Outline

• The problem of thrombosis in the cancer patient
  – Mechanisms of coagulation activation
  – Clinical implications

• Prevention and treatment of venous thromboembolic disease (VTE) in cancer

• Low-molecular-weight heparins as antineoplastic agents
Blood Coagulation and Cancer

• Coagulation system is activated in cancer
  – Cancer is a hypercoagulable state
  – Cancer treatments (chemotherapy, surgery, radiation) amplify coagulation activation

• Implications of coagulation activation in cancer
  – Thrombosis (arterial and venous)
  – Enhanced tumor growth
  – Poor clinical outcomes
Coagulation Balance: Activators

Intrinsic system

- XII → XIIa
- XI → Xla
- IX → IXa

Extrinsic system

- Cellular tissue factor
- VIIa
- Ca^{2+}

- Xa → Xa
- Va → Ca^{2+}
- PL

- Thrombin → IIa

- Fibrinogen → Soluble fibrin
- Fibrin (clot)

Coagulation Balance: Inhibitors

Intrinsic system

Extrinsic system

Endogenous inhibitors

Mechanisms of Tumor-Mediated Hypercoagulable States

- Tumor cell surface tissue factor
- Other tumor-derived procoagulants
- Macrophage tissue factor
- Tumor-mediated platelet activation and accumulation
- Expression of cell surface phospholipids that support coagulation activation
- Tumor-induced endothelial cell activation

Malignant Tumor
Thrombosis in Cancer

- Clinically evident in up to 15% of cancer patients
- Discovered post mortem in 20% to 50% of patients with metastatic cancer
- May be presenting feature of occult malignancy
  - Standardized incidence ratio for cancer 2.3 (2.0–2.7) within 1 year of VTE episode (Sorensen et al. *N Engl J Med.* 1998;338:1169-1173)
- Life-threatening complication of advanced cancer
  - Second most common cause of death in hospitalized solid-tumor cancer patients
Cancer and the Natural History of DVT: Outcome After First Episode of All-Cause DVT

8-year follow-up: 355 patients with symptomatic DVT

- Post-thrombotic syndrome: 25%
- Recurrent DVT: 30%
- Death: 9%
- Subsequent new malignancy (idiopathic DVT–Trousseau’s syndrome): 7%
- (Presumed) no post-thrombotic sequelae: 29%

# Rates of VTE in Different Malignancies

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Rate of VTE per 10,000 Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head/neck</td>
<td>16</td>
</tr>
<tr>
<td>Breast</td>
<td>22</td>
</tr>
<tr>
<td>Uterus</td>
<td>44</td>
</tr>
<tr>
<td>Prostate</td>
<td>55</td>
</tr>
<tr>
<td><strong>Noncancer inpatients</strong></td>
<td><strong>57</strong></td>
</tr>
<tr>
<td>Lung</td>
<td>61</td>
</tr>
<tr>
<td>Liver</td>
<td>69</td>
</tr>
<tr>
<td>Colon</td>
<td>76</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Rate of VTE per 10,000 Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia</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>98</td>
</tr>
<tr>
<td>Pancreas</td>
<td>110</td>
</tr>
<tr>
<td>Brain</td>
<td>117</td>
</tr>
<tr>
<td>Ovary</td>
<td>120</td>
</tr>
</tbody>
</table>

VTE Risk in Cancer: Breast Cancer as an Example

- Estimated risk in untreated stage I and II disease: ~0.2% in 4 years (~ background risk)
- Increased risk with chemotherapy/hormonal therapy: ~5% to 8% in 1 year
- Risk in metastatic disease under treatment ~5% to 8% in 6 months

Prevention and Treatment of VTE in Cancer
VTE and Cancer: Prevention Challenges

• No markers reliably predict risk
• Thromboprophylaxis must be individualized
  – Extended perioperative thromboprophylaxis is superior
  – Central venous catheter thromboprophylaxis
    • LMWH modestly effective
  – Standard prophylactic doses of LMWH may be inadequate for cancer patients (Alikhan et al. *Blood*. 2001;98(part 1):266a)
VTE and Cancer: Diagnostic Challenges

• Asymptomatic VTE common
  – ~50% undetected before death

• D-dimer may be falsely negative
  – Due to fibrinolytic defect with cancer (?)
  – Rarely negative in noncancer patients with VTE
  – Sensitive D-dimer tests required for diagnosis

• Recurrent VTE common
  – 28% with cancer; 8% without cancer
  – Lower incidence of recanalization of previously affected veins than in noncancer patients (59% without vs 23% with cancer)
VTE and Cancer: Treatment Challenges

