), and
  - total health care costs ($74,959 versus $41,691 per patient) (all P < 0.0001).

- Mean VTE-related costs: $9247 / patient / year

- Adjusted mean incremental all-cause costs of VTE: $30,538 /patient

Khorana et al, Clin Econ Outcomes Res; 2013
Why You Should Care: Costs

Khorana et al, *Clin Econ Outcomes Res*; 2013
Why You Should Care:
Prevalence, Consequences, Costs

Predicting VTE in Cancer

Preventing VTE in Cancer
Risk Factors

- Primary Site
- Histology
- Grade
- Initial period

Cancer-related

- Platelet counts
- Leukocyte counts
- Hemoglobin
- Tissue factor
- D-dimer
- P-selectin
- Thrombin generation potential

Treatment-related

- Surgery/hospitalization
- Chemotherapy
- Anti-angiogenics
- CVCs
- ESA/transfusions

Patient-related

- Age
- Ethnicity
- Comorbidities

Biomarkers
Risk of VTE by Primary Site

- Control: 1.4%
- Stomach: 15.8%
- Pancreatic: 19.2%
- Ovarian: 11%
- Bladder: 8.2%
- Colorectal: 10.6%
- Lung: 13.9%

*P* < 0.0001 for all comparisons vs controls

Khorana AA et al, Cancer 2012
Risk with Bevacizumab

- 2-fold increased risk of arterial events\(^1\)
- Possible increased risk of VTE [RR=1.29 (95% CI, 1.03-1.63)]\(^2\)
- Not significant if adjusted for exposure time [RR 1.10 (95% CI, 0.89-1.36)]\(^3\)
- Not seen in a newer pooled analysis (OR 1.14; 95% CI, 0.96 to 1.35; P = .13)\(^4\)

Risk with Other Anti-Angiogenic Agents

• Sunitinib and sorafenib are associated with risk of arterial events [RR 3.03 (95% CI, 1.25 to 7.37; P = .015)]¹

• VEGFR-TKIs (pazopanib, sunitinib, sorafenib and vandetanib) are not associated with VTE (RR = 0.912, 95% CI: 0.617-1.348, p = 0.643)²

• Risk of VTE with thalidomide- and lenalidomide-based regimens is well-known³

1. Choueiri et al JCO 2010; 28:2280-2285
Risk with Other Targeted Therapies

- Anti-EGFR agents are associated with risk of VTE
  - RR 1.32 (95% CI 1.07–1.63; \( P = 0.01 \))
  - Risk primarily with antibodies (RR 1.34; \( P = 0.01 \)) rather than oral TKIs (RR 1.16; \( P = 0.65 \))

Biomarkers

• Leukocyte count
• Platelet count
• Hemoglobin
• Tissue factor
• D-dimer
• Factor VIII
TF and VTE

Systemic TF by ELISA\(^1\)

Systemic TF-MPs by flow cytometry\(^2\)

DVT
Fatal PE

\(P = .04\)
Elevated TF was significantly associated with TE in a logistic regression analysis, (OR = 1.22, p = 0.04)

Elevated TF was also associated with overall survival (HR = 1.05, p = 0.01)

Median survival was 98.5 days vs. 231 days for high vs low TF (p< 0.0001)

Correlated with D-dimer and leukocyte count
TF and VTE: Not So Fast

- N = 348
- MP-TF activity was not associated with future VTE
- MP-TF activity was associated with mortality in pancreatic cancer
- MP-TF activity correlated with D-dimer in pancreatic cancer
Elevated D-dimer (>75th percentile, 1.44µg/mL); HR 2.2 (95% CI: 1.3 - 3.6), p=0.003

- No consensus on cut-off levels
- Widely available
- Potential to discriminate intermediate-risk patients
- Poor person’s TF?

