Thrombosis and Clinical Oncology

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Faculty Disclosure

Nothing to Disclose
"I have always been struck with the frequency with which cancerous patients are affected with painful oedema of the superior or inferior extremities...."

New Syndenham Society – 1865
Ironically, Trousseau died of gastric carcinoma 6 months after writing to his student, Peter, on January 1st, 1867:

“I am lost . . . the phlebitis that has just appeared tonight leaves me no doubt as to the nature of my illness.”
Impact of Thrombosis on Oncology Patients

► Oncology patients have a 4- to 6-fold increased risk for thrombosis (VTE) compared to non-cancer patients.
► Oncology patients have a 3-fold increased risk for recurrence of VTE compared to non-cancer patients.
► Cancer patients undergoing surgery have a 2-fold increased risk for postoperative VTE.
► Death rate from cancer is four-fold higher if patient has coexisting thrombus.
► VTE 2nd most common cause of death in ambulatory cancer patients comparable to infection.
**Thrombosis and Clinical Oncology**

*Key Questions*

1. Why is the coagulation system activated in cancer patients?

2. What increases the risk of thrombosis in oncology patients?

3. How prevalent is thrombosis in oncology patients and what therapies are effective to prevent and treat thrombosis?

4. Do any anticoagulants work to prolong cancer survival?

5. How could the “new anticoagulants” alter oncology practice?
Virchow’s Triad: Oncology and Thrombosis?

**Stasis**
- Bed rest
- Tumor pressing on blood vessels

**Vascular Injury**
- Tumor invading blood vessels
- Central venous catheters damaging vessels
- Chemotherapy damaging blood vessels
- Tumor derived cytokines altering vessels

**Hypercoagulability**
- Tumor cells and immune response to tumors produce procoagulant molecules (tissue factor and VEGF)
- Endothelial cells have reduced anticoagulant defense mechanisms
- Enhanced adhesive interactions between tumor cells and vascular endothelial cells, platelets, and leukocytes
Risk of Thrombosis in Oncology Patients?

- Patient
- Tumor
- Treatment
Patient-Related Factors and Thrombotic Risk

- Advanced age
- Race
- Comorbid factors: obesity
- Platelet count before chemotherapy
- White cell count before chemotherapy
- Hemoglobin level than 10.0
- Prothrombotic genes
- Prior DVT/PE
Incidence of Venous Thromboembolism By Quartiles of Pre-chemotherapy Platelet Count

Incidence Of VTE Over 2.4 Months(%)

Pre-chemotherapy Platelet Count/mm $^3$ (x1000)

Tumor-related Factors

- Tumor types: pancreas, GI, brain
- Newly diagnosed cancer: 3-6 months
- Presence of metastatic disease
Thrombosis Risk and Tumor Type

Relative Risk Ranged From 1.02 to 4.34

High Tissue Factor Expression Correlates with Thrombosis in Pancreatic Cancers

Tumor Cells Express Tissue Factor and Promote VEGF Production

- TF regulates VEGF expression in human cancer cell lines
- Human cancer cells with increased TF are more angiogenic (and, therefore, more “metastatic’) in vivo due to high VEGF production

Activation of Blood Coagulation in Cancer 

*Biological Significance?*

► **Epiphenomenon?**

Is this a generic secondary event where thrombosis is an incidental finding

*or, is clotting activation ...*

► **A Primary Event?**

Linked to malignant transformation
Oncogenes Can Induce Cancer and DIC

The *MET* oncogene induces DIC in a mouse liver carcinoma model

“MET Oncogene Drives a Genetic Program Linking Cancer to Hemostasis”

Mouse Model of Trousseau’s Syndrome

- MET upregulated PAI-1 and COX-2 genes with 2-3x ↑ circulating protein levels

- Using either PAI-1 inhibitor or COX-2 inhibitor resulted in inhibition of clinical and laboratory evidence for DIC in the mice
“MET Oncogene Drives a Genetic Program Linking Cancer to Thrombosis”

