Cancer and Thrombosis: Tissue (factor) is the issue

Kinsey McCormick
Hematology conference 2/8/13
Overview

- Case presentation
- Epidemiology of cancer-associated venous thromboembolism
- Role of tissue factor in pathophysiology of cancer and thrombosis
- Role for primary thromboprophylaxis?
Case presentation

• 45 yo male presented with SOB, hypoxia
• CTA with diffuse lung disease, bilateral PEs
• Subsequent work up revealed multiple liver, bone lesions consistent with metastases
• Oncology consulted regarding further work up, management recommendations
Cancer and thrombosis

• In 1865, Trousseau first to make connection between cancer and thrombosis
• Cancer patients have 4 to 6-fold increased risk of venous thromboembolism (VTE) compared to general population\(^1\)
• ~20% of all new venous thromboembolic events associated with cancer\(^2\)

\(^1\) Heit JA, Arch Intern Med 2002
\(^2\) Noble S, Br J Cancer 2010
Not all cancer patients created equal (with regard to VTE risk)

<table>
<thead>
<tr>
<th>Site</th>
<th>Rate of DVT/PE per 10,000 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head/neck</td>
<td>16</td>
</tr>
<tr>
<td>Bladder</td>
<td>22</td>
</tr>
<tr>
<td>Breast</td>
<td>22</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>43</td>
</tr>
<tr>
<td>Uterus</td>
<td>44</td>
</tr>
<tr>
<td>Cervix</td>
<td>49</td>
</tr>
<tr>
<td>Prostate</td>
<td>55</td>
</tr>
<tr>
<td>Lung</td>
<td>61</td>
</tr>
<tr>
<td>Rectal</td>
<td>62</td>
</tr>
<tr>
<td>Liver</td>
<td>69</td>
</tr>
<tr>
<td>Colon</td>
<td>76</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>81</td>
</tr>
<tr>
<td>Renal</td>
<td>84</td>
</tr>
<tr>
<td>Stomach</td>
<td>85</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>96</td>
</tr>
<tr>
<td>Pancreas</td>
<td>110</td>
</tr>
<tr>
<td>Brain</td>
<td>117</td>
</tr>
<tr>
<td>Ovary</td>
<td>20</td>
</tr>
</tbody>
</table>

Noble S, Br J Cancer 2010
Other risk factors for cancer-associated VTE

- **Demographics**: Age, gender, race
- **Cancer-related factors**: Stage, time since diagnosis
- **Treatment-related factors**: Surgery, hospitalization, chemo, hormonal therapy, anti-angiogenic agents, ESAs

Adapted from Khorana AA, Thromb Res 2007
Incidence of cancer-associated VTE increasing

Noble S, Br J Cancer 2010
Why are cancer patients hypercoagulable?

- Lots of proposed mechanisms...
- I would be crazy to try to cover them all
- You would stop listening
- This talk will focus on:
  - Role of tissue factor
  - Role of tissue factor-expressing microparticles
What is tissue factor?

- Membrane protein essential for hemostasis
- Constitutively expressed by subendothelial, nonvascular cells
- Expression tightly regulated
- Collagen, TF exposed when vessel wall breeched

Image: Furie B, NEJM 2008
What does tissue factor do?

Bluff JE, Br Ca Res 2008
Strict regulation of TF expression lost in carcinogenesis

- Khorana et al. evaluated TF expression in normal pancreas, and resected noninvasive, invasive pancreatic lesions (n=250)
- Tumor cells express TF; normal cells do not
  - 31/40 (77%) of PanINs
  - 64/70 (91%) of IMPNs
  - 116/130 (89%) of cancers
  - 0/10 normal tissue

Khorana AA, Clin Cancer Res 2007
Increased TF expression associated with increased VTE risk

- Rate of VTE greater in pancreatic cancer patients with high vs. low TF expression (p=0.04)

Khorana AA, Clin Cancer Res 2007
TF expression and VTE risk, cont

• TF expression generally higher in advanced vs. early stage cancers
• More thrombogenic cancers (e.g. pancreas, brain) also with higher levels of TF expression; less thrombogenic cancers with lower levels (e.g. breast)
Summary: Role of TF in hypercoagulability of malignancy

- TF initiates coagulation
- Tumor cells upregulate/express TF
- Higher levels of TF expression seem to be associated with increased risk of VTE

But, how does TF, a membrane-bound receptor, cause systemic coagulation disturbances?