- Cancer treatment–related DVT common
  - Chemotherapy
  - Radiotherapy
  - Hormonal therapy
  - Antiangiogenic drugs (eg, thalidomide + chemotherapy)
  - Surgery (3X greater risk of DVT with cancer than without)
  - Central venous catheters

- Bleeding common
  - Bleeding lesions, anticoagulants, thrombocytopenia

- More extensive, harder to treat than in those without cancer
The CORTES Study: Lab Results in Cancer and Noncancer Patients With DVT

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cancer (n = 125)</th>
<th>Noncancer (n = 1012)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prothrombin F1.2 (ng/mL)</td>
<td>1.88</td>
<td>1.66</td>
<td>.037</td>
</tr>
<tr>
<td>D-dimer (ng/mL)</td>
<td>559</td>
<td>437</td>
<td>.004</td>
</tr>
<tr>
<td>Factor XIIa (ng/mL)</td>
<td>2.79</td>
<td>2.42</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>TFPI (μ/mL)</td>
<td>159</td>
<td>141</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Marder score at presentation</td>
<td>27</td>
<td>25</td>
<td>.021</td>
</tr>
<tr>
<td>Phlebographic response at 3 weeks (%)</td>
<td>37</td>
<td>50</td>
<td>.013</td>
</tr>
<tr>
<td>Clinical recurrence at 3 months (%)</td>
<td>8.8</td>
<td>3.3</td>
<td>.007</td>
</tr>
</tbody>
</table>

Treatment Options for VTE in Cancer Patients

Medical Treatment

- Outpatient SC UFH, oral AC
- IVC filter w/o AC
- Inpatient IV UFH, oral AC
- Inpatient SC LMWH, oral AC
- Outpatient SC LMWH, oral AC
- Inpatient and/or Outpatient SC LMWH
<table>
<thead>
<tr>
<th>Drug</th>
<th>Prevention</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fragmin®</strong> (dalteparin)</td>
<td>2500 IU qd</td>
<td><strong>200 IU/kg qd</strong> (Europe only)</td>
</tr>
<tr>
<td></td>
<td>5000 IU qd</td>
<td></td>
</tr>
<tr>
<td><strong>Innohep®</strong> (tinzaparin)</td>
<td><strong>75 IU/kg qd</strong> (Europe only)</td>
<td>175 IU/kg qd</td>
</tr>
<tr>
<td><strong>Lovenox®</strong> (enoxaparin)</td>
<td>40 mg qd</td>
<td>1 mg/kg q12h</td>
</tr>
<tr>
<td></td>
<td>30 mg q12h</td>
<td>1.5 mg/kg qd</td>
</tr>
</tbody>
</table>
Initial Treatment of VTE in Cancer: UFH vs LMWH

<table>
<thead>
<tr>
<th>Unfractionated Heparin</th>
<th>LMWH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous IV infusion</td>
<td>bid or qd subcutaneous injection</td>
</tr>
<tr>
<td>Primarily administered in the hospital</td>
<td>Administered in hospital, office, or home</td>
</tr>
<tr>
<td>Usually administered by health care professionals</td>
<td>Administered by patient, caregiver, or professional</td>
</tr>
<tr>
<td>Monitoring and dosing adjustments</td>
<td>No monitoring; fixed or weight-based dosing</td>
</tr>
<tr>
<td>Potential for dosing errors</td>
<td>More precise dosing</td>
</tr>
<tr>
<td>Risk of thrombocytopenia and osteoporosis</td>
<td>Decreased risk of adverse events</td>
</tr>
<tr>
<td>Inexpensive, but not cost-effective</td>
<td>More cost-effective</td>
</tr>
<tr>
<td>Requires 5–7 days in the hospital</td>
<td>Requires 0–2 days in the hospital</td>
</tr>
<tr>
<td></td>
<td>Possible cancer survival benefit</td>
</tr>
<tr>
<td></td>
<td>Possibly superior to UFH for cancer VTE</td>
</tr>
</tbody>
</table>

Initial VTE Treatment in Cancer and Noncancer Patients: LMWH vs UFH—Results of Meta-Analysis

<table>
<thead>
<tr>
<th>Event</th>
<th>Summary OR*</th>
<th>Frequency in UFH Group (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>0.57†</td>
<td>1.9</td>
</tr>
<tr>
<td>Recurrent thromboembolism</td>
<td>0.85</td>
<td>5.4</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>0.71†</td>
<td>6.8</td>
</tr>
</tbody>
</table>