D-dimer and VTE
Risk Assessment
ASCO 2013 Guideline Update

“Individual risk factors, including biomarkers or cancer site, do not reliably identify cancer patients at high risk for VTE”

## Risk Score

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>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, GU excluding prostate)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Platelet count ≥ 350,000/mm³</strong></td>
<td>1</td>
</tr>
<tr>
<td><strong>Hb &lt; 10g/dL or use of ESA</strong></td>
<td>1</td>
</tr>
<tr>
<td><strong>Leukocyte count &gt; 11,000/mm³</strong></td>
<td>1</td>
</tr>
<tr>
<td><strong>BMI ≥ 35 kg/m²</strong></td>
<td>1</td>
</tr>
</tbody>
</table>

Risk Model Validation

- **Development cohort**
  - Low (0): 0.8%
  - Intermediate (1-2): 1.8%
  - High (≥3): 7.1%

- **Validation cohort**
  - Low (0): 0.3%
  - Intermediate (1-2): 2.0%
  - High (≥3): 6.7%

Vienna CATS validation

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

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

Ay et al *Blood* 2011
External Validation of Risk Score

Table 5. Multivariate 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>.15</td>
</tr>
<tr>
<td>Male</td>
<td>1</td>
<td>1.00 to 1.00</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.31</td>
<td>0.91 to 1.88</td>
<td></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>.51</td>
</tr>
<tr>
<td>White</td>
<td>1</td>
<td>1.00 to 1.00</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>0.87</td>
<td>0.41 to 1.85</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>1.43</td>
<td>0.74 to 2.76</td>
<td></td>
</tr>
<tr>
<td>KPS (per 10-unit increase)</td>
<td>0.92</td>
<td>0.86 to 0.98</td>
<td>.02</td>
</tr>
<tr>
<td>Central venous catheter/pacemaker</td>
<td>1.61</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>1.00 to 1.00</td>
<td></td>
</tr>
<tr>
<td>Locally advanced</td>
<td>0.84</td>
<td>0.41 to 1.72</td>
<td></td>
</tr>
<tr>
<td>Metastatic</td>
<td>1.03</td>
<td>0.50 to 2.13</td>
<td></td>
</tr>
<tr>
<td>Khorana risk group</td>
<td></td>
<td></td>
<td>.04</td>
</tr>
<tr>
<td>Low</td>
<td>1</td>
<td>1.00 to 1.00</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>1.33</td>
<td>0.81 to 2.16</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>2.06</td>
<td>1.16 to 3.65</td>
<td></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 (years)</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.

1Moore et al, J Clin Oncol 2011
2Mandala et al, Ann Onc 2012
# Evaluation of Risk Score

*N=10,694*

<table>
<thead>
<tr>
<th>Study</th>
<th>Type, duration</th>
<th>N</th>
<th>Low-risk (score = 0)</th>
<th>Intermediate-risk (score = 1-2)</th>
<th>High-risk (score ≥3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khorana et al, 2008</td>
<td>Development cohort, 2.5 months</td>
<td>2701</td>
<td>0.8%</td>
<td>1.8%</td>
<td>7.1%</td>
</tr>
<tr>
<td>Khorana et al, 2008</td>
<td>Validation cohort, 2.5 months</td>
<td>1365</td>
<td>0.3%</td>
<td>2%</td>
<td>6.7%</td>
</tr>
<tr>
<td>Kearney et al, 2009</td>
<td>Retrospective, 2 years</td>
<td>112</td>
<td>5%</td>
<td>15.9%</td>
<td>41.4%</td>
</tr>
<tr>
<td>Price et al, 2010</td>
<td>Retrospective, pancreatic, NA</td>
<td>108</td>
<td>- *</td>
<td>14%</td>
<td>27%</td>
</tr>
<tr>
<td>Ay et al, 2010</td>
<td>Prospective, 643 days</td>
<td>819</td>
<td>1.5%</td>
<td>9.6% (score=2)</td>
<td>17.7%</td>
</tr>
<tr>
<td>Khorana et al, 2010</td>
<td>Prospective**, 3 months</td>
<td>30</td>
<td>- ***</td>
<td>-</td>
<td>27%</td>
</tr>
<tr>
<td>Moore et al, 2011</td>
<td>Retrospective, cisplatin-based chemo only</td>
<td>932</td>
<td>13%</td>
<td>17.1%</td>
<td>28.2%</td>
</tr>
<tr>
<td>Mandala et al, 2012</td>
<td>Retrospective, phase I patients only, 2 months</td>
<td>1415</td>
<td>1.5%</td>
<td>4.8%</td>
<td>12.9%</td>
</tr>
</tbody>
</table>