The Mouse Model of Trousseau’s Syndrome

- Targeting human MET to the mouse liver with lentiviral vector causes progressive hepatocarcinogenesis
- Before you see the cancer, thrombosis develops in tail vein and is followed by fatal internal hemorrhage
- Syndrome characterized by ↑ D-dimer and PT and ↓ platelet count (DIC)
Treatment Related Factors and Thrombosis

- Chemotherapy infusions
- Hormonal therapy
- Central venous catheters
- Recent surgery
- Erythropoietin therapy
- Anti-angiogenic therapy
## Thrombotic Risk and Impact of Therapy

<table>
<thead>
<tr>
<th>Oncology Setting</th>
<th>VTE Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer (Stage I &amp; II) w/o further treatment</td>
<td>0.2%</td>
</tr>
<tr>
<td>Breast cancer (Stage I &amp; II) w/ chemo</td>
<td>2%</td>
</tr>
<tr>
<td>Breast cancer (Stage IV) w/ chemo</td>
<td>8%</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphomas w/ chemo</td>
<td>3%</td>
</tr>
<tr>
<td>Hodgkin’s disease w/ chemo</td>
<td>6%</td>
</tr>
<tr>
<td>Advanced cancer (1-year survival=12%)</td>
<td>9%</td>
</tr>
<tr>
<td>High-grade glioma</td>
<td>26%</td>
</tr>
<tr>
<td>Multiple myeloma (thalidomide + chemo)</td>
<td>28%</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>43%</td>
</tr>
<tr>
<td>Solid tumors (anti-VEGF + chemo)</td>
<td>47%</td>
</tr>
<tr>
<td>Wilms tumor (cavoatrial extension)</td>
<td>4%</td>
</tr>
</tbody>
</table>

Thrombosis and Survival
Likelihood of Death After Hospitalization

## Risk Score and Thrombosis Rate in Clinical Oncology

<table>
<thead>
<tr>
<th>Score</th>
<th>Thrombotic Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 points</td>
<td>&lt; 0.8 %</td>
</tr>
<tr>
<td>1-2 points</td>
<td>~ 2 %</td>
</tr>
<tr>
<td>3 points</td>
<td>~ 7 %</td>
</tr>
</tbody>
</table>

*Blood, 2008 vol 111, 4902-4907: Results validated in prospective clinical study*
Thrombotic Risk in Ambulatory Oncology Patients

- Very high risk tumors: 2
- High risk tumors: 1
- Elevated platelet count >350 K: 1
- Body Mass index: >55 kg/m²: 1
Is Low Molecular Weight Heparin Effective in Surgical Oncology?

- Enoxacan I and II documented safety and efficacy in surgical oncology.
  - Enoxacan I: Heparin 5,000 units t.i.d. vs. enoxaparin 40 mg sq q.d.
  - Enoxacan II: Duration enoxaparin 21 days post-op superior.

- Medical oncology studies are limited.
Efficacy of Low Molecular Weight Heparin in Oncology Extrapolated from General Medical Studies

- MEDENOX – Enoxaparin 40 mg qd
- PREVENT – Dalteparin 5000 units qd
- ARTEMIS – Fondaparinux

**Trials demonstrated efficacy in preventing DVT in medically ill patients. Ultrasound screening for DVTs

Cancer patients in MEDENOX had risk of DVT reduced in Lovenox arm. Recent meta analysis published from other smaller studies confirmed findings.
Standard Treatment of VTE
Can We Do Better Than This?

