The hypercoagulable state of cancer in the era of new oral anticoagulants

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Objectives

1. Review Incidence and causes of thrombotic complications in cancer patients
2. Outline Standard of care treatment of thrombosis in cancer patients
3. Review efficacy, dosing and side effects of DOACs (Direct oral anticoagulants)
4. Present data for use of DOACs in cancer patients

Scope of the problem

- Symptoms
- Additional medications
- Interference with cancer treatment
- Complications
- Survival

Natural History of VTE

- ~10% of patients with symptomatic DVTs develop severe post-thrombotic syndrome within 5 years, and recurrent ipsilateral DVT increases this risk.
- The majority of patients with symptomatic proximal DVT and without chest symptoms have evidence of PE on lung scans; in 40% to 50% of such patients the lung scan shows “high-probability” perfusion defects.
- ~10% of symptomatic PEs are fatal within 1 hour of onset of symptoms, and an additional 5% cause death later, despite diagnosis and treatment.
- ~50% of diagnosed PEs are associated with right ventricular dysfunction, which is associated with a ≈5-fold greater in-hospital mortality.
- There is ≈50% resolution of PE after 1 month of treatment, and perfusion eventually returns to normal in two thirds of patients.
- ~5% of treated patients with PE develop pulmonary hypertension as a result of poor resolution.

Circulation 2003; 107:I22-I30
Thrombosis and Cancer

- Annual incidence of VTE in general population is 1:1000
- Cancer increases risk of VTE by 4-6 fold
- Annual incidence of VTE in cancer patients 1 in 250
- 10-20% of all patients with VTE have cancer
- Incidence varies based on tumor type, stage and treatment

5-10% of patients presenting with idiopathic VTE will be diagnosed with cancer in the next 12-24 months

VTE has been found in 20-50% of cancer patients at autopsy

Cancer may be detected by symptoms-oriented radiologic imaging

Lower GI bleed may lead to detection of colon cancer in anticoagulated patients

VTE incidence in cancer patients

<table>
<thead>
<tr>
<th>General Population of Olmstead County</th>
<th>12 per 10,000 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicare database 1988-1990</td>
<td>VTE per 10,000 patients</td>
</tr>
<tr>
<td>Breast</td>
<td>22</td>
</tr>
<tr>
<td>Esophagus</td>
<td>43</td>
</tr>
<tr>
<td>Prostate</td>
<td>55</td>
</tr>
<tr>
<td>Lung</td>
<td>61</td>
</tr>
<tr>
<td>Colon</td>
<td>76</td>
</tr>
<tr>
<td>Leukemia</td>
<td>81</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>98</td>
</tr>
<tr>
<td>Pancreas</td>
<td>110</td>
</tr>
<tr>
<td>Brain Tumors</td>
<td>117</td>
</tr>
<tr>
<td>Ovary</td>
<td>120</td>
</tr>
</tbody>
</table>

Screening for underlying malignancy in patients with unprovoked VTE

- Patients with unexplained (unprovoked) thrombosis should undergo age-appropriate cancer screening
  - Lung Cancer screening
  - Colon Cancer screening
  - Prostate cancer-in select patients
  - Mammogram
Case 1

- 48 y/o Woman with RIGHT peroneal vein thrombosis, started on Lovenox and Coumadin
- Lovenox for 3 days, INR subtherapeutic
- increasing swelling of right leg
- Temporary IVC filter placed, requires thrombolysis x 3 and stent placement in right iliac vein
- returns after 1 week with increasing pain and swelling of LEFT leg, INR is 3.1
- switched to LMWH bid sc
- 5 days later presents to ER with SOB, CT
- CT was performed and shows new, acute PE and a large pulmonary mass

Myth Buster!

ALTERED VESSELS
VENOUS STASIS
ALTERED COAGULABILITY

Virchow's triad

What makes cancer patients so hypercoagulable?

Professor Armand Trousseau
1801-1867

Phlegmasia alba dolens (painful white inflammation) caused by venous thrombosis as a manifestation of a hypercoagulable paraneoplastic syndrome (Trousseau syndrome)

Nonbacterial thrombotic endocarditis and multiple ischemic strokes associated with an underlying cancer (also a component of Trousseau syndrome)

Trousseau: Phlegmasia alba dolens. Clinique medicale de l'Hôtel-Dieu de Paris
Paris: Bailliere 1865;3: 654-712
Trousseau’s syndrome

- Professor Trousseau died of gastric carcinoma
- “I am lost, the phlebitis that has just appeared tonight leaves me no doubt as to the nature of my illness (January 1, 1867)

Predisposing factors

- General factors
- Tumor-specific factors
- Treatment-related factors
- Thrombosis is a multifactorial process!