Microparticles?
What are microparticles?

• Vesicles derived from blebbing of plasma membrane of activated or apoptotic cells
• Share membrane proteins with parent cell
• Present in healthy individuals\(^1\)
• Platelets (>80%), other hematopoietic cells (<20%) major source of microparticles (MP)\(^1\)

\(^1\)Falanga, Thromb Res 2012
Hypothesis:
Tumor cells shed TF-expressing MP, which circulate systemically, and contribute to prothrombotic state of cancer
Zwicker et al. measured levels of TF-bearing MP (TF+ MP) in cancer patients (n=96) and cancer-free controls
Do cancer patients have higher levels of TF+ MP?

- Yes.
- Pancreatic, colorectal cancer patients more likely to have elevated levels of TF+ MP than controls (<0.001, p=0.03, respectively)

Zwicker JI, Clin Cancer Res 2009
Where do these excess MP come from?

• ~50% of circulating TF+ MP also positive for MUC-1 (n=3)
• TF+ MP levels decreased following resection

MUC-1 = Antigen expressed by epithelial malignancies, NOT hematopoietic cells

Zwicker JI, Clin Cancer Res 2009
Do TF+ MP increase VTE risk?

- Conducted case-control study to evaluate association between presence of TF+ MP and acute VTE
  - Patients with cancer/VTE (n=30), cancer/no VTE (n=60) and idiopathic VTE (22)

Zwicker JI, Clin Canc Res 2009
TF+ MP and VTE risk, cont

- Cancer/VTE patients significantly more likely to have detectable TF+ MP than cancer/no VTE and idiopathic VTE patients (60%, 27%, 23%, respectively)
- Cancer/VTE patients have higher levels of TF+ MP than other 2 subgroups
TF+ MP as biomarker for VTE?

• Determined 1 yr cumulative incidence of VTE in cancer/no VTE cohort according to presence/absence of TF+ MP (n=60)
Cancer patients have increased levels of circulating TF+ MP compared to healthy controls, but do these MP express functionally active TF?
Tesselaar et al. first to measure MP-associated TF activity in pancreatic/breast cancer patients (n=50), healthy controls (n=37), patients with idiopathic VTE (n=7)
Do cancer patients have higher levels of MP TF activity?

• Yes, TF+ MP can initiate coagulation

• Breast, pancreatic cancer patients have higher levels of MP-associated TF activity than controls (p<0.004)

Tesselaar MET, J Thromb Haem 2006
Association between MP TF activity and development of VTE?

- Mean MP TF activity higher in cancer patients with VTE vs. those without VTE
- Mean MP TF activity: pancreas > lung > colon
- (Incidence of VTE: pancreas > lung > colon)
Summary: Microparticles and thrombosis

• Healthy patients have low levels circulating TF+ MP (derived from hematopoietic cells)
• Cancer patients have pathologic increase in TF+ MP (derived from tumor cells)
• TF+ MP are functional
• Evidence to support association between TF+ MP and development of VTE
• Utility of TF+ MP as biomarker of VTE risk not yet established
Rationale for 1° thromboprophylaxis in cancer patients

- VTE common in certain cancer subgroups
- Associated with significant morbidity\(^1\)
  - Increased risk of recurrence
  - Increased risk of suffering anticoagulation-related complications
- 2\(^{nd}\) leading cause of death among cancer patients\(^1\)
- Increases utilization of health care resources\(^2\)

