Management of Cancer Associated Thrombosis (CAT) - where data is lacking

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Contents

- Overview of the statistics and aetiology for Cancer Associated Thrombosis (CAT)
- When should we use CT scans to detect cancer in those with unprovoked VTE?
- Thrombocytopenia in CAT patients
- Recurrent VTE in CAT patients
- Bleeding in CAT patients
Cancer-associated VTE  *(Thein et al 2016)*

- Cancer-associated thrombosis (CAT) accounts for about 20% of all thrombosis worldwide.
- Risk for VTE in cancer patients is 4-7 times higher than baseline.
- Risk for recurrent VTE, 3 times higher in cancer patients compared to those without Cancer.
- Survival of cancer patients with VTE, lower than that of patients without VTE - ?effects of VTE or increased tumour aggression
Why does Cancer increase the risk for VTE? (Watson H, BCSH 2015)

- Expression of tissue factor and cytokines on tumour cells & microparticles
- Interaction between tumour cells and endothelium, causing endothelial damage & platelet activation
- Prothrombotic properties of Mucins
- Mass effect impairing venous return
- Surgery, IV catheters, chemoradiotherapy & intercurrent medical problems eg infection
VTE & Cancer

• VTE is second most common cause for death after the malignancy itself in cancer patients (Korhana 2010)

• Highest risk sites are: Lung, brain, pancreas, stomach, ovary, kidney, Lymphoma & Myeloma

• VTE + Cancer also leads to increased risk for hospitalisation, bleeding, recurrent VTE on anticoagulants (Trujilo-Santos 2008)
Investigating patients with unprovoked VTE for Cancer - background

• Historically, ‘unprovoked’ VTE associated with occult cancer in 10% of patients within a year (Carrier, 2008)

• NICE: CG 144 (2012) states that in patients >40 years, with first unprovoked VTE, CT scan of abdomen & pelvis (& mammograms in women) is recommended.

• More recent data has placed the incidence of occult cancer lower at 4%
CT scans for unprovoked VTE

- CT scans convey a high exposure to radiation - equivalent to 234 CXRs or 39 mammograms
- Psychological and biological morbidity may be associated with further investigations
- Significant cost associated with false positive findings (‘incidentalomas’) requiring further investigations
- Incorrect to assume that earlier detection results in improved clinical outcomes
Suggested routine screening for unprovoked VTE

- History: Older age, smoking
- Worrying symptoms:
  - Weight loss
  - GI bleeding
  - Constitutional symptoms
- Physical examination
- CXR
- Basic blood tests:
  - FBC, Ca, LFTs, PSA, Igs,
- Urinalysis
Cancer screening in VTE (SOMIT study)
2 years follow-up

Screened group

- 13/99 detected occult cancer by 1/12
- 1 cancer became apparent later
- Cancer related mortality 2.0%

Non-screened group

- 10/102 developed cancer later - mean of 11.6 months
- Cancer related mortality 3.9%

Piccioli et al JTH 2004
## VTE cancer screening: 630 idiopathic VTE

<table>
<thead>
<tr>
<th></th>
<th>Extensive Screen</th>
<th>Standard Care</th>
<th>HR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cancers</td>
<td>8.8%</td>
<td>7.3%</td>
<td></td>
</tr>
<tr>
<td>Curable Ca</td>
<td>3.8%</td>
<td>3.8%</td>
<td></td>
</tr>
<tr>
<td>All cause mortality</td>
<td>7.6%</td>
<td>8.3%</td>
<td>1.22 (0.7-2.2)</td>
</tr>
<tr>
<td>Cancer death</td>
<td>5%</td>
<td>2.8%</td>
<td>1.8 (0.75-4.3)</td>
</tr>
</tbody>
</table>

Associated cost analysis: Routine screening = E165 v Extensive screening = E530 mainly investigating from false positive findings (86 patients)  

*Van Doormaal et al JTH 2011*
Patients with unprovoked VTE should undergo a thorough medical history and physical examination, basic laboratory investigations (complete blood counts, metabolic profile and liver function tests) and chest X-ray.

We suggest that if not up-to-date, patients undergo age and gender-specific cancer screening (i.e. cervical, breast, prostate and colon).
Limited v Extensive Cancer screening in unprovoked VTE *(Khan F, BMJ 2017)*

<table>
<thead>
<tr>
<th>Study</th>
<th>Study &amp; (Size)</th>
<th>Frequency of occult Cancers diagnosed</th>
<th>Cancer deaths</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robertson 2015</td>
<td>Cochrane review of 2 studies (396)</td>
<td>OR 1.32 (P=0.5)</td>
<td>OR 0.49 (P=0.26)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Carrier 2015</td>
<td>RCT (845)</td>
<td>19 v 14 (P=0.28)</td>
<td>1.4% v 0.9% (P=0.75)</td>
<td>High</td>
</tr>
<tr>
<td>Robin 2016</td>
<td>RCT (394)</td>
<td>4 v 11 (P=0.065)</td>
<td>2.5% v 1.0%</td>
<td>High</td>
</tr>
<tr>
<td>Prandoni 2016</td>
<td>RCT (195)</td>
<td>8 v 10 (P=0.81)</td>
<td>4% v 2%</td>
<td>Moderate</td>
</tr>
<tr>
<td>Salih 2016</td>
<td>Meta-analysis unpublished (1250)</td>
<td>OR 1.36 (P=0.25)</td>
<td>OR 0.57 (P=0.22)</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
What should we tell patients currently?

