Cancer Associated Venous Thromboembolism

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Cancer Associated Venous Thrombosis: Discussion Outline

- Nature of the problem
- Appropriate work up for occult cancer
- Cancer VTE treatment trials
- What to do when treatment fails

Annual VTE Events in the U.S. Population

Average annual VTE events: 495,669 per year
- Current or recent hospitalization: 257,783 (52%)
- In-hospital VTE events: 64,747 (25%)
- No recent hospitalization: 237,886 (48%)

Prevalence of Major VTE Risk Factors By Calendar Year; 1988 - 2010

Cancer and Venous Thromboembolism Facts

- Cancer accounts for up to 20% of all incident VTE cases
- Cancer without chemotherapy increases risk 4 fold
- Cancer with chemotherapy increases the risk 6.5 fold
- Biological aggressiveness of cancer is associated with thrombogenic potential
Cancer Stage and Risk of VTE

Danish national registry data 1997-2005

Incidence rate of hospitalization for VTE by cancer stage (Ref: general population)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Incidence /1000 p-y</th>
<th>Adjusted Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>4.4</td>
<td>2.9 (1.5-5.5)</td>
</tr>
<tr>
<td>II</td>
<td>4.9</td>
<td>2.9 (2.4-3.5)</td>
</tr>
<tr>
<td>III</td>
<td>11.1</td>
<td>7.5 (6.0-9.4)</td>
</tr>
<tr>
<td>IV</td>
<td>27.7</td>
<td>17.1 (12.6-23.3)</td>
</tr>
</tbody>
</table>

Time Since Cancer Diagnosis and VTE Risk

Dutch MEGA case-control study

<table>
<thead>
<tr>
<th>Duration between malignancy diagnosis and VTE</th>
<th>Adjusted Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to &lt; 3 months</td>
<td>53.5 (6.6-324.3)</td>
</tr>
<tr>
<td>3 months to &lt; 1 year</td>
<td>14.3 (5.8-30.5)</td>
</tr>
<tr>
<td>1 year to &lt; 3 years</td>
<td>3.6 (2.0-6.5)</td>
</tr>
<tr>
<td>3 years to &lt; 5 years</td>
<td>3.0 (1.5-6.7)</td>
</tr>
<tr>
<td>5 years to &lt; 10 years</td>
<td>2.6 (1.4-4.7)</td>
</tr>
<tr>
<td>10 years to &lt; 15 years</td>
<td>2.3 (0.9-6.8)</td>
</tr>
<tr>
<td>&gt; 15 years</td>
<td>1.1 (0.6-2.2)</td>
</tr>
</tbody>
</table>

Cancer Treatment and VTE Risk

- Chemotherapy increases the VTE risk 6.5 fold
  - Tamoxifen
  - IMIDs (thalidomide, lenalidomide, pomalidomide)
  - Cisplatin
  - L-asparaginase
  - 5-fluorouracil
  - Bevacizumab
  - Gemtuzumab ozogamicin
  - Recombinant erythropoietin
  - Leucocyte growth factors (G-CSF and GM-CSF)

Cumulative VTE Recurrence Rate for Cancer Associated vs Idiopathic vs Other Secondary VTE

- 5-Year Cumulative Recurrence Rate:
  - Cancer: 43%
  - Idiopathic: 27%
  - Other secondary: 18%

Survival following Cancer-Associated VTE

12% vs 36% survival at 1 year p<0.001
**CANCER ASSOCIATED VTE: Summary**

- One-fifth of all incident VTE is attributed to cancer
- VTE recurrence rate is higher in patients with active cancer than those without cancer
- Cancer site, stage and treatment along with (non-cancer) patient characteristics are associated with risk of incident and recurrent VTE

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**Cancer Associated Venous Thrombosis: Discussion Outline**

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**58-year-old male**

Three week history of cough and dyspnea. Recent travel between Rochester and Fargo (6 hours). No additional trauma or surgery.

General: Dyspneic
Heart: Normal JVP. No RV lift. No murmurs or gallops.
Extremities: No edema.

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After recovery and discharge from the hospital, what is the appropriate assessment for occult malignancy for this patient?

1. GME with age/gender appropriate screening
2. #1 plus US abdomen
3. #1 plus CT chest abdomen, pelvis
4. #1 plus FDG PET/CT
5. #1 plus pan-endoscopy
Occult Cancer in Patients with Idiopathic or Unprovoked VTE

• Unprovoked VTE carries a **4 fold increased risk** of occult malignancy.
• 10% will have **new cancer diagnosis** in 1st yr
• Most common tumors include:
  • Ovary
  • Pancreas
  • Liver

Is extensive screening for cancer in idiopathic VTE warranted?

