Thrombosis and Cancer: Recent Updates

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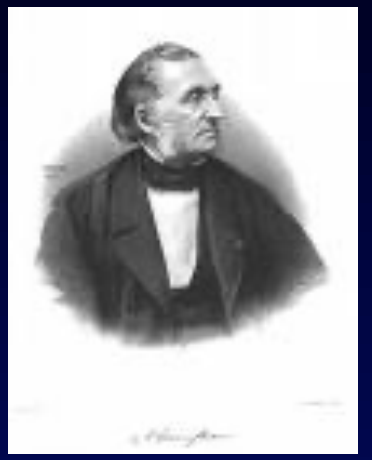
VTE in Cancer Patients

- 5x higher rate of first VTE
- 3x higher rate of post-op VTE
- 3x higher recurrent VTE rate
  including recurrences on anticoagulation



Symptomatic VTE affects 15% of cancer patients

Hutten et al. *J Clin Oncol* 2000;18:3078-83
Donati MB. *Haemostasis* 1994;24:128-31
Lip et al. *Lancet Oncol* 2002;3:27-34

VTE in Cancer Patients

- Second most common cause of death in hospitalized cancer patients
- Accounts for 10% of all deaths in ambulatory patients receiving chemotherapy

Khorana et al. JCO 2006; 24:484
Khorana et al. JTH 2007;5:632

Cancer patients with VTE had a 2.2-fold increase in mortality compared to matched cancer patients without VTE VTE

Sorensen et al. NEJM 2000; 343:1846

Risk Factors for Thrombosis in Cancer Patients

- Type of cancer
  - eg, pancreas 28% vs prostate 2%
- Disease stage
  - advanced stage > early stage
- Inherited thrombophilias
- Immobilization, surgery, indwelling lines, obesity, chemotherapy, age

Levine MN. *Thromb Haemost* 1997;78:133
Caine et al. *Neoplasia* 2002;4:465-73

The Problem

- Prophylaxis is under-utilized in cancer patients (particularly in ambulatory setting)
  - Under-recognition of risks of VTE?
  - Lack of awareness of data and guidelines?
  - Concern about bleeding?

2022 International Clinical Practice Guidelines

- International Initiative on Thrombosis and Cancer – expert working group
- Regularly updated based on published data
  - (2013, 2016, 2019 and 2022)
- Consensus on VTE prophylaxis and treatment in cancer patients
- Recommendations similar to ASCO 2019 Guidelines on VTE Prophylaxis and Treatment

Farge et al. Lancet Oncology 2022; **23:e334**
Key et al. JCO 2019; 38:496

Grading Recommendations

Levels of recommendation

- 1 = Strong
- 2 = Weak
- Guidance = best clinical practice in absence of data, based on experience and consensus

Levels of evidence

- A = High
- B = Moderate
- C = Low
- D = Very low

Prevention of VTE in Cancer Patients

Predictive Model for VTE in Ambulatory Cancer Patients

Patient Characteristics	Risk Score
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, NHL, gyn, bladder, testicular)	1
Pre-chemo platelets > 350K	1
Hgb < 10 or ESA use	1
Pre-chemo leukocytes > 11,000	1
BMI 35 kg/m2 or greater	1

Khorana et al; Blood 2008 111:4902,

Validation of Khorana Score in Ambulatory Patients Initiating Chemotherapy

Score Points	Validation Cohort (N=1365) VTE Risk after 2.5 months	Independent Cohort (N=819) VTE Risk after 6 months
0 (low)	0.3%	1.5%
1-2 (intermediate)	2%	3.8% (1pt); 9.6% (2pts)
3 or more (high)	6.7%	17.7%

Khorana et al; Blood 2008 111:4902

Ay et al; Blood 2010 116:5377

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2022 Guideline Updates on VTE Prophylaxis in Cancer Patients

- Looked at data published up to Jan 1, 2022
- Endorsed by ISTH (International Society of Thrombosis and Hemostasis)
- Available since mid-2022

Recommendations for VTE Prevention in Cancer Patients (CrCl >30)

	Type of Cancer	Duration of Treatment	LMWH/UH	DOAC	Notes
Post-surgery	All	7-10 days	1A	2B	
Post-abd/pelvic surgery	All	28 days	1A	NR	
Hospitalization	All	Until discharge	1B	NR	Fondaparinux 1B
Ambulatory	Advanced pancreatic	On chemo	1A	1B	Low risk of bleeding
Ambulatory	All with Khorana risk score >2	On chemo	NR	1B	Low risk of bleeding