- NICE states: ‘Consider’ screening for cancer with CT.
- Most recent data suggests 1 in 25 people with unprovoked VTE may have underlying cancer.
- Limited evidence to support the benefit of extensive screening, particularly involving harm from ionising radiation.
- All such patients should receive routine cancer screening plus additional investigations depending on signs and symptoms.
- If patients opt out of CT scanning, maintain low threshold for suspicion of cancer.
Bleeding  Thrombosis
Thrombocytopenia *(BCSH, 2015)*

- When present, the risk-benefit balance of anticoagulation needs reassessment.

- In first 3 months after VTE, risk for recurrence is higher - every effort should be made to maintain safe administration of therapeutic anticoagulation.

- Full anticoagulation is probably safe when platelets are >50x10⁹/l *(Carrier 2013)*
Thrombocytopenia in CAT: Considerations

- Causes (consider potential to reverse):
  - Chemotherapy effect
  - ITP
  - DIC
  - TTP
  - HITT

- Increased risks for bleeding
  - Advanced age,
  - Renal failure
  - Abnormal clotting eg Vit K deficiency
Thrombocytopenia, Cancer & VTE  BCSH, 2015

- Support platelet count (to >50 x10⁹/l) to allow full dose anticoagulation to continue through highest risk period for recurrence (3/12). (2D)

- Temporary IVC filter should be considered if thrombocytopenia is persistent and difficult to overcome or other bleeding risk is present.

- If platelet count cannot be increased, then consider giving 50% dose LMWH with platelets 25-50 x10⁹/l with frequent assessment (2D)

- Below 25 x 10⁹/l, withhold anticoagulation (1D)

- Some evidence that prophylactic LMWH dose may be beneficial (Drakos, 1992)
Thrombocytopenia in patients with CAT

(Lee A, Blood 2013 122:2310-2317)

A

Acute VTE event

- Platelet count $\geq 50 \times 10^9$/L
  - Weight-based full dose LMWH

- Platelet count $< 50 \times 10^9$/L
  - Transfuse to maintain platelet count $\geq 50 \times 10^9$/L
    - Weight-based full dose LMWH
  - Platelet count 20-50 $\times 10^9$/mL
    - Half-dose LMWH
  - Platelet count $<20 \times 10^9$/mL
    - Hold anticoagulation

B

Subacute/Chronic VTE event

- Platelet count $\geq 50 \times 10^9$/L
  - Weight-based full dose LMWH

- Platelet count 20-50 $\times 10^9$/L
  - Half-dose LMWH

- Platelet count $<20 \times 10^9$/L
  - Hold anticoagulation
Risk of Bleeding associated with Anticoagulation in patients with CAT

- Increased risk for bleeding in patients with CAT receiving VKA - 12%. 1/3 in initial stage of anticoagulation (Prandoni, 2002)

- No correlation between risk for bleeding and INR level in patients with cancer (Paleretti 2000)

- Similar bleeding rates: LMWH & VKA (Hull 2006)

- Bleeding risk in cancer patients dependent on many patient factors: Type and location of Ca, need for biopsies, thrombocytopenia, DIC, renal & liver impairment and sepsis.
Management of Bleeding associated with anticoagulation in patients with CAT (BCSH)

- Individual assessment of bleeding versus recurrent thrombotic risk before starting anticoagulation.
- Minor bleeding: continue full dose anticoagulation with close follow-up.
- In patients with moderate to serious bleeding or absolute contraindications to anticoagulation: withhold and consider IVC filter.
- Platelet transfusions may allow anticoagulation according to previous flow-chart.
Recurrent VTE in cancer patients

- Cancer confers higher risk for recurrent VTE than those without cancer (4-fold increase)
  - Both during & after anticoagulation
- Assess for compliance with anticoagulation
- Assess for mechanical compression of large vein from tumour masses
- Consider HITT
- Registries show very heterogeneous approach to recurrent VTE in patients with cancer
Anticoagulation for Recurrent VTE in CAT

- The optimal duration of primary anticoagulation in CAT is unknown (*NICE suggests 6 months & review*)