Prospective controlled cohort study
288 “Limited Screening” group
  • H&P, basic labs, chest X-ray
342 “Extensive Screening” group
  • CT chest/abd/pelvis and mammography
Baseline cancer detection
  • Limited 2.4%
  • Extensive 3.5%
  • 6 additional cancers detected (3 curable)

Is extensive screening for cancer in idiopathic VTE warranted?

Mortality Rates @ 2.5 years follow up:
• Limited 8.3%
• Extensive 7.8%
• HR 1.22 (95% CI, 0.69-2.22).

Cancer related deaths @ 2.5 years follow up:
• Limited 2.8%
• Extensive 5.0%
• HR 1.79 (95% CI, 0.74-4.35).

Extensive screening for occult malignancy in idiopathic VTE

“SOME Trial”

Patients: Idiopathic VTE

CT abd/pelvis virtual endoscopy

854 patients

Limited testing

Primary endpoint: cancer @ 1 year missed by initial screening

Extensive screening for occult malignancy in idiopathic VTE

**SOME Trial**

<table>
<thead>
<tr>
<th>New cancer diagnosis: overall 3.9%</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Limited                        3.2%  p=0.28</td>
</tr>
<tr>
<td>• CT                              4.5%</td>
</tr>
</tbody>
</table>

During follow up, 9 additional cancers confirmed

| • Limited | 4 | p=1.0 |
| • CT       | 5 |      |

During follow up, 9 additional cancers confirmed

| • Limited | 4 | p=1.0 |
| • CT       | 5 |      |

**PET/CT for occult malignancy screening in unprovoked VTE**

**“MVTEP Trial”**

**NO Difference in new cancer diagnoses**

| • PET/CT | 5.1% |
| • Limited | 2.0% |
| Risk difference 3.6% (95% CI -0.4 to 7.9, p=0.07)

**NO Difference in survival**

**NO Difference in cancer stage at diagnosis**

**Screening for Occult Cancer: Bottom Line**

Patients with unprovoked VTE should undergo a thorough history and physical examination, basic lab testing (CBC, metabolic profile and LFTs) and CXR.

Age and gender-specific cancer screening are also warranted.

Extensive imaging/screening is neither warranted nor cost effective.

**Cancer Associated VTE Guidelines**

American Society of Clinical Oncology (ASCO)
National Comprehensive Cancer Network (NCCN)
European Society for Medical Oncology (ESMO)
Compared to warfarin, which of the following statements is true regarding VTE treatment in cancer patients?

1. LMWH improves efficacy (recurrent VTE).
2. LWMH improves safety (major bleeding).
3. LMWH improves survival
4. DOAC therapy leads to increased VTE recurrence
5. DOAC therapy leads to increased major bleeding

Cancer Associated VTE Treatment has a High Risk of Complications

- Risk of anticoagulant associated major bleeding can be as high as 12%.
- Risk of recurrent VTE on warfarin may be as high as 21%.

Managing VTE in Cancer is Complicated!

Increased thrombosis risk
- Cancer-specific prothrombotic activity,
- Hormonal therapy
- Angiogenesis inhibitors,
- Central venous catheters
- Surgery

Increases bleeding risk
- Chemotherapy-related hepatic and renal injury,
- Thrombocytopenia,
- Tumor friability
- Surgery

Morbidity of Cancer-Associated VTE

HR 0.48 (95%CI, 0.30 to 0.77; P<0.002).
NNT 12

LMWH vs. Warfarin for the Prevention of Recurrent VTE in Cancer Patients the CLOT Trial

Patients: Cancer with acute symptomatic VTE

672 patients

Dalteparin 200 IU/kg/d x 1 month
150 IU/kg/d x 5 months

Dalteparin bridged to warfarin

Primary endpoint: Symptomatic VTE recurrence

**LMWH Reduced Thrombosis Outcomes**

<table>
<thead>
<tr>
<th>Event</th>
<th>Dalteparin (N=334)</th>
<th>Oral Anticoagulant (N=336)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep-vein thrombosis alone</td>
<td>14</td>
<td>37</td>
</tr>
<tr>
<td>Nonfatal pulmonary embolism</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Fatal pulmonary embolism</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>55</td>
</tr>
</tbody>
</table>

Safety

Major bleeding: 6% Dalteparin, 4% Warfarin

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**Mortality did not Differ**

![Graph showing mortality did not differ between Dalteparin and Oral Anticoagulant over time.]

