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VENOUS THROMBOEMBOLISM (VTE) IN THE SETTING OF CANCER:
CLINICAL CONUNDRUMS

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VTE incidence

General population:

CDC:
1-2 / 1000.

Cancer:

8-19% in first year after initiation of chemotherapy

On average, 13% in first year of therapy (1.4% in matched controls).[1]

Overall risk ranges from 1.3% to 20% depending on cancer type[2]

Cancer with highest risk?

Primary brain cancer.

Although, cancers that metastasize to brain have a lower incidence than those that metastasize elsewhere.[1]

What about Cancer incidence in unprovoked VTE?

A significant concern….

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CANCER ASSOCIATION WITH UNPROVOKED DVT

10% of patients with unprovoked DVT were found to have cancer over the following year[3]

562 patients with unprovoked DVT

Followed for 1 year: 5.06% had a cancer diagnosis

Mostly smokers and patients > 60 years old[4]

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Cancer is a known hypercoagulable state

More likely to have surgery, CVC, and limited mobility

Chemotherapy does amplify the procoagulant state[5]

Systemic chemotherapy increases risk of VTE 6-7 fold[1]

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MAKING THE DIAGNOSIS

- Diagnosis will be made doppler
  - If clinical exam still suspicious with negative doppler, repeat exam is recommended in 1-2 weeks
  - Explicitly describe this in the discharge instructions
- D-Dimer?

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D-DIMER IS NOT USEFUL TO RULE OUT VTE IN CANCER

- On average cancer patients have a 3-fold increase in D-Dimer
- 2014 meta analysis 10,002 patients
  - Of the cancer patients, 9% had both a negative D-Dimer and "unlikely" Wells score
  - 2.2% of these still had VTE[6]

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TREATMENT

- Noncancer patients:
  - Low molecular weight heparin (LMWH) for 5-10 days followed by warfarin
  - Direct oral anticoagulants (DOACs)
- Cancer patients:
  - LMWH for 6 months
  - Full Dose for 1 month and 75% dose for next 5 months.
  - American College of Chest Physicians recommends continuing while cancer is active[8]

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WARFARIN IN MALIGNANCY?

- Multiple factors lead to decreased efficacy of warfarin
  - Higher recurrence
  - Multiple drug interactions with chemo
  - Possible liver involvement with malignancy
  - Malnutrition
  - Difficulty in maintaining an INR
  - Higher incidence of major bleeding
  - Acceptable alternative for long-term therapy if LMWH is not available/feasible[9,10]

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TREATMENT – DIRECT ORAL ANTICOAGULANTS (DOACS)

- Clinical trials comparing these to warfarin were non-inferiority studies
- Only 2-9% were cancer patients
- Subsequent meta analysis suggested that DOACs may be more efficacious than warfarin; no direct comparisons have been done.[8]

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TREATMENT - DOACS

- Multiple guidelines
  - "There are insufficient data to suggest that direct oral anticoagulants would be appropriate for treatment of cancer associated VTE."[8,10]
- Contraindications
  - In addition to normal contraindications, keep in mind renal function, age, weight, etc.

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RASKOB ET.AL: EDOXABAN VS. LMWH - 2018[11]

- Edoxaban
  - Recurrent VTE: 7.9%
  - Major Bleeding 6.9%
- LMWH
  - Recurrent VTE: 11.3%
  - Major Bleeding 4.0%

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TREATMENT OF INCIDENTAL PE – NONCANCER PATIENTS

Goy et al. in 2015

- *Review of 2213 patients with a diagnosis of subsegmental PE*
- *Showed that whether or not anticoagulation was given, there were no recurrent PEs, yet 5% of anticoagulated patients developed life-threatening bleeding*[12]

The 2018 ACEP Clinical Policy on Acute Venous Thromboembolic Disease:

Withholding anticoagulation in patients with subsegmental PE a Level C recommendation and states: "Given the lack of evidence, anticoagulation treatment decisions for patients with subsegmental PE without associated DVT should be guided by individual patient risk profiles and preferences [Consensus recommendation]."[7]

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TREATMENT OF INCIDENTAL VTE IN MALIGNANCY

- Similar rate of recurrent VTE and mortality for those found to have incidental/asymptomatic VTE vs. symptomatic VTE
- Therefore, treat all VTE[8,10]

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SIGNIFICANT RISK TO ANTICOAGULATE PATIENTS WITH ACTIVE CANCER

The decisions seems simple

VTE = Treat

We must appreciate the bleeding risk in the cancer patient

- 4.7% recurrent DVT
- 8.9% bleeding event,
- 4.6% major bleeding event
- In the first 3 months of anticoagulation, 1.4% had fatal recurrence of PE
- 1.9% died of a fatal bleed[13]