Excludes patients with MM or brain cancer
DOAC = rivaroxaban, apixaban

Farge et al. Lancet Oncology 2022; **23:e334**

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Treatment of VTE in Cancer Patients

2022 Guideline Updates on Treatment of VTE in Cancer Patients

- Treatment recommendations are the same for incidental VTE and symptomatic VTE

- 4 recently published studies confirmed rivaroxaban and apixaban were non-inferior to LMWH for both initial and extended treatment
  - In patients with CrCl >30
  - In patients NOT at high risk of GI or GU bleeding

2022 Guideline Updates on Treatment of VTE in Cancer Patients

- Tx duration with LMWH or DOAC minimum 6 months
- Tx duration with LMWH or DOAC proven beneficial up to 12 months

2022 Guidelines Special Circumstances

- VTE tx in patients with CrCl <30 (guidance)
  - UH followed by warfarin
  - LMWH dose adjusted for anti-Xa levels
- VTE tx in patients with brain tumors (2A)
  - LMWH or DOAC
- VTE prevention in patients underdoing neurosurgery (1A)
  - LMWH/UH post-op for VTE prevention

2022 Guidelines Special Circumstances (Thrombocytopenia)

- VTE treatment (guidance)
  - Full anticoagulation for PLTs > 50,000, and NO evidence of bleeding
  - Case by case decision for PLTs < 50,000
- VTE prevention (guidance)
  - Pharmacologic prophy for PLTs > 80,000
  - Case by case with careful monitoring for PLTs < 80,000

Summary: Therapy for VTE in Cancer Patients

- DOAC (Anti-Xa) and LMWH preferred treatment
  - Continue until cancer treatment is completed and cancer not active
- If warfarin is used in cancer patients (CrCl <30):
  - reduced time in therapeutic range
    - nutrition, drug interactions, etc
  - requires very careful monitoring
  - recurrent VTE more likely

Recurrent VTE in Cancer Patients

	Cancer n=181	No Cancer n=661	HR (95% CI)
Event incidence at 12 months			
Recurrent VTE	20.7%	6.8%	3.2 (1.9-5.4)
Major Bleeding	12.4%	4.9%	2.2 (1.2-4.1)

Prandoni et al, Blood 2002;100:3484

LMWH vs Oral Anticoagulant in Cancer Patients With VTE (CLOT Trial)

- Patients with cancer and first episode of DVT or PE (n = 672)
- All received LMWH (dalteparin) 200 u/kg/d X 5-7 days
- Then were randomized to either:
  - warfarin with target INR 2.5 for 6 months, or
  - dalteparin for 6 months

LMWH vs Oral Anticoagulant in Cancer Patients With VTE (CLOT Trial)

672 Evaluable Patients

	Dalteparin (5–7 days)* + OA (6 mo) (n = 336)	Dalteparin (6 mo)† (n = 336)	*P* Value
Recurrent VTE	**17.4%**	**8.8%**	**.0017**
Major bleeding	**3.6%**	**5.6%**	**.27**
Cumulative mortality	**41%**	**39%**	**NR**

*Dalteparin = 200 IU/kg SC; OA = target INR 2.5

†Dalteparin = 200 IU/kg SC for 1 mo, 150 IU/kg SQ for 5 mo

Lee et al, NEJM 2003;349:146.

LMWH vs Coumadin in Cancer Patients with VTE

- Patients with cancer and VTE (n = 146)
- All received LMWH (enoxaparin) 1.5mg/kg/d initially and then randomized to:
  - LMWH X 3 months, or
  - warfarin INR 2-3 X 3 months
- Study stopped because of slow accrual before achieving desired sample size of 240

LMWH vs Oral Anticoagulant in Cancer Patients With VTE

146 Evaluable Patients

	Enoxaparin + OAC (3 mo) (n=75)	Enoxaparin (3 mo) (n = 71)	*P* Value
Recurrent VTE & Major bleeding	21.1%	10.5%	.09
Cumulative mortality	22.7%	11.3%	.07

Meyer et al, Arch Int Med, 2002;162:1729

FAMOUS Trial

- Large randomized controlled trial
- 382 patients with advanced malignancies randomized to dalteparin 5000u/d x 1 y vs placebo
- Overall effect on survival NSS
  - for patients surviving > 17 months survival at 2 and 3 years better in LMWH group

Kakkar et al, JCO 2004;22:1944.

MALT Trial

- Large randomized placebo-controlled trial
- 302 patients with solid tumors without VTE
  - treatment group received therapeutic dose of LMWH (nadroparin) X 6 weeks
- Overall no survival differences
- For subgroup with better prognosis
  - significant survival advantage

Klerk et al, J Clin Onc 2004