Predisposing factors

- **General factors**
  - Age
  - Immobility/Inactivity
  - Post-surgery
  - Dehydration
  - Intravascular access devices (PICC, PORT)
  - Inflammatory response to neoplasm
  - Obesity
  - Underlying hypercoagulable states

Age as a risk factor for VENOUS THROMBOSIS

- Risk of thrombosis increases significantly with age.
- 1:100,000 at 40 y.o.
- 1:100 at 75 y.o.
**Predisposing factors**

**Tumor–specific factors = Tumor cell activities**
- Procoagulant factors secreted by Tumor cells
- Anti-Fibrinolytic
- Inflammatory and angiogenic cytokine production
- Direct interaction with platelets, leucocytes and endothelial cells
- Neovascularization


**Predisposing factors**

**Treatment-related factors**
- Chemotherapy (cyclophosphamide, chlorambucil, nitrogen mustards)
- Radiotherapy
- Hormone therapy (Tamoxifen)
- Antiangiogenic therapy (Thalidomide, Lenalidomide, Bevacizumab)


**Case 2**
- 55 y/o WM with small cell carcinoma of the lung, currently undergoing chemotherapy and Radiation
- Anemic
- At the end of 2nd U PRBC becomes suddenly dyspneic with Hypoxia and chest wall pain
- Platelets are 36 K
- Imaging results

*Blood 2007; 110:1723*
Myth Buster!

- Venous clot can occur at any platelet count!

Practice points

- Be aware of symptoms and signs of VTE
- DVT: swelling, pain, redness, warmth, “charley horse”
- PE: SOB, CP, tachycardia, hypoxia, arrest, change in exercise capacity

The earliest known use of the term is from the Boston Globe, 17 July 1886:

Several years ago, says the Chicago Tribune, Joe Quest, now of the Athletics, gave the name of “Charlie horse” to a peculiar contraction and hardening of the muscles and tendons of the thigh, to which base ball players are especially liable from the sudden starting and stopping in chasing balls, as well as the frequent slides in base running.

Cancer, VTE and Survival

[Graph showing the probability of death over time for different conditions]
Cancer patients with VTE have higher mortality than those without VTE.

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**Treatment of VTE**
- Traditionally:
  - At least 5 days of heparin
  - Start of warfarin on day 1 or 2, continue concurrent treatment of heparin until INR >2 x 2 consecutive days
Case 3

-60 yo male with recent Dx of invasive bladder cancer
-PMH: left lower extremity DVT. Patient presents today with
-24 hours of acute onset right-sided pleuritic chest discomfort, non-radiating, sharp, constant, and relieved intermittently by p.o. Morphine and Percocet.
-small productive cough, with whitish sputum. No hemoptysis.
-He has had persistent left lower extremity edema ever since he was diagnosed with his DVT.
-Per patient, the edema of his left lower extremity has remained stable. No erythema.

Myth buster!

- You don’t need to have leg swelling for a PE to have occurred

Case 4

Patient’s INRs are as follows:
12/24 2.0 continue 5mg daily except 7.5mg Mon & Wed
1/09 3.3 changed to 5mg daily except 7.5mg on Mon
1/22 2.5 continue 37.5mg/wk
2/22 2.5 continue 37.5mg/wk
3/23 2.1 continue 37.5mg/wk
4/24 2.4 continue 37.5mg/wk

Today 2.3

-CT Chest shows new bilateral PE’s

Myth Buster!

- Even if warfarin is at target INR, patients can “break through” apparent adequate anticoagulation
Case 5

- Recurrent Liposarcoma of retroperitoneum
- DVT Right leg, Filter placed
- On chemo-nauseated, poor po intake
- On warfarin
- Enterocutaneous fistula
- Absorption issues, malnutrition

Treatment issues with warfarin

- Drug interactions, malnutrition, GI disturbances, liver dysfunction
- Thrombocytopenia and invasive procedures require interruption of therapy
- Poor venous access for monitoring
- “Warfarin resistance”

Cancer and Thrombosis

- Cancer patients have higher rates of recurrent VTE and bleeding than patients without cancer

