Thrombosis and Cancer

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- Off-label medication use: none

Patient Presentation (1)

- 42 year old woman presents with symptomatic bilateral pulmonary emboli
- She is not using any estrogen-containing oral contraceptives or supplements
- She has had no problems with weight loss, cough, change in bowel habits, etc.
- She has no family history of VTE, and no family history of early-onset cancer
- What studies, if any, would you use to screen for cancer?

Independent risk factors for VTE

Baseline Characteristic	Odds Ratio	95% CI
Body mass index (kg/m ²)	1.08	1.05, 1.11
Major surgery	18.95	9.22, 38.97
Hospitalization for acute medical illness	5.07	3.12, 8.23
Nursing home confinement	4.63	2.77, 7.74
Trauma/fracture	4.56	2.46, 8.46
Active cancer	14.64	7.73, 27.73
Pregnancy or post-partum	4.24	1.30, 13.84
Oral contraceptives	4.03	1.83, 8.89
Non-contraceptive estrogen + progestin	2.53	1.38, 4.63

Heit JA, et al. J Thromb Thrombolys, 2016; 41: 3-14

Major VTE risk factors, 1988-2010

- Population-based cohort study of all residents of Olmsted County, MN, from 1981-2010
- 3,293 residents with a first, life-time VTE
- 1.23 (95% Cl, 1.18, 1.27) per 1,000 person-years incident VTE annually



Heit JA, et al. Thromb Haemost, 2017; 117: 390-400

Period prevalence of cancer up to 12 months following a new VTE



Carrier M, et al. Ann Intern Med, 2017; 167: 410-7

Extensive vs Limited Screening

- Extensive screening more frequently included mammography, CT of chest/abdomen/ pelvis
- Extensive screening found more occult cancer than limited screening at the time of screening

Prevalence of Cancer by Subgroup

 But unclear if earlier diagnosis had any impact on cancer outcome...

My practice

- Focused evaluation based on symptoms or signs
- Perform age-appropriate cancer screening tests
- Take into consideration family history of malignancy

Patient Presentation (2)

- 58 year old man with NSCLC metastatic to the liver is incidentally found to have bilateral segmental pulmonary emboli on a follow-up pulmonary CT scan
- He also has stage 3 chronic kidney disease with an estimated creatinine clearance of 45 mL/min/1.73 m²
- Bilateral lower extremity US is negative for DVT
- What is the best treatment for this patient?

VTE in Cancer Patients

 1,934 consecutive cancer patients (13 excluded with a known positive history of VTE)



Incidental PE and Outcomes

• Retrospective cohort study

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den Exter PL, *et al*. J Clin Oncol, 2011; 29: 2405-9

Management of Incidental VTE

VTE in Cancer Treated with Warfarin

- 842 patients with VTE, 181 with cancer at time of diagnosis
- Treatment: UFH/LMWH followed by warfarin



CLOT Study

• Randomized, prospective study comparing LMWH alone to LMWH transitioned to warfarin in patients with cancer and VTE

CATCH Study

- Randomized, open label study in patients with active cancer and DVT/PE
- Tinzaparin 175 IU/kg daily vs. warfarin, target INR 2-3



CATCH Study

Lee AY, et al, JAMA, 2015; 314: 677-86

CLOT vs CATCH: Why the difference?

- Lower than anticipated thrombotic event rate in the warfarin group
 - Fewer patients with metastatic disease in CATCH
 - Fewer patients with an ECOG performance status of 2 in CATCH
 - Fewer patients receiving anticancer therapy in CATCH
 - Fewer patients had previous history of VTE in CATCH
- Lower 6-month mortality in CATCH compared to CLOT
- CLOT used a lower dose of LMWH after the first month, whereas CATCH used therapeutic dose LMWH for the entire course

Direct Oral Anticoagulants

	Dabigatran etexilate	Rivaroxaban	Apixaban	Edoxaban
Target	Thrombin	Factor Xa	Factor Xa	Factor Xa
Bioavailability	6.5%	80%	50%	62%
Time to peak plasma concentration	0.5-2 hr	2-4 hr	3-4 hr	1-2 hr
Half-life	12-14 hr	7-13 hr	8-13 hr	8-10 hr
Routine monitoring	No	No	No	No
Elimination	80% renal	67% renal	25% renal	50% renal
Potential drug interactions*	P-glycoprotein inhibitors and inducers	Inhibitors of CYP3A4 and P- glycoprotein	Inhibitors of CYP3A4 and P- glycoprotein	Strong P- glycoprotein inhibitors

* Inhibitors of p-glycoprotein include ketoconazole, quinidine, and amiodarone. Inhibitors of CYP3A4 include macrolide antibiotics, ritonavir. Rifampicin is an inducer of p-glycoprotein and CYP3A4.