\(^1\) Khorana AA, JCO 2006
\(^2\) Young A, Nature Rev 2012
Already recommended for certain cancer subgroups

1. Cancer patients undergoing major surgery
2. Cancer patients hospitalized for acute medical illness
3. Multiple myeloma patients receiving lenalidomide- or thalidomide-based combination regimens

NCCN Guidelines: Venous thromboembolic disease, 2010
What about ambulatory patients with advanced cancer receiving chemotherapy, another high risk population?
SAVE-ONCO Study

• Double-blind, placebo-controlled trial
• N=3,212 pts with metastatic or locally advanced cancer of lung, pancreas, stomach, colon/rectum, bladder or ovary beginning chemo
• Semuloparin vs. placebo
• Study drug continued for duration of chemo
• Primary endpoint: Composite of symptomatic DVT, any nonfatal PE, or death related to VTE

Agnelli G, NEJM 2012
Study Population

- Groups well-balanced
- Median age 59
- White (76%) > Asian (17%) > Black (1.5%)
- Lung, colon/rectum most common cancers
- ~2/3 with metastatic cancer
Kaplan-Meier curves for primary efficacy outcome

Agnelli G, NEJM 2012
Table 1: Primary efficacy outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Semuloparin (N=1608)</th>
<th>Placebo (N=1604)</th>
<th>Hazard Ratio (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any VTE or VTE-related death — no. (%)</td>
<td>20 (1.2)</td>
<td>55 (3.4)</td>
<td>0.36 (0.21–0.60)</td>
</tr>
<tr>
<td>Symptomatic deep-vein thrombosis</td>
<td>11 (0.7)</td>
<td>34 (2.1)</td>
<td>0.32 (0.15–0.62)</td>
</tr>
<tr>
<td>Upper limbs</td>
<td>3 (0.2)</td>
<td>9 (0.6)</td>
<td>0.33 (0.07–1.18)</td>
</tr>
<tr>
<td>Lower limbs</td>
<td>8 (0.5)</td>
<td>25 (1.6)</td>
<td>0.32 (0.13–0.69)</td>
</tr>
<tr>
<td>Proximal</td>
<td>4 (0.2)</td>
<td>19 (1.2)</td>
<td>0.21 (0.06–0.58)</td>
</tr>
<tr>
<td>Distal</td>
<td>4 (0.2)</td>
<td>12 (0.7)</td>
<td>0.33 (0.09–0.99)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>10 (0.6)</td>
<td>24 (1.5)</td>
<td>0.41 (0.19–0.85)</td>
</tr>
<tr>
<td>Nonfatal</td>
<td>3 (0.2)</td>
<td>15 (0.9)</td>
<td>0.20 (0.05–0.63)</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>3 (0.2)</td>
<td>12 (0.7)</td>
<td>0.25 (0.06–0.83)</td>
</tr>
<tr>
<td>Detected during tumor evaluation</td>
<td>0</td>
<td>3 (0.2)</td>
<td>NE</td>
</tr>
<tr>
<td>Any VTE-related death</td>
<td>7 (0.4)</td>
<td>9 (0.6)</td>
<td>0.77 (0.27–2.13)</td>
</tr>
</tbody>
</table>

Agnelli G, NEJM 2012
Table 1, cont: Primary efficacy outcome by cancer subgroups

<table>
<thead>
<tr>
<th>Outcome according to primary cancer site</th>
<th>Semuloparin (N=1608)</th>
<th>Placebo (N=1604)</th>
<th>Hazard Ratio (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>9/591 (1.5)</td>
<td>25/589 (4.2)</td>
<td>0.36 (0.17–0.77)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>3/126 (2.4)</td>
<td>14/128 (10.9)</td>
<td>0.22 (0.06–0.76)</td>
</tr>
<tr>
<td>Stomach</td>
<td>1/204 (0.5)</td>
<td>4/207 (1.9)</td>
<td>0.25 (0.03–2.20)</td>
</tr>
<tr>
<td>Colon or rectum</td>
<td>5/464 (1.1)</td>
<td>9/461 (2.0)</td>
<td>0.54 (0.18–1.60)</td>
</tr>
<tr>
<td>Bladder</td>
<td>1/32 (3.1)</td>
<td>3/31 (9.7)</td>
<td>0.30 (0.03–2.95)</td>
</tr>
<tr>
<td>Ovary</td>
<td>1/191 (0.5)</td>
<td>0/188</td>
<td>NE</td>
</tr>
</tbody>
</table>