NA=not available; *=pancreatic cancer patients assigned a score of 2 based on site of cancer and therefore no patients in the low-risk category; **=included 4-weekly screening ultrasonography; ***=enrolled only high-risk patients
Q6. VTE Risk Assessment

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

Risk Assessment: The Future
High coverage LC-MS/MS

>50637 spectra
2145 unique peptides
149 proteins
116 protein groups
Differential expression
9 proteins p <0.05
23 proteins p < 0.10

Match criteria: 3 peptide minimum and 95% probability of match
Connolly et al, ISTH 2013
Applying Risk Assessment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer: high risk (stomach, pancreas)</td>
<td>1</td>
</tr>
<tr>
<td>Cancer: high risk (lung, lymphoma, gynecologic, GU bleeding prostate)</td>
<td>1</td>
</tr>
<tr>
<td>Platelet count &gt; 350,000/mm$^3$</td>
<td>1</td>
</tr>
<tr>
<td>Hgb/dl or use of ESA</td>
<td>1</td>
</tr>
<tr>
<td>Platelet count &gt; 11,000/mm$^3$</td>
<td>1</td>
</tr>
</tbody>
</table>

- **Patient Awareness and Education**
- **Screening?**
- **Prophylaxis?**
Q6. VTE Risk Assessment

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

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 anti-neoplastic therapy.
Applying Risk Assessment Screening

- Baseline: N=3/27
- Ultrasound 4 wks: N=0/18
- Ultrasound 12 wks: N=0/17
- Ultrasound 8 wks: N=1/15

Additional 2 symptomatic DVTs, wks 1-4: 11%
Additional 2 asymptomatic PE on CT, wks 6 and 9: 7%

Khorana AA et al. ASH 2010
Why You Should Care:
Prevalence, Consequences, Costs

Predicting VTE in Cancer

Preventing VTE in Cancer
Preventing VTE in Cancer

Cancer Patients
Clinical setting

Major cancer surgery
- ENOXACAN-1
- Canadian Colorectal DVT Prophylaxis
- ENOXACAN-2
- FAME
- CANBESURE

Hospitalization for acute medical illness
- MEDENOX
- PREVENT
- EXCLAIM

Outpatient chemotherapy
- PROTECHT
- CONKO-004
- FRAGEM
- SAVE-ONCO
Despite Evidence, Prophylaxis Is Underused

**ENDORSE**¹

<table>
<thead>
<tr>
<th></th>
<th>Medical</th>
<th>Surgical</th>
</tr>
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<tbody>
<tr>
<td>No. of patients</td>
<td>37,356</td>
<td>30,827</td>
</tr>
<tr>
<td>At risk for VTE</td>
<td>42%</td>
<td>64%</td>
</tr>
<tr>
<td>Received prophylaxis (ACCP)</td>
<td>40%</td>
<td>59%</td>
</tr>
</tbody>
</table>

**IMPROVE**²

<table>
<thead>
<tr>
<th></th>
<th>United States</th>
<th>Other Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>3,410</td>
<td>11,746</td>
</tr>
<tr>
<td>VTE prophylaxis</td>
<td>1852 (54%)</td>
<td>5788 (49%)</td>
</tr>
<tr>
<td>LMWH</td>
<td>476 (14%)</td>
<td>4657 (40%)</td>
</tr>
<tr>
<td>UFH</td>
<td>717 (21%)</td>
<td>1014 (9%)</td>
</tr>
</tbody>
</table>