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**Cancer VTE Guidelines**

- LMW Heparin preferred (2B)
- *Extend treatment* regardless of bleeding risk (1B)
- *Same* anticoagulant used for first 3 months

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**LMWH has Limitations**

- Injections painful and cause ecchymoses
- Cost prohibitive @ $100/day
- Thrombocytopenia
  - Cancer or cancer treatments limit its use
  - Raise concerns regarding HIT
- No effective or proven antidote
- Renal failure may limit its use

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**Oral Direct Factor Inhibitors**

Apixaban
Rivaroxaban
Edoxaban

**FDA approval (VTE): November 2012**
**DOAC and Cancer-Associated VTE**

**XX Trial**

Patients: Cancer with acute symptomatic VTE

XX patients $\xrightarrow{\text{DOAC}}$ Dalteparin 200IU/d x 1 m, 150 IU/d

Primary endpoint: Recurrent VTE or major bleeding

**EFFICACY: Recurrent VTE**

<table>
<thead>
<tr>
<th>HOKUSAI Cancer VTE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edoxaban</td>
<td>7.9%</td>
</tr>
<tr>
<td>LMWH</td>
<td>11%</td>
</tr>
<tr>
<td>SELECT D</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>4%</td>
</tr>
<tr>
<td>LMWH</td>
<td>11%</td>
</tr>
<tr>
<td>ADAM VTE</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Apixaban</td>
<td>0.7%</td>
</tr>
<tr>
<td>LMWH</td>
<td>6.3%</td>
</tr>
</tbody>
</table>

**SAFETY: Major Bleeding**

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<td>LMWH</td>
<td>4%</td>
</tr>
<tr>
<td>SELECT D</td>
<td>NS</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>6%</td>
</tr>
<tr>
<td>LMWH</td>
<td>4%</td>
</tr>
<tr>
<td>ADAM VTE</td>
<td>NS</td>
</tr>
<tr>
<td>Apixaban</td>
<td>0%</td>
</tr>
<tr>
<td>LMWH</td>
<td>1.4%</td>
</tr>
</tbody>
</table>

**Overall Mortality**

<table>
<thead>
<tr>
<th>HOKUSAI Cancer VTE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edoxaban</td>
<td>39.5%</td>
</tr>
<tr>
<td>LMWH</td>
<td>36.5%</td>
</tr>
<tr>
<td>SELECT D</td>
<td>NS</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>25%</td>
</tr>
<tr>
<td>LMWH</td>
<td>30%</td>
</tr>
<tr>
<td>ADAM VTE</td>
<td>NS</td>
</tr>
<tr>
<td>Apixaban</td>
<td>16%</td>
</tr>
<tr>
<td>LMWH</td>
<td>11%</td>
</tr>
</tbody>
</table>

**DOACs and Cancer-Associated VTE: Conclusions**

Hokusai Cancer VTE (edoxaban), SELECT-D (rivaroxaban), and ADAM VTE (apixaban) suggest that DOACs are as effective as dalteparin in the treatment of cancer associated VTE

Bleeding complications remain a concern particularly GI bleeds in patients with upper GI malignancies

Apixaban appears to lower the rate of major bleeding

Premature discontinuation: Apixaban 6 (4%) vs. Dalteparin 22 (15%), p=0.0012
**Ongoing Cancer VTE Trials**

**CARAVAGGIO Trial**
- Apixaban vs. Dalteparin for acute VTE treatment
- Status: Completed

**CANVAS Trial**
- Any DOAC for acute VTE treatment
- Status: Enrolling

**EVE Trial**
- Extended Apixaban (2.5 mg vs. 5 mg) for secondary prevention
- Status: Enrolling

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**Cancer Associated Venous Thrombosis:**

**Discussion Outline**

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**71 y/o Female**

2017
- August 16: Localized pancreatic cancer
- August 23: Expl laparoscopy “negative”
- August 26: Port placed, FOLFIRINOX started
- October 22: Develops dyspnea and chest pain

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**What would you recommend now?**

1. IVC filter
2. Add aspirin
3. Change to a DOAC
4. Increase LMWH dose by 25%
5. Not clear from what you have presented
Anticoagulation Failures in Cancer Patients

Learning objectives
To understand the nature of the problem
To define a strategy for working through the evaluation and management of AC failures in Cancer patients.

Anticoagulant Failure in Cancer: Nature of the Problem

USA
- 1,735,350 new cancer diagnoses (2018)
- > 14 M cancer survivors
- 1 in 5 cancer patients develop thrombosis
- ~ 3 M cancer patients with VTE

What is the risk of developing a new thrombus on anticoagulants (anticoagulation failure) in cancer patients?