Cumulative incidence of recurrent VTE during anticoagulant therapy

20.7 vs 6.8% at 12 mo HR 3.2 adjusted for age
Anticoagulation therapeutic 83 vs 57%
Cumulative incidence of clinically important bleeding during anticoagulant therapy

Risk of bleeding is unrelated to INR in cancer patients

<table>
<thead>
<tr>
<th>INR</th>
<th>Cancer</th>
<th>No cancer</th>
<th>Cancer</th>
<th>No cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2.0</td>
<td>54.0</td>
<td>15.9</td>
<td>30.6</td>
<td>0</td>
</tr>
<tr>
<td>2.0-3.0</td>
<td>18.9</td>
<td>7.2</td>
<td>11.2</td>
<td>0.8</td>
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<tr>
<td>&gt;3.0</td>
<td>18.4</td>
<td>6.4</td>
<td>0</td>
<td>6.3</td>
</tr>
<tr>
<td>Overall</td>
<td>27</td>
<td>9</td>
<td>13.3</td>
<td>2.1</td>
</tr>
</tbody>
</table>

CLOTH Recurrence Rate

Cancer patients with DVT and/or PE:
- initial: Dalteparin
- long term: Warfarin, Dalteparin

Dose: Dalteparin 200u/kg sc qd x 1 month, then 150 U/kg x 5 months
Long term warfarin INR 2-3
Practice points

- Standard of care for Patients with cancer and either DVT or PE: LMWH for 3-6 months, then either continuation of LMWH or switch to warfarin
- Continue anticoagulation indefinitely or until cancer resolved

Mr. M

- 48 y/o WM with metastatic pancreatic cancer, receiving 2nd line chemotherapy with Xeloda. He presents with extensive Right leg DVT. He elects not to be treated and takes aspirin instead. He has a repeat Doppler US 8 days later which shows persistent thrombosis. He then gets started on LMWH and transitioned to warfarin
- Pharmacist calls reporting difficulties regulating his INR (1-11).

Mr. M continued

- Patient does not respond to chemotherapy and therapy is stopped.
- Shortly thereafter, he develops increased swelling of his right leg and groin pain
- US Doppler shows extension of his known DVT into external iliac vein
- Admitted to the hospital, hematology consult called
Mr. M

- H and P:
- Patient as been splitting his dose of LMWH into twice daily but unequal doses.
- Repeat CT staging done earlier shows bilateral PE as incidental finding.
- Symptoms of swelling and pain are improving on iv UFH

Antithrombotic choices

- Progressive disease/goals of care discussion
- Hypercoagulable State (Trousseau's syndrome)
- Has he failed LMWH?
  -> anti-X a factor inhibitor (fondaparinux)
  -> continue UFH iv as inpatient/outpatient
  -> DOACs?
  ? filter

IVC filter

- Chest 2004: if cancer patient fails anticoagulation, place IVC filter=WITHDRAWN
- IVC filter does not treat acute clot
- IVC filter does not treat underlying hypercoagulable state
- Introduces another nidus for thrombus formation
- Associated with increased morbidity

Practice points

- 1. Cancer is a very hypercoagulable state
- 2. Encourage the patients to adhere to prescribed regimen. ASK!
- 3. Thrombosis occurrence or progression may signal progressive neoplastic disease
- 4. alternative strategies needed
- 5. Patient preferences/goals need to be considered
Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update 2014

- Most hospitalized patients with active cancer require thromboprophylaxis throughout hospitalization.
- Data are inadequate to support routine thromboprophylaxis in patients admitted for minor procedures or short chemotherapy infusion.
- Routine thromboprophylaxis is not recommended for ambulatory patients with cancer. It may be considered for highly select high-risk patients.
- Patients with multiple myeloma receiving antiangiogenesis agents with chemotherapy and/or dexamethasone should receive prophylaxis with either LMWH or low-dose aspirin to prevent VTE.
- Patients undergoing major cancer surgery should receive prophylaxis starting before surgery and continuing for at least 7 to 10 days.
- Extending postoperative prophylaxis up to 4 weeks should be considered in those undergoing major abdominal or pelvic surgery with high-risk features.

LMWH is recommended for the initial 5 to 10 days of treatment of established deep vein thrombosis and pulmonary embolism as well as for long-term secondary prophylaxis for at least 6 months.

- Use of novel oral anticoagulants is not currently recommended for patients with malignancy and VTE.

