Cancer and Venous Thrombosis: Ongoing Challenges

Thrombosis UK, Edinburgh
May 5, 2016

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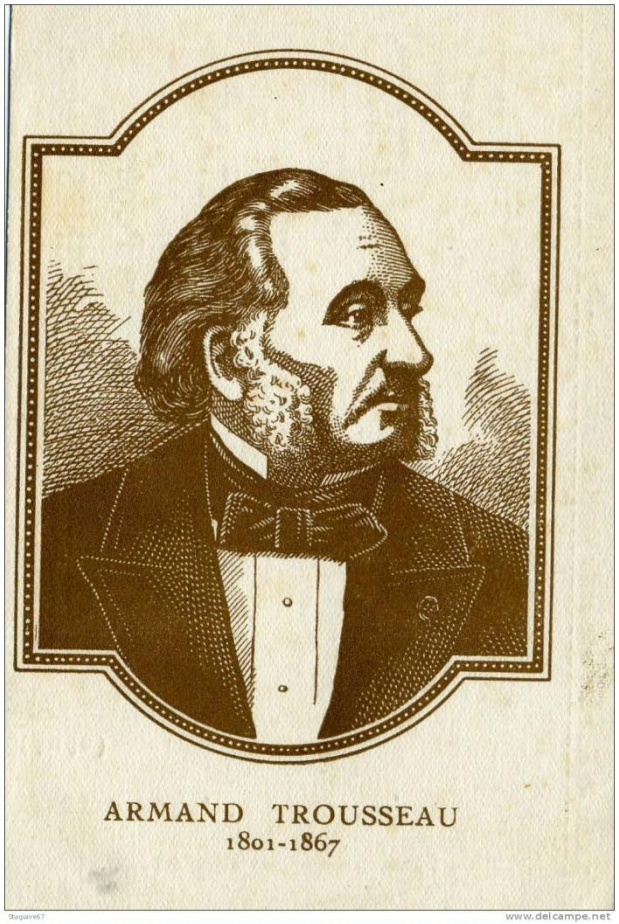
- No disclosures to announce

Trousseau Syndrome



French internist

Described recurrent episodes of vessel inflammation due to blood clots at different locations over time - "thrombophlebitis migrans"

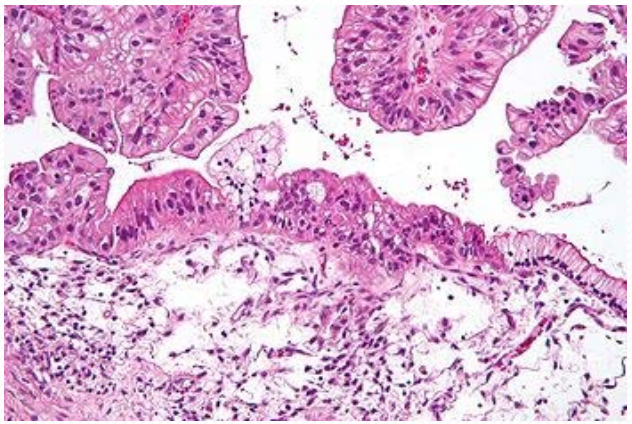
Cancer and Venous Thrombosis

- Various mechanisms well evaluated
  - Shared risk factors e.g. smoking
  - Tissue factor expression on tumour cells

Tissue factor is a protein (CD142) found in sub-endo -thelial tissue and leucocytes necessary for thrombin generation

Cancer/VTE - mechanisms

- Prothrombotic properties of mucins produced by cancer



Micrograph of a mucin-producing ovarian tumour

- Creation of a pro-angiogenic state
- Contributing factors such as surgery, chemotherapy, radiotherapy and sepsis, direct invasion of blood vessel walls and obstruction

Cancer and Venous Thrombosis

- Certain cancers hold a strong association with venous thrombosis
  - Lung, brain, pancreas, ovary, stomach, kidney, lymphoma
  - In association with venous thrombosis, overall prognosis poorer

Today's Talk at a Glance

- How we treat symptomatic cancer-associated venous thrombosis
  - The evidence behind low molecular weight heparin as the treatment of choice
  - Pros and cons, and alternatives
  - How to manage a recurrence of thrombosis when a patient is fully anticoagulated
- How we approach the management of "incidental" venous thrombosis
- Should we screen for cancer in patients with unprovoked venous thrombosis?

Treating symptomatic cancer associated venous thrombosis

- Low molecular weight heparin is the current treatment of choice
  - CLOT trial (Lee et al, 2003) demonstrated that treatment with 6 months LMWH resulted in a significantly lower recurrence rate after 6 months than treatment with warfarin (INR adjusted)
  - Supported by 2 other trials (Meyer et al, 2002 and Hull, 2006)
  - Each trial used a different brand of LMWH

Lee et al. 2003 NEJM 349 146-153
Hull et al 2006 Am J Med 119 1062-72
Meyer et al 2002 Arch Int Med 162 1729-1735

Treating symptomatic cancer associated venous thrombosis

- In CLOT a full dose (200 units/Kg dalteparin sc once daily) given for one month followed by a dose reduction of 70-80% for months 2-6
- None of the studies demonstrated increased bleeding
- No direct comparison of 3 months versus 6 months duration

Barriers to use of LMWH

- The need for daily subcutaneous injection
- Renal function must not be impaired and body weight maintained
  - LMWH dose needs reduced in renal impairment (each brand differs but dose needs reduced if creatinine clearance <30ml/min) and may require LMWH antiXa monitoring
  - In patients with very low body weight, the dose of LMWH may need reduced

Barriers to use of warfarin

- Numerous drug interactions
- Need for frequent INR monitoring
- Slow onset and offset of action
- Oral administration – may be difficult in patients undergoing chemotherapy (e.g. mucositis, nausea)

DOACs (direct oral anticoagulants)

- Clinical trials of dabigatran, rivaroxaban, apixaban and edoxaban for venous thrombosis contained only a small number of a patients with cancer.
- No comparison with LMWH has been made
- May be similar in efficacy towarfarin
- Current 2015 BCSH guidance recommends "…for patients who cannot have or are unable to tolerate subcutaneous low molecular weight heparin we suggest warfarin or a DOAC…."