Outcome according to no. of risk factors for VTE

<table>
<thead>
<tr>
<th>No. of risk factors</th>
<th>Semuloparin (N=1608)</th>
<th>Placebo (N=1604)</th>
<th>Hazard Ratio (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>9/923 (1.0)</td>
<td>23/932 (2.5)</td>
<td>0.39 (0.18–0.84)</td>
</tr>
<tr>
<td>1 or 2</td>
<td>9/652 (1.4)</td>
<td>27/632 (4.3)</td>
<td>0.32 (0.15–0.68)</td>
</tr>
<tr>
<td>≥3</td>
<td>2/33 (6.1)</td>
<td>5/40 (12.5)</td>
<td>0.56 (0.11–2.93)</td>
</tr>
</tbody>
</table>

Agnelli G, NEJM 2012
Did semuloparin improve survival?

• No.
• Rate of death 43.4% in semuloparin group vs. 44.5% in placebo group (HR 0.96; 95% CI 0.86 to 1.06; p=0.40)

Agnelli G, NEJM 2012
<table>
<thead>
<tr>
<th>Bleeding Events</th>
<th>Semuloparin (N = 1589)</th>
<th>Placebo (N = 1583)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically relevant bleeding</td>
<td>45 (2.8)</td>
<td>32 (2.0)</td>
<td>1.41 (0.89–2.25)</td>
</tr>
<tr>
<td>Major bleeding†</td>
<td>19 (1.2)</td>
<td>18 (1.1)</td>
<td>1.05 (0.55–2.04)</td>
</tr>
<tr>
<td>Clinically relevant nonmajor bleeding‡</td>
<td>26 (1.6)</td>
<td>14 (0.9)</td>
<td>1.86 (0.98–3.68)</td>
</tr>
</tbody>
</table>

Agnelli G, NEJM 2012
Conclusions from SAVE-ONCO

- LMWH reduced incidence of VTE among patients with advanced cancer receiving chemotherapy
- No increase in risk of major bleeding
- *But*, overall incidence of primary efficacy outcome only 3.4% in placebo arm and no survival benefit
- Is hassle of thromboprophylaxis worth it?
Conclusions

• Cancer is risk factor for VTE
• Cancer promotes thrombosis via variety of mechanisms
  – Evidence that TF, TF-bearing MP play important role
• Certain subgroups of ambulatory cancer patients at high risk of VTE and likely to benefit from primary thromboprophylaxis
• Still working to better identify those subgroups
Thank you to Dr. Konkle!
References

• Zwicker JI. Predictive value of tissue factor bearing microparticles in cancer associated thrombosis. Thromb Res 2010;suppl 2:S89.
End.
MicroTEC Study (Phase II)

- Patients with adv cancer of colon, pancreas, NSCLC, ovary, stomach
- Beginning 1\textsuperscript{st} or 2\textsuperscript{nd} line chemo
- No h/o VTE

*All patients will have screening LE US q2 mo x 6 mo

http://clinicaltrials.gov/show/NCT00908960
More evidence that TF+ MP tumor-derived

- 63% of patients with metastatic breast, pancreatic cancer had MUC-1+ MP
- MUC-1+ MP not detected in healthy subjects, idiopathic VTE subjects*
- Elevated MP-TF activity correlated with presence of MUC-1+ MP (r=0.38, p=0.01)

Tesselaar MET, J Thromb Haem 2006