Chest guidelines 2016 -Updates

1. For VTE and no cancer, as long-term anticoagulant therapy, we suggest
   - dabigatran (Grade 2B),
   - rivaroxaban (Grade 2B),
   - apixaban (Grade 2B), or
   - edoxaban (Grade 2B) over vitamin K antagonist (VKA) therapy, and suggest VKA therapy over low-molecular-weight heparin (LMWH; Grade 2C).

2. No compression stockings routinely recommended

3. Against IVC filter!
Hint: patient has new PE and extremely swollen legs bilaterally

**IVC filters in a nutshell**

- IVC filters reduce the risk of PE in patients with acute, proximal DVT and contra-indications to AC.
- IVC filters do not address the underlying hypercoagulable state.
- Anatomic variants of the Vena cava must be recognized and considered before placement.
- Filters do not prevent propagation or long-term sequelae of DVT.
- The risks of filters increase with prolonged in-dwell time.
- Vigilance on the part of the implanting physician for patient recall and retrieval if indicated.

<table>
<thead>
<tr>
<th>Warfarin</th>
<th>LMWH Dalteparin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td>VTE Tx and PPs</td>
<td>Non-valvular A fib</td>
<td>Non-valvular A fib</td>
<td>Non-valvular A fib</td>
<td>Non-valvular A fib</td>
</tr>
<tr>
<td>Post-op MI/angina</td>
<td>Post-op</td>
<td>VTE Tx</td>
<td>VTE Tx</td>
<td>VTE Tx</td>
<td>VTE Tx</td>
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<tr>
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<td></td>
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</tr>
<tr>
<td>Monitoring</td>
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<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Dosing</td>
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<td>qd-bid</td>
<td>bid</td>
<td>qd</td>
<td>qd</td>
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<tr>
<td>Half-Life</td>
<td>40-60hrs</td>
<td>4-7hrs</td>
<td>8-15hrs</td>
<td>7-11hrs</td>
<td>12 hrs</td>
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<tr>
<td>10-14 hrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal Clearance</td>
<td>No</td>
<td>&gt;90%</td>
<td>80%</td>
<td>33%</td>
<td>25%</td>
</tr>
<tr>
<td>50% Careful if CreaCl&gt;95</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic clearance</td>
<td>Highly variable</td>
<td>N/A</td>
<td>Large variability in Child B</td>
<td>Avoid in Child B/C or in coagulopathy associated with Liver disease</td>
<td>No dose adjustments in mild liver disease</td>
</tr>
</tbody>
</table>

| Apixaban < 25 ml/min > 2.5 mg bid |
| Rivaroxaban 15-50 ml/min > 2.5 mg qd |
| Edoxaban 15-50 ml/min > 30 mg qd |
| not rec if >98 |

- Highly variable
- Large variability in Child B
- Avoid in Child B/C or in coagulopathy associated with Liver disease
- No dose adjustments in mild liver disease
- Avoid in Child’s B/C

<p>| Table 4: Factors That May Influence Which Anticoagulant is Chosen for Initial and Long-Term Treatment of VTE |</p>
<table>
<thead>
<tr>
<th>Total Anticoagulant</th>
<th>Warfarin</th>
<th>LMWH</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>More so if just diagnosed, extensive VTE, metastatic cancer, very symptomatic; yielding, on cancer chemotherapy, possibly</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| VTE Tx              | Warfarin; apixaban; edoxaban; LMWH; NOACs contraindicated if PR due to liver disease; VTE difficult to control and NOACs may not effective │
| Acute MI/angina     | NOACs contraindicated if PR due to liver disease; VTE difficult to control and NOACs may not effective; antithrombotic effect. |
| Liver disease and coagulopathy | NOACs contraindicated with severe renal impairment; limiting of NOACs with levels of renal impairment; offer with the NOACs and among jurisdictions. |
| Dyspepsia or history of GI bleeding | NOACs contraindicated with severe renal impairment; limiting of NOACs with levels of renal impairment; offer with the NOACs and among jurisdictions. |
| Poor compliance | NOACs contraindicated with severe renal impairment; limiting of NOACs with levels of renal impairment; offer with the NOACs and among jurisdictions. |
| Thrombolytic therapy use | NOACs contraindicated with severe renal impairment; limiting of NOACs with levels of renal impairment; offer with the NOACs and among jurisdictions. |
| Reversal agent needed | NOACs contraindicated with severe renal impairment; limiting of NOACs with levels of renal impairment; offer with the NOACs and among jurisdictions. |
| VTE, MI | NOACs contraindicated with severe renal impairment; limiting of NOACs with levels of renal impairment; offer with the NOACs and among jurisdictions. |
| Potential for other agents to cross the placenta | NOACs contraindicated with severe renal impairment; limiting of NOACs with levels of renal impairment; offer with the NOACs and among jurisdictions. |