- Patients with recurrent VTE can either be:
  - Bridged with LMWH if on VKA
  - Transitioned to treatment dose LMWH if already using prophylaxis
  - Treated with full dose escalation (e.g., Enoxaparin 1mg/kg twice daily)

- If primary anticoagulation discontinued because of bleeding risk, consider IVC filter. This may not reduce recurrence risk (*Decousus 1998*)
Cancer Patients with Symptomatic Recurrent VTE

(Korhana A. J Thromb Thrombolysis. 2016)

- Therapeutic anticoagulation with an agent other than LMWH: Transition to therapeutic LMWH.
- Optimal anticoagulation with LMWH: Continue LMWH at a higher dose, starting at an increase of ~25% of the current dose.
- Non-therapeutic dose at the time of recurrence: Switch to therapeutic dose of LMWH.
- Do not use IVC filters except in presence of absolute contraindications to anticoagulation (e.g. active bleeding). Retrievable filters should be used.
Recurrent VTE in CAT  (Lee A, Blood 2013)

Recurrent VTE during anticoagulant therapy

Exclude HIT and Non-compliance

Sub-therapeutic anticoagulation

VKA

Bridge with LMWH or UFH and resume VKA (target INR 2-3)

LMWH

Switch to full dose LMWH

Therapeutic anticoagulation

VKA

Shift to full dose of LMWH

LMWH

Increase LMWH by 20-25%

Reassess in 1 week

No Improvement

Peak anti-Xa level

Adjust LMWH dose to target peak anti-Xa level

OD peak 1.0-2.0 U/mL

OR

BID peak 0.8-1.0 U/mL
Summary

- Cancer increases VTE risk 4 fold
- Those with cancer & VTE have worse prognosis
- CT scanning for patients with unprovoked VTE identifies cancer in about 4% of people. Current advice is that routine screening and clinical history generally sufficient to rule out cancer.
- Bleeding is generally higher in anticoagulated Cancer patients
- Thrombocytopenia is relatively common and needs monitoring in those anticoagulated with CAT, with platelet support if necessary
- Bleeding needs careful assessment of patient and IVC filter if anticoagulation essential
- Recurrent VTE requires increased anticoagulation where possible
Preventing Catheter-related thrombosis

- Prospective study (Bern 1990): 82 patients showed benefit of low dose warfarin in reducing risk of catheter-related thrombosis.

- WARP study (Young 2009): RCT of 812 patients randomized to warfarin or no therapy found no difference in risk for catheter-related thrombosis.

- Cochrane review (Akl 2011): demonstrated that neither warfarin or prophylactic LMWH reduced risk for catheter-related thrombosis.

- Routine anticoagulation is not recommended (1A)
Thromboprophylaxis in cancer patients admitted to hospital

- Patients with active cancer should be considered for thromboprophylaxis when admitted to hospital, as long as benefit outweighs risk for bleeding. (Kahn, 2012)
- ‘Active Cancer’ should be considered in those diagnosed or treated within the previous 6 months or recurrent / metastatic cancer.
Thromboprophylaxis in ambulatory Cancer patients

- Cochrane review of 9 RCTs (3538 patients) in cancer patients, comparing controls against LMWH (8) or warfarin (1), found reduction in VTE risk with LMWH, without a significant increase in bleeds (DeNisio, 2012)

- 60 patients treated to prevent 1 VTE, indicates that TP should not be routine but considered in those with particularly high VTE risk (BCSH, 2015)

- Identification of these high risk patients may be done using scoring systems (Khorana 2008, Farge 2013)
## Predictive model for Chemotherapy-related VTE (Khorana et al 2008)

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Risk score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very high risk for VTE: stomach &amp; pancreas</td>
<td>2</td>
</tr>
<tr>
<td>High risk for VTE: Lung, NHL, Gynae, bladder, testicular</td>
<td>1</td>
</tr>
<tr>
<td>Pre-chemotherapy platelet count</td>
<td>1</td>
</tr>
<tr>
<td>Haemoglobin level &lt;100g/l or use of ESA’s</td>
<td>1</td>
</tr>
<tr>
<td>Pre-chemotherapy leucocyte count &gt;11 x 10⁹/l</td>
<td>1</td>
</tr>
<tr>
<td>Body Mass Index &gt;35 kg/m²</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th>Actual Score</th>
<th>Thrombosis rate per 2-5 months (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
<td>0.3 - 0.8</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1-2</td>
<td>1.8 - 2.0</td>
</tr>
<tr>
<td>High</td>
<td>&gt;2</td>
<td>6.7 - 7.1</td>
</tr>
</tbody>
</table>
Incidental VTE

- Cancer patients with incidental PE or DVT should be therapeutically anticoagulated as for symptomatic disease (1C)
- In Plymouth about 50 incidental VTE events per year for last 6 years.
- >75% of these are cancer-related events.
- >75% dead one year later.