Prophylaxis is underutilized in cancer patients

Figure 3  Results of logistic regression: predictors of use of any prophylaxis in study population.
Order Entry Alerts Improve Compliance and Reduce VTE

Prevention:

*CAT is an outpatient illness*

Khorana et al ASH 2011
Rates of VTE in Recent Prophylaxis Studies

Agnelli et al *Lancet Onc* 2009
Riess et al *ISTH* 2009
Maraveyas et al *ESMO* 2009
Agnelli et al *NEJM* 2012

Agnelli et al *Lancet Onc* 2009
Riess et al *ISTH* 2009
Maraveyas et al *ESMO* 2009
Agnelli et al *NEJM* 2012
How To Approach Outpatient Prophylaxis?

“Specific” studies
- CONKO, FRAGEM, Myeloma
- Very high event rates
- Homogenous populations (pancreas, myeloma)
- But: smaller effect on public health burden

“General” studies
- PROTECHT, SAVE-ONCO
- Lower event rates
- Heterogenous populations (multiple sites, stages, chemo)
- But: potential greater effect on public health burden
Risk Assessment: The Future-Prophylaxis

PROTECHT by Risk Score


<table>
<thead>
<tr>
<th>Score</th>
<th>All</th>
<th>Score 0-2</th>
<th>Score &gt;=3</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNT</td>
<td>50</td>
<td>77</td>
<td>15</td>
</tr>
</tbody>
</table>

## Guideline recommendations

<table>
<thead>
<tr>
<th>Patients</th>
<th>ASCO(^1)</th>
<th>NCCN(^2)</th>
<th>ESMO(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cancer outpatients</td>
<td>Routine prophylaxis not recommended</td>
<td>Routine prophylaxis not recommended</td>
<td>Routine prophylaxis not recommended</td>
</tr>
<tr>
<td>Myeloma patients, receiving imid-based regimens</td>
<td>Aspirin or LMWH for low-risk and LMWH for high-risk patients is recommended</td>
<td>Aspirin for low-risk and LMWH or warfarin for high-risk patients is recommended</td>
<td>Consider LMWH, aspirin or adjusted-dose warfarin (INR ~ 1.5)</td>
</tr>
<tr>
<td>“High-risk” outpatients</td>
<td>Consider LMWH prophylaxis on a case-by-case basis in highly select outpatients with solid tumors on chemotherapy.</td>
<td>“Consider patient conversation about risks and benefits of prophylaxis in Khorana score ≥ 3 population”</td>
<td>Consider in high-risk ambulatory cancer patients. Predictive model may be used to identify patients clinically at high risk for VTE</td>
</tr>
</tbody>
</table>

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2. NCCN guidelines, 2013
Conclusions

The problem is bigger than we imagined

• “Unacceptably high” burden
• Incidental VTE is an emerging major clinical problem
• Association with cancer outcomes, including mortality

We have made progress

• Electronic alerts increase compliance and reduce clots
• Validation of the Risk Score by multiple groups represents a new era in collaboration and testing of predictive models
• Candidate biomarkers are being vetted in large-scale studies
• Multiple RCTs have addressed prevention of CAT in the outpatient setting
Outpatient prophylaxis is safe, feasible and effective

- Multiple RCTs have shown benefit, but with low event rates

Risk-adapted approaches to prophylaxis

- Identifying high-risk patients reduces NNT and optimizes risk-benefit ratio
- Slouching toward a consensus: targeted prophylaxis
The Future of CAT

Precision medicine

• “Big data” and pan-omics can be harnessed to precisely estimate the risk of primary and recurrent VTE
• Prevention and treatment can be individualized to patients based on risk of VTE and risk of bleeding