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- Warfarin
- LMWH Dalteparin
- Dabigatran
- Rivaroxaban
- Apixaban
- Edoxaban
Choice of Anticoagulant Based on Patient Characteristics

- Dabigatran and Edoxaban both require lead-in with LMWH for 5-10 days
- DOACs are effective and safe in special populations including
  - elderly
  - PE
  - body weight >100 kg

New anticoagulants-No monitoring

Dabigatran (Pradaxa) 2010: oral direct thrombin inhibitor
- slightly less bleeding risk than warfarin but increased GI bleeding
- Small MI signal
- Blister pack, Crea >30
- Bid drug, requires lead-in with LMWH

Rivaroxaban (Xarelto) 2011: oral Factor Xa inhibitor
- VTE treatment, 15 mg bid x 3 weeks, then 20 mg qd
- Only once daily drug
- Better absorbed with food

Apixaban (Eliquis) 2012: oral Factor Xa inhibitor
- for treatment of acute DVT/PE (10mg bid x7 days, then 5mg bid)
- Less bleeding events
- No dose adjustments in liver disease

New anticoagulants-Vitamin K is not an issue

Edoxaban (Savaysa) 2015: oral anti-Xa inhibitor
- daily dosing, requires lead-in with LMWH
- Careful if CreaCl >95 (fast metabolized)
- Avoid in liver disease

Reversal agents-Dabigatran

10/2015 Idarucizumab (Praxbind) approved
- Fully humanized antibody fragment that given iv x 2 doses, fully reverses Pradaxa
- Phase 1 trial: immediate, complete and sustained reversal of dabigatran-induced anticoagulation in healthy humans
- Onset of action of the antidote was detected immediately after completion of 5 min infusion and thrombin time was reversed
- Thrombin time is the preferred lab test to assess dabigatran
- Reversal of anticoagulation effect was complete and sustained in 7 of 9 patients given the 2 gram dose and in 8/8 after given the 4 gram dose.
Reversal agents-Rivaroxaban and apixaban

- NOT FDA approved yet
- Andexanet alfa (ANDEXANET) is a biologic agent, a modified recombinant derivative of factor Xa (fXa). It acts as a decoy receptor — it has a higher affinity to the fXa inhibitor than natural fXa, and consequently the inhibitor binds to the drug rather than to fXa itself
- Results from three separate Phase 2 proof-of-concept studies demonstrated that andexanet alfa immediately reversed the anticoagulation activity of
  -Apixaban
  -Rivaroxaban
  -and enoxaparin, in healthy volunteers.
  -Andexanet alfa has been shown to be well tolerated in clinical studies, which have included more than 100 volunteers, with no thrombotic events or antibodies to Factor Xa or Factor X observed.

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Use of DOACs in cancer patients

- 1500 cancer patients in the 6 clinical trials with DOACs
- Subgroup analysis (active cancer definition, older, lower CreaCl)
- Most common: Colon, Prostate, breast
- Stage IV 13%
- Seems as effective/safe
- Concerns:
  -No head-to-head comparison with LMWH as standard of care (edoxaban vs LMWH started)
  -nausea, vomiting
  -chemotherapy-induced mucosal abnormalities influencing absorption
  -interactions with chemotherapy agents

DOACs and Chemotherapy

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- LMWH is recommended for the initial 5 to 10 days of treatment of established deep vein thrombosis and pulmonary embolism as well as for long-term secondary prophylaxis for at least 6 months.

Use of novel oral anticoagulants is not currently recommended for patients with malignancy and VTE.

- Anticoagulation should not be used to extend survival of patients with cancer in the absence of other indications.
- Patients with cancer should be periodically assessed for VTE risk.
- Oncology professionals should educate patients about the signs and symptoms of VTE.

Summary

- 1. Cancer is a risk factor for thrombotic complications
- 2. Cancer is a risk factor for bleeding complications on anticoagulation
- 3. Long-term LMWH remains the standard of care without requiring anticoagulant monitoring
- 4. To date, the DOACs are NOT recommended in cancer patients. Further studies are needed to compare DOACs with LMWH in cancer patients and are pending.
- 5. DOACs are as affective as warfarin and are the preferred treatment for patients without cancer.