Risk of Anticoagulant Failure: Oral Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Trial</th>
<th>Trial Duration (days)</th>
<th>Treatment failures (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edoxaban</td>
<td>Hokusai Cancer VTE</td>
<td>365</td>
<td>7.9%</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>SELECT D</td>
<td>180</td>
<td>4%</td>
</tr>
<tr>
<td>Warfarin</td>
<td>CLOT</td>
<td>180</td>
<td>16%</td>
</tr>
<tr>
<td></td>
<td>CATCH</td>
<td>127</td>
<td>10.5%</td>
</tr>
</tbody>
</table>

Risk of Anticoagulant Failure: Parenterals

<table>
<thead>
<tr>
<th>Agent</th>
<th>Trial</th>
<th>Trial Duration (days)</th>
<th>Treatment failures (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalteparin</td>
<td>Hokusai VTE</td>
<td>365</td>
<td>13.5%</td>
</tr>
<tr>
<td></td>
<td>SELECT D</td>
<td>180</td>
<td>11%</td>
</tr>
<tr>
<td></td>
<td>DALTECAN</td>
<td>180</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>365</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td>CLOT</td>
<td>180</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>Tinzaparin</td>
<td>CATCH</td>
<td>160</td>
</tr>
</tbody>
</table>

Lots of data: Let’s summarize AC Failure rates

DOACs: 4% at 6 months (Riva), 8% at 1 year (Edoxa)
Warfarin: ~ 2.5% failure rate per month
(CLOT 16% @ 6 mos. CATCH 10.5% @ 4 mos)
LMWH: 10% at 6 months or 14% at 1 year
How does this compare to no therapy?
30% annual recurrence off anticoagulants

Are there Risk Factors for Anticoagulant Failure in Cancer?

Cancer Specific Risk Factors
- Stomach or Pancreas vs. Other Cancers
  HR 5.55 (95%CI 1.97 – 15.66)
- Lymphoma, Lung, GYN, or Bladder vs. Other Cancers
  HR 2.69 (95%CI 1.11 – 6.53)
- Metastatic disease vs. Nonmetastatic disease
  HR 2 - 3

VTE Specific Risk Factors
- Symptomatic vs. Incidental PE
  HR 2.78 (95%CI 1.20 – 6.41)
- VTE within 3 months of Cancer Diagnosis

Anticoagulant Failures in Cancer: Bottom Line
- Cancer associated VTE is common
- Anticoagulation Failures are also common
- These failures are Anticoagulant specific, Cancer specific, and VTE presentation type specific

What Factors Should We Consider In Cancer Patients With Anticoagulant Failure?
1. Has there truly been an Anticoagulant Failure?
   - The original VTE must be reviewed and confirmed (US, venography, CT, or MRI).
   - Recurrent VTE must be distinguished from the original by comparing serial imaging.
   - To be classified as a recurrent event, there must be new filling defects evident on the second study not appreciated on the original images or an interval study clearly showing thrombus resolution.

2. Is drug metabolism normal?
   - Is the dose correct?
   - Can you check a drug level prior to discontinuing?
   - Is the patient “hyper-clearing”? (LMHW, dabigatran, edoxaban)
   - Are there drug interactions? (CYP 3A4 inducers)
   - Is the patient taking the drug appropriately? (Drug absorption, meals, and rivaroxaban)
   - Is there altered GI motility? (Gastric bypass or resection)

3. Is the patient compliant?
   - Drug levels
   - Pill counts
   - Pharmacy review
   - Recent interruptions for procedures

4. Is there drug specific complications?
   - Heparin induced thrombocytopenia
   - Antiphospholipid syndrome

5. Is the anticoagulant failure due to tumor thrombus?
   - Renal cell carcinoma
   - Sarcoma

Back to our patient
Leg imaging was not performed with the original PE......
Renal Cell Carcinoma with “Tumor Thrombus”

What are the Predictors of VTE Recurrence among Cancer Patients?

Predicting VTE Recurrence in Cancer Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IV Pancreatic</td>
<td>6.38</td>
<td>2.68 – 15.13</td>
</tr>
<tr>
<td>Brain</td>
<td>4.57</td>
<td>2.07 – 10.09</td>
</tr>
<tr>
<td>Myeloprol/myelodyspl</td>
<td>3.49</td>
<td>1.59 – 7.68</td>
</tr>
<tr>
<td>Ovarian</td>
<td>3.22</td>
<td>1.57 – 6.59</td>
</tr>
<tr>
<td>Stage IV cancer</td>
<td>2.85</td>
<td>1.74 – 4.57</td>
</tr>
<tr>
<td>Lung</td>
<td>2.73</td>
<td>1.63 – 4.55</td>
</tr>
<tr>
<td>Cancer stage progression</td>
<td>2.14</td>
<td>1.30 – 3.52</td>
</tr>
</tbody>
</table>

Independent predictors of VTE recurrence among patients with active cancer

Cumulative incidence of VTE recurrence by VTE predictor status

Treatment Failure: Guidance

Symptomatic recurrent VTE despite therapeutic anticoagulation (non-LMWH agent) transition to therapeutic LMWH.

If symptomatic recurrence on LMWH, increase current dose by 25%.

Avoid IVC filters unless anticoagulation is contraindicated (e.g. active bleeding). Then consider retrievable filter.