*A summary OR <1.0 favors LMWH, a summary OR >1.0 favors UFH
†P < .05

Adapted from Hirsh et al. Chest. 2001;119:64S-94S.
Initial VTE Treatment in Cancer Patients: LMWH vs UFH—The CORTES Study

<table>
<thead>
<tr>
<th></th>
<th>UFH (n = 41)</th>
<th>LMWH bid (n = 33)</th>
<th>LMWH qd (n = 51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phlebographic response (%)</td>
<td>19</td>
<td>46.7 (P = .03 vs UFH)</td>
<td>46.3 (P = .03 vs UFH)</td>
</tr>
<tr>
<td>Clinical recurrence (%)</td>
<td>17.1</td>
<td>3.0 (P = .068 vs UFH)</td>
<td>5.9</td>
</tr>
</tbody>
</table>

LMWHs Are Dissimilar

• Dosing differences produce clinical differences

• Differences in biological effects (potency):
  – Anti-Xa activity
  – Anti-IIa activity
  – TFPI release from vascular endothelium
VTE and Cancer: Anticoagulant Considerations for Secondary Prophylaxis (1)

- Should continue until cancer treatment is completed and cancer is no longer active (lifelong for many)
- Warfarin
  - Requires careful monitoring
  - Cancer patients have reduced time in therapeutic INR range
    - Nutrition, drug interactions, liver metastases
  - Bleeding more common in cancer patients
  - Recurrent VTE more common
  - Relatively inexpensive drug; expenditures for monitoring, complications
VTE and Cancer: Anticoagulant Considerations for Secondary Prophylaxis (2)

- **LMWH**
  - Lower rates of recurrent VTE and major bleeding than warfarin
  - More stable anticoagulation; no routine monitoring
  - Injection
  - Osteopenia
  - Expensive drug; few expenditures for ancillary services
**LMWH vs Oral Anticoagulant in Cancer Patients With VTE**

672 Evaluable Patients

Randomize

<table>
<thead>
<tr>
<th></th>
<th>Dalteparin (5–7 days)(^*) + OA (6 mo) (n = 336)</th>
<th>Dalteparin (6 mo)(^†) (n = 336)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
<td>17.4%</td>
<td>8.8%</td>
<td>.0017</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>3.6%</td>
<td>5.6%</td>
<td>.27</td>
</tr>
<tr>
<td>Cumulative mortality</td>
<td>41%</td>
<td>39%</td>
<td>NR</td>
</tr>
</tbody>
</table>

\(^*\)Dalteparin = 200 IU/kg SC; OA = target INR 2.5

\(^†\)Dalteparin = 200 IU/kg SC for 1 mo, 150 IU/kg SQ for 5 mo

Special Considerations in Thrombosis Management
Plasma anti-Xa (A) and anti-IIa (B) levels prior to the first injection (day 0) and at peak levels after subcutaneous injection of tinzaparin (175 anti-Xa IU/kg) on days 2, 5, 7, and 10 (n = 30, mean age = 87, mean creatinine clearance = 40.4 mL/min)

Mean (SE) anti-Xa and anti-IIa activity in increased-weight and historical control healthy normal-weight subjects receiving 175 IU/kg tinzaparin via SC injection

Effects of Heparins on Human Cancer
Perioperative Heparin and Cancer Survival


**Proportion Surviving**

<table>
<thead>
<tr>
<th>Months From Operation</th>
<th>Heparin</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>6</td>
<td>0.95</td>
<td>0.95</td>
</tr>
<tr>
<td>12</td>
<td>0.90</td>
<td>0.90</td>
</tr>
<tr>
<td>18</td>
<td>0.85</td>
<td>0.85</td>
</tr>
<tr>
<td>24</td>
<td>0.80</td>
<td>0.80</td>
</tr>
<tr>
<td>30</td>
<td>0.75</td>
<td>0.75</td>
</tr>
<tr>
<td>36</td>
<td>0.70</td>
<td>0.70</td>
</tr>
</tbody>
</table>

**Number of cases**

- Heparin: 163
- Control: 168

**3-year mortality (%)**

- Heparin: 7.6
- Control: 12.5

**Disseminated disease mortality (%)**

- Heparin: 9.2
- Control: 21.4

*(RR: 2.33; 95% CI: 1.33–4.09)*
Heparin for Small Cell Carcinoma of the Lung

281 Evaluable Patients

Randomize

(+) HEPARIN (n = 138)
CR (%) 37
Median survival (days) 317

(−) HEPARIN (n = 139)
CR (%) 23
Median survival (days) 261

\(P = .004\)
\(P = .01\)

