



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

RYAN OFFMAN DO FACEP
PROGRAM DIRECTOR: EMERGENCY MEDICINE RESIDENCY

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Management of VTE in malignancy:
Shot of Lovenox



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Clinical Questions

- 73 yo being treated for MDS, platelet count is 45,000
- 65 yo lung cancer patient on warfarin diagnosed with DVT 2 months prior
- 55 yo with colon CA undergoes CT abd/pelvis with incidental subsegmental PE
- 79 yo inquisitive surgeon with colon cancer and leg pain.
- You diagnose a simple DVT in a cancer patient with a strong aversion to needles.
- 52 yo with multiple metastatic lesion in her brain is diagnosed with DVT
- Your patient return after 4 months of proper treatment with a recurrent DVT.

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VTE incidence

<p>General population:</p> <p>CDC: 1-2 / 1000.</p>	<p>Cancer:</p> <p>8-19% in first year after initiation of chemotherapy</p> <p>On average, 13% in first year of therapy (1.4% in matched controls).¹</p> <p>Overall risk ranges from 1.3% to 20% depending on cancer type²</p>	<p>Cancer with highest risk?</p> <p>Primary brain cancer.</p> <p>Although, cancers that metastasize to brain have a lower incidence than those that metastasize elsewhere.¹</p>	<p>What about Cancer incidence in unprovoked VTE?</p> <p>Turns out this is a big concern.</p>
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CANCER ASSOCIATION WITH UNPROVOKED DVT

10% of patients with unprovoked DVT were found to have cancer over the following year³

562 patients with unprovoked DVT

Followed for 1 year: 5.06% had a cancer diagnosis

Mostly smokers and patients > 60 years old⁴



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Cancer is a known hypercoagulable state

More likely to have surgery, CVC, and limited mobility

Chemotherapy does amplify the procoagulant state⁵

Systemic chemotherapy increases risk of VTE 6-7 fold¹


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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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Active cancer Treatment or palliation within 6 months	<input checked="" type="checkbox"/> No 0	<input type="checkbox"/> Yes +1	<h2>JUST DON'T</h2> <table border="1"> <tbody> <tr> <td>Clinical signs and symptoms of DVT</td> <td><input checked="" type="checkbox"/> No 0</td> <td><input type="checkbox"/> Yes +3</td> </tr> <tr> <td>PE is #1 diagnosis OR equally likely</td> <td><input checked="" type="checkbox"/> No 0</td> <td><input type="checkbox"/> Yes +3</td> </tr> <tr> <td>Heart rate > 100</td> <td><input checked="" type="checkbox"/> No 0</td> <td><input type="checkbox"/> Yes +1.5</td> </tr> <tr> <td>Immobilization at least 3 days OR surgery in the previous 4 weeks</td> <td><input checked="" type="checkbox"/> No 0</td> <td><input type="checkbox"/> Yes +1.5</td> </tr> <tr> <td>Previous, objectively diagnosed PE or DVT</td> <td><input checked="" type="checkbox"/> No 0</td> <td><input type="checkbox"/> Yes +1.5</td> </tr> <tr> <td>Hemoptysis</td> <td><input checked="" type="checkbox"/> No 0</td> <td><input type="checkbox"/> Yes +1</td> </tr> <tr> <td>Malignancy w/ treatment within 6 months or palliative</td> <td><input checked="" type="checkbox"/> No 0</td> <td><input type="checkbox"/> Yes +1</td> </tr> </tbody> </table> 	Clinical signs and symptoms of DVT	<input checked="" type="checkbox"/> No 0	<input type="checkbox"/> Yes +3	PE is #1 diagnosis OR equally likely	<input checked="" type="checkbox"/> No 0	<input type="checkbox"/> Yes +3	Heart rate > 100	<input checked="" type="checkbox"/> No 0	<input type="checkbox"/> Yes +1.5	Immobilization at least 3 days OR surgery in the previous 4 weeks	<input checked="" type="checkbox"/> No 0	<input type="checkbox"/> Yes +1.5	Previous, objectively diagnosed PE or DVT	<input checked="" type="checkbox"/> No 0	<input type="checkbox"/> Yes +1.5	Hemoptysis	<input checked="" type="checkbox"/> No 0	<input type="checkbox"/> Yes +1	Malignancy w/ treatment within 6 months or palliative	<input checked="" type="checkbox"/> No 0	<input type="checkbox"/> Yes +1
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Bedridden recently >3 days or major surgery within 12 weeks	<input checked="" type="checkbox"/> No 0	<input type="checkbox"/> Yes +1																						
Calf swelling >3 cm compared to the other leg Measured 10 cm below tibial tuberosity	<input checked="" type="checkbox"/> No 0	<input type="checkbox"/> Yes +1																						
Collateral (nonvaricose) superficial veins present	<input checked="" type="checkbox"/> No 0	<input type="checkbox"/> Yes +1																						
Entire leg swollen	<input checked="" type="checkbox"/> No 0	<input type="checkbox"/> Yes +1																						
Localized tenderness along the deep venous system	<input checked="" type="checkbox"/> No 0	<input type="checkbox"/> Yes +1																						
Pitting edema, confined to symptomatic leg	<input checked="" type="checkbox"/> No 0	<input type="checkbox"/> Yes +1																						
Paralysis, paresis, or recent plaster immobilization of the lower extremity	<input checked="" type="checkbox"/> No 0	<input type="checkbox"/> Yes +1																						
Previously documented DVT	<input checked="" type="checkbox"/> No 0	<input type="checkbox"/> Yes +1																						
Alternative diagnosis to DVT as likely or more likely	<input checked="" type="checkbox"/> No 0	<input type="checkbox"/> Yes -2																						