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CONTRAINDICATIONS TO ANTICOAGULATION – INTRACRANIAL LESIONS

- Intracranial hemorrhage occurred int 20-50% of patients with brain metastasis
- No significant difference in occurrence between those receiving LMWH and match controls not on anticoagulation[14]
- Guidelines:
  - Relative contraindication by American Society of Clinical Oncology[15]
  - Absolute contraindication by National Comprehensive Cancer Network[16]

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CONTRAINDICATIONS TO ANTICOAGULATION – THROMBOCYTOPENIA

- Less than 50,000/uL is a relative contraindication
  - Transfuse up to 50,000/uL and then treat
- Between 25,000-50,000/uL
  - Consider 50% dose of LMWH
- Under 20,000/uL
  - No anticoagulation[10]

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Contraindications to anticoagulation in cancer patients with VTE[10]

Active, ongoing bleeding.

Severe, uncontrolled malignant hypertension

Severe coagulopathy (liver failure)

Severe, thrombocytopenia/platelet dysfunction

Surgery or invasive procedure, including LP, epidural catheters, etc

*Relative contraindications: CNS lesions, GI ulcerations, active but non-life threatening, CNS bleeding within 4 weeks, and Major surgery within 2 weeks.

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PATIENTS IN WHOM ANTICOAGULATION HAS UNCERTAIN BENEFIT:

- End of life or Hospice care
- Very limited life expectancy with no palliative or symptom reduction benefit
- Asymptomatic VTE with high risk of bleeding

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Perioperative VTE prophylaxis?

Patients undergoing cancer surgery have 2-3 fold increased risk of VTE

VTE is the most common cause of death in first 30 days of surgery

For planned surgery, 7-10 days of therapeutic LMWH, and up to 30 days for large abdominal pelvic surgeries or those with limited post operative mobility

For emergent or urgent surgeries, start LMWH 12 hours before surgery[16]

Important to HOLD prophylaxis prior to neurosurgery!

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VTE PROPHYLAXIS IN HIGH RISK PATIENTS

- High-grade glioma has high incidence of VTE (12-30%)[17]
  - PRODIGE trial:
    - 99 patients treated with LMWH: 5.1% major bleeds, 9.1% thrombotic events
    - 87 patients received placebo: 1.2% major bleeds, 14.9% thrombotic events
  - Prophylaxis is not generally recommended[18]

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EMPIRIC THERAPEUTIC ANTICOAGULATION

- Mostly an outpatient question
- Khorana score utilized by oncology team
- Certain cancer/chemo combinations have extremely high risk[19]
  - Eg. Multiple Myeloma receiving thalidomide- or lenalidomide-based regimens with chemotherapy and/or dexamethasone have extremely high risk.
  - High grade glioma: extremely high risk

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RECURRENT VTE

- Incidence
  - 3-4 time risk of recurrent VTE while on therapy compared to those without cancer
  - 10-17% in first 6 months for those on warfarin therapy
  - 6-9% in first 6 month for those on LMWH therapy[20]
- Treatment
  - Consider increasing dose of LMWH by 20-25%
  - IVC filters: Should be avoided except for those with absolute contraindication to anticoagulation
- **1 year mortality = 50% in this situation[21]**

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Answers to Clinical Conundrums

1. Is thrombocytopenia a contraindication to anticoagulation?
If less than 20K, yes. If 25-50 either transfuse to 50 or use LMWH at 50% dose

2. Is warfarin an option for VTE in cancer?
Numerous factors contribute to lack of utility. Reasonable as a last resort

3. What about incidental of asymptomatic VTE, do these require the same treatment?
Yes, but recognize the significant risk of anticoagulation in the cancer patient

4. Are intracranial lesions a contraindication to therapeutic anticoagulation
Basically a strong relative contraindication. Discussion between patient, family, and oncology.

5. Are DOACs approved for VTE in cancer?
Insufficient data to recommend their use. Increased risk of major bleeding compared to LMWH in one small study. However, they seem to be noninferior to warfarin

6. What are the options with recurrent VTE?
Increase dose of LMWH by 20-25%.
"Off-label DOAC"

7. Are there cases in which prophylaxis/empiric anticoagulation warranted?
Yes, Khorana score, but not really our jobs. Consider prophylaxis for general surgical procedures but not neurosurgical procedures.

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