Watson et al. 2015 BJ Haem 170 640-8

Recurrent VTE

- Reported in 6-9% patients with cancer associated VTE on LMWH, and 10-17% patients on warfarin
- Limited evidence about best approach
- If on warfarin, then switch to full dose LMWH

Recurrent VTE

- Patients receiving dalteparin at 75% of normal dose, after 1st month of treatment, should be increased to usual weight-based dose
- If already on LMWH full dose, some evidence to increase dose by 20-25% (Carrier et al, 2009)
- If evidence of ongoing thrombosis then increase LMWH dose and monitor LMWH antiXa levels
  - What levels?
  - 1.6 – 2.0 for once daily regimen, and 0.8 – 1.0 for twice daily regimen
  - Benefit of dividing doses unclear
- Use of IVC filter not recommended for recurrence alone

Watson et al. 2015 BJ Haem 170 640-8

Incidental venous thrombosis

Incidental venous thrombosis

- In patients who had undergone CT scanning of chest for reasons other than PE estimated prevalence of incidental PE: 2.6%
- Higher rates in cancer patients with estimated prevalence of 3.1%
- Estimated that in 40-50% of cases, patients were not truly “asymptomatic” but had the symptoms of venous thrombosis either overlooked, or attributed to the underlying cancer.

- Natural history poorly understood and limited studies, no randomised controlled studies

- Seems to be an overall higher mortality in cancer patients irrespective of incidental or symptomatic presentation

Incidental venous thrombosis (cont^{d})

- Studies of small groups of patients (cohorts) who were either of too high bleeding risk to give anticoagulation, or symptoms had not been recognised, show a symptomatic recurrent thrombosis risk of 5-11% within 3 months

- Current American College of Chest Physicians (ACCP) and BCSH Guidance(2015) favour anticoagulant therapy for incidental venous thrombosis if diagnosis is secure

Watson et al. 2015 BJ Haem 170 640-8; Kearon et al 2012 Chest 141 (2 Suppl) e419S-494S

Screening Strategies

Screening Strategies

- Unprovoked VTE may be an early sign or “occult” sign of cancer; currently a diversity of practice regarding screening in patients with idiopathic VTE

- Some experts have opted for extensive screening for cancer in such patients

- Potential harms from this approach include procedure-related morbidity, the psychological impact of false-positive tests and the cost of screening

- Early detection of cancer is only of benefit if there is potentially curative therapy

Screening for Occult Malignancy in Unprovoked Venous Thromboembolism: SOME Trial

- SOME Investigators sought to assess a screening strategy for occult cancer
  - Multicentre Canadian, open-label, RCT
  - Randomly assigned to undergo limited occult cancer screening (basic blood testing, CXR, screening for breast, cervical and prostate cancer)or occult cancer screening plus CT

Carrier et al. NEJM 2015 373 697 - 704

SOME Trial

- Primary outcome measure was confirmed cancer missed by the screening strategy and detected by the end of 1 year follow up

- (limited screening plus CT: virtual colonoscopy and gastroscopy, biphasic enhanced CT of liver, parenchymal pancreatography, uniphasic enhanced CT of distended bladder: standardised)

Carrier et al. NEJM 2015 373 697 - 704

SOME Trial

- Results: 854 pts underwent randomisation
  - 33 (3.9%) had a new diagnosis of occult cancer between randomisation and follow up at 1 yr
    - 14of 431 pts in the limited screening group
    - 19 of 423 patients in the limited screening plus CT group
    - P=0.28

Carrier et al. NEJM 2015 373 697 - 704

SOME Trial

- In the primary outcome analysis, 4 occult cancers (29%) were missed by the limited screening strategy, whereas 5 (26%) were missed by the strategy of limited screening plus CT (p=1.0)

- There was no significant difference between the 2 study groups in the mean time to a cancer diagnosis (4.2 months in the limited screening group and 4.0 months in the limited screening group plus CT group, p=0.88) or in cancer-related mortality (1.4% and 0.9%, p=0.75).

Carrier et al. NEJM 2015 373 697 - 704

SOME Trial

- Conclusions: the prevalence of occult cancer was low among patients with a first unprovoked VTE. Routine screening with CT abdo/pelvis did not provide a clinically significant benefit.

Carrier et al. NEJM 2015 373 697 - 704

Who do I screen?

- Patients presenting with bilateral DVTs
- Patients who have had recurrent venous thrombosis
- Patients who have high D-dimer levels (>4000 mcg/L equivalent units)

Summary

- LMWH is currently the **treatment of choice** for patients with cancer -associated venous thrombosis
- The position of DOACs is currently unclear, but may play a role if a patient is intolerant of LMWH
- Beyond 6 months, **optimal management needs to be tailored to the patient**, and his/her response to cancer therapies and overall prognosis, plus patient wishes

Summary

- Management of **recurrent venous thrombosis** involves switching to LMWH if on warfarin or another anticoagulant, and optimising the dose using LMWH antiXa levels if necessary

- International consensus is to treat **incidental thrombosis** when found on staging scans

- Recent high quality evidence from clinical trials examining **screening strategies** show that routine screening over and above taking a conventional history and examination plus routine bloodwork does not provide a clinically significant benefit, and may help to reduce unnecessary anxiety for patients