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- A word about D-Dimer
 - 2 main assays
 - D-dimer units (DDU)
 - Fibrin equivalent units (FEU)
 - All major studies used d-Dimers measure in FEU
 - FEUs are $\text{age} \times 10 \text{ ug/L}$
 - DDUs are $\text{age} \times 5 \text{ ug/L}^7$



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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 active⁸



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SO, THAT'S A NO ON WARFARIN?

- Multiple factors lead to decreased efficacy
 - 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

- 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 - 2018¹¹

- | | |
|--|---|
| <ul style="list-style-type: none"> ■ Edoxaban <ul style="list-style-type: none"> ■ Recurrent VTE: 7.9% ■ Major Bleeding 6.9% | <ul style="list-style-type: none"> ■ LMWH <ul style="list-style-type: none"> ■ 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 bleeding¹²

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]."¹⁷

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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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ANTICOAGULATION IN THE CANCER PATIENT

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 bleed¹³



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CONTRAINDICATIONS TO ANTICOAGULATION – INTRACRANIAL LESIONS

- Intracranial hemorrhage occurred in 20-50% of patients with brain metastasis
- No significant difference in occurrence between those receiving LMWH and match controls not on anticoagulation¹⁴
- Guidelines:
 - Relative contraindication by American Society of Clinical Oncology¹⁵
 - Absolute contraindication by National Comprehensive Cancer Network¹⁶



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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 anticoagulation¹⁰



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Table 4. Contraindications and Other Considerations to Withhold Therapeutic Anticoagulant Therapy in Patients With Cancer and VTE*

Contraindication/Consideration
Absolute contraindications†
Active major, serious, or potentially life-threatening bleeding not reversible with medical or surgical intervention, including but not limited to any active bleeding in a critical site (ie, intracranial, pericardial, retroperitoneal, intraocular, intra-articular, intraspinal)
Severe, uncontrolled malignant hypertension
Severe, uncompensated coagulopathy (eg, liver failure)
Severe platelet dysfunction or inherited bleeding disorder
Persistent, severe thrombocytopenia (< 20,000/ μ L)
Surgery or invasive procedure, including but not limited to lumbar puncture, spinal anesthesia, and epidural catheter placement
Relative contraindications‡
Intracranial CNS bleeding or CNS bleeding
Active peptic or other GI ulceration at high risk of bleeding
Active but non-life-threatening bleeding (eg, trace hematuria)
Intracranial or CNS bleeding within past 4 weeks
Major surgery or serious bleeding within past 2 weeks
Persistent, severe thrombocytopenia
Patients for whom the potential benefit is of uncertain benefit
Patient receiving end-of-life/hospice care
Very limited life expectancy with no palliative or symptom reduction benefit
Asymptomatic thrombosis with concomitant high risk of serious bleeding
Patient characteristics and values
Preference or refusal
*CNS lesions, GI ulcerations, active but non-life threatening, CNS bleeding within 4 weeks, and Major surgery within 2 weeks.
Abbreviation: VTE, venous thromboembolism.
†These criteria are specific for therapeutic doses of anticoagulation and should not be applied to prophylactic doses of anticoagulation.
‡Absolute contraindications are situations in which anticoagulation should not be administered because the risk of harm associated with bleeding is likely to exceed the potential benefit from anticoagulation.
§Relative contraindications are situations in which anticoagulation may be administered if the risk of recurrent or progressive thrombosis is estimated to exceed the risk of bleeding.

Contraindications to anticoagulation in cancer patients with VTE¹⁰

Severe coagulopathy (liver failure)

Severe, thrombocytopenia/platelet dysfunction

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



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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 surgery¹⁶

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 recommended¹⁸



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EMPIRIC THERAPEUTIC ANTICOAGULATION

- Mostly an outpatient question
- Khorana score utilized by oncology team
- Certain cancer/chemo combinations have extremely high risk¹⁹
 - 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 therapy²⁰
- 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 situation²¹**



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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 or asymptomatic VTE, do these require the same treatment?
Yes, but recognize the significant risk of anticoagulation in the cancer patient

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

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

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

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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