Initial treatment 5 to 7 days
LMWH or UFH

Long-term therapy ≥ 3 months
Vitamin K antagonist (INR 2.0 - 3.0)
### Recurrent VTE in Cancer

Subset Analysis of the Home Treatment Studies

(UH/VKA vs. LMWH/VKA)

<table>
<thead>
<tr>
<th></th>
<th>Recurrent VTE</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events per 100 patient years</td>
<td></td>
</tr>
<tr>
<td>Malignant</td>
<td>27.1</td>
<td></td>
</tr>
<tr>
<td>Non-Malignant</td>
<td>9.0</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Oral Anticoagulant Therapy in Cancer Patients: Problematic

► Warfarin therapy is complicated by:

- Difficulty maintaining tight therapeutic control, due to anorexia, vomiting, drug interactions, etc.
- Frequent interruptions for thrombocytopenia and procedures
- Difficulty in venous access for monitoring
- Increased risk of both recurrence and bleeding

► Is it reasonable to substitute long-term LMWH for warfarin? When? How? Why?
Primary VTE Prophylaxis

- Recommended for hospitalized cancer patients

- Not recommended or generally used for outpatients
  - Very little data
  - Heterogeneous

Need for risk stratification
CANCER PATIENTS WITH ACUTE DVT or PE

\[ N = 677 \]

- Primary Endpoints: Recurrent VTE and Bleeding
- Secondary Endpoint: Survival

### Bleeding in CLOT Study

<table>
<thead>
<tr>
<th></th>
<th>Dalteparin (N=338)</th>
<th>OAC (N=335)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleed</td>
<td>19 (5.6%)</td>
<td>12 (3.6%)</td>
<td>0.27</td>
</tr>
<tr>
<td>Any bleed</td>
<td>46 (13.6%)</td>
<td>62 (18.5%)</td>
<td>0.093</td>
</tr>
</tbody>
</table>

* Fisher’s exact test

Dalteparin Reduces in Recurrent VTE

Probability of Recurrent VTE, %

Risk reduction = 52%

$p$-value = 0.0017

Days Post Randomization

Lee AY, Levine, Kakkar, Rickles et.al.

Dalteparin Prolongs Survival in Oncology Patients with Local Disease

Patients Without Metastases (N=150)

HR = 0.50  P-value = 0.03

Lee A, et al. ASCO. 2003
Prophylaxis for Central Venous Access Devices

► Recent studies demonstrate a low incidence of symptomatic catheter-related thrombosis (~4%).

► Routine prophylaxis is not warranted to prevent catheter-related thrombosis, but catheter patency rates/infections have not been studied.

► Low-dose LMWH and fixed-dose warfarin have not been shown to be effective for preventing symptomatic and asymptomatic thrombosis.
ASCO Recommendation

- Patients hospitalized with cancer for surgery, chemotherapy, or any other reason should receive preventive treatment with an anticoagulant.

- Patients who will undergo major surgery should therapy to prevent blood They should receive this treatment within 24 hours after surgery.

- Patients who develop a blood clot should be treated with an anticoagulant for at least six months and even longer if they are receiving cancer treatment.

- Regular use of an anticoagulant for people with cancer who are not hospitalized and are receiving chemotherapy is not recommended.

- Patients with multiple myeloma being treated with thalidomide or lenalidomide along with chemotherapy should get thromboprophylaxis.
How Will the “New Anticoagulants” Alter Oncology Practice?

- Orally active anti-thrombin and anti-Xa will become available soon.
- Will they be safe?
- Will they be effective?
- What impact will they have on survival?
- Will studies be designed for oncology patients?
- Will they have an impact on catheter thrombosis?
- Be cautious and look for cancer-specific data!
Thrombosis and Clinical Oncology

Key Questions and Answers

1. Why is the coagulation system activated in cancer patients? **Impact of cancer and therapy on Virchow’s triad.**

2. What increases the risk of thrombosis in oncology patients? **Factors associated with patient, tumor and treatment.**

3. How prevalent is thrombosis in oncology patients and what therapies are effective to prevent and treat thrombosis? **Major problem for surgical and medical oncology patients. Low mol wt heparins have had an impact.**

4. Do any anticoagulants work to prolong cancer survival? **Yes in some settings. More work needed.**

5. How could the “new anticoagulants” alter oncology practice? **May be easier to administer.**