LMWH for Small Cell Carcinoma of the Lung

48 Evaluable Patients

Randomize

<table>
<thead>
<tr>
<th></th>
<th>CEV (18 weeks)</th>
<th>CEV (18 weeks) + LMWH</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 25)</td>
<td>(n = 23)</td>
<td></td>
</tr>
<tr>
<td>CR and PR (%)</td>
<td>36</td>
<td>78</td>
</tr>
<tr>
<td>Progression-free</td>
<td>5 (range, 2–13)</td>
<td>9 (range, 4–24)</td>
</tr>
<tr>
<td>survival (months)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P = .004
P = .02

CEV = cyclophosphamide, epirubicin, vincristine; LMWH = dalteparin
LMWH in Malignant Melanoma: A Pilot Study

Lower symbol: Stage IV melanoma survival estimates with chemoimmunotherapy

LMWH vs UFH: Overall Cancer Survival After Surgery

Log Rank: $P = .006$
UFH, $n = 147$
$P = .083$

LMWH vs UFH: Survival After Breast Cancer Surgery


Probability Estimate vs Days

- LMWH, n = 94
- UFH, n = 91

Log Rank:
- LMWH, *P* = .316
- UFH, *P* = .726
LMWH vs UFH: Survival After Pelvic Cancer Surgery


Log Rank: $P = .0139$
UFH, n = 56
LMWH, n = 46

$P = .063$
LMWH vs UFH: Effect on Total and Cancer-Related Mortality

Cancer Mortality According to DVT Treatment

Follow-up (days)

Patients Alive (%)

warfarin

LMWH

P = .07

1.5 mg/kg/d enoxaparin vs warfarin × 3 months for cancer

Limitations:
- Stages
- Treatments
- Tumor types (breast most common)

LMWH and Survival in Advanced Cancer: FAMOUS

Patients with advanced cancer and without VTE treated for 1 year with placebo or LMWH

LMWH and Survival in Advanced Cancer: FAMOUS

“Good-prognosis” patients

Placebo (n = 47)
Dalteparin (n = 53)

Heparin Effect in Cancer

Heparin

Inhibits
- Angiogenesis
- Proteases
- Growth factors
- Coagulation factors
- Oncogene expression

Stimulates
- Immune system
- Differentiation and apoptosis
Antiangiogenic effect of tinzaparin in VEGF-induced angiogenesis in the CAM model

Chick Chorioallantoic Membrane Model of Human Colon Cancer

Antiangiogenic effect of tinzaparin on colon carcinoma–induced angiogenesis in the chick chorioallantoic membrane (CAM) model

Effect of tinzaparin on tumor growth in the CAM-tumor implant model

LMWH and Tumor-Induced Thrombocytopenia and Metastasis

TFPI in Thrombosis and Cancer

Dual pathways of action

TFPI

TF/VIIa

Procoagulant Effects

Thromboembolism

Noncoagulant Effects

Inflammation, Angiogenesis
TFPI Biologic Actions

- Anti–TF/VIIa/Xa
- Anticoagulation
- Antiplatelet
- Cell adhesion molecule modulation
- Cytoprotection/ Anti-inflammation
- Antiangiogenesis
Comparative Pharmacodynamics of TFPI Release by LMWHs

Dose: 100 U/kg IV

TFPI (ng/mL) vs. Time (min)

- Dalteparin
- Enoxaparin
- Tinzaparin
Future Directions
Superiority of LMWH vs UFH for Cancer

- Greater inhibition of
  - Angiogenesis, heparin-binding growth factors, key enzymes (Xa, thrombin, heparinase)
- Greater stimulation of TFPI release
- Greater protection of platelets (ie, less thrombocytopenia)
Advantages of LMWH vs UFH for Prospective, Randomized Cancer Trials

- Predictable pharmacokinetics
- Ease of administration
  - Self-injected, outpatient, no routine monitoring
  - Improved quality of life
- Safety
  - Less HIT, bleeding, osteoporosis
- Potentially superior anticancer effect
Challenges for Cancer Clinical Trials
With LMWH

• Prospective, randomized trials are needed
• Cancer-outcome end point is essential
• Must be controlled for
  – Tumor type
  – Stage
  – Performance status
  – Treatment
Low-Molecular-Weight Heparins in Cancer: Summary

• Excellent antithrombotic activity
  – May be superior to UFH for initial treatment of cancer-associated VTE
  – May be superior to oral anticoagulants for secondary prophylaxis

• Significant anticancer activity
  – Multiple possible anticancer mechanisms
  – Well-designed clinical trials needed to define role in cancer treatment