Cancer in patients in the DOAC VTE trials

• Six studies were included in a meta-analysis (two with dabigatran, two with rivaroxaban, one with edoxaban, and one with apixaban), accounting for a total of 1,132 patients.

VTE Recurrence



Cancer in patients in the DOAC VTE trials

Major Bleeding

Clinically Relevant Bleeding

Vedovati MC, et al. Chest, 2015; 147: 475-83

Hokusai VTE-Cancer

 Adult cancer patients with symptomatic or incidental proximal lower extremity DVT and/or PE

Hokusai VTE Cancer: Results



Raskob GE, et al. N Engl J Med, 2018; 378: 615-24

SELECT-D: Rivaroxaban in Cancer VTE

SELECT-D: Outcomes

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Young AM, et al, J Clin Oncol, 2018; 36: 2017-23

SELECT-D: Sites of Major Bleeding

Site*	Dalteparin (n=203)	Rivaroxaban (n=203)
Gastrointestinal	4	8
Genitourinary	0	1
Other	2	2
Total	6	11

* Patients could have more than one site of bleed

Young AM, et al, J Clin Oncol, 2018; 36: 2017-23

SELECT-D: Sites of clinically-relevant, non-major bleeding

Site*	Dalteparin (n=203)	Rivaroxaban (n=203)
Gastrointestinal	3	9
Genitourinary	2	11
Other	3	7
Total patients	7	25

* Patients could have more than one site of bleed

Young AM, et al, J Clin Oncol, 2018; 36: 2017-23

Cancer-associated VTE and DOAC's

 "The use of direct oral anticoagulants should be avoided in patients with a creatinine clearance of less than 30 ml per minute, and their use in patients with gastrointestinal cancer should be based on patient preference. Some patients may choose the convenience of an oral agent despite an increased risk of gastrointestinal bleeding."

Drug Interactions with Direct Oral Anticoagulants



Patient Presentation (2)

- Patient is started on enoxaparin, 1 mg/kg twice a day, for 7 days, then switched to edoxaban 30 mg daily
- Two weeks later, he develops new dyspnea, and is found to have a new segmental PE in the lower left lung
- What would you do now for this patient?

Recurrent VTE in Cancer Patients

• When should an IVC filter be considered?

Schulman S. Blood, 2017; 129: 3285-93

PRÉVENTION DU RISQUE D'EMBOLIE PULMONAIRE PAR INTERRUPTION CAVE STUDY

- 400 patients with proximal DVT randomized to receive an IVC filter or no filter, and also LMWH or UFH
- Recurrent VTE, death, and major bleeding analyzed at day 12 and two years

PREPIC 2

SSC Guidance Statement

- We recommend against IVC filter insertion in the absence of contraindications to anticoagulation.
- We suggest IVC filter insertion in cancer patients with contraindications to anticoagulation and a high risk of potentially fatal PE.
- We recommend resuming anticoagulation with LMWH and removing the retrievable filter in cancer patients when the contraindication has resolved.
- (Inserting a retrievable IVC filter in a patient who has a recurrent VTE on anticoagulation may be beneficial, but can make things worse...)*

* tlo, no data

Patient Presentation (2)

- Patient is switched back to enoxaparin, 1 mg/kg twice daily with monitoring anti-factor Xa levels
- He is also started on a new therapeutic regimen for his NSCLC, which has progressed on his most recent imaging studies
- His baseline platelet count was 160,000/ μ L, but this has now dropped to 45,000/ μ L
- He has no symptoms of bleeding
- What would you do now for this patient?

Treating VTE during thrombocytopenia



Lee AYY & EA Peterson. Blood, 2013; 122: 2310-7

Questions?