Cancer and Venous Thromboembolism

- Objectives
  1. Epidemiology of thrombosis in patients with malignancy
  2. Anticancer agents and thrombosis
  3. Current treatment protocols at UHN
  4. Prevention of DVT
  5. Asymptomatic DVT
  6. Newer antithrombotic agents

Epidemiology of Thrombosis in Patients with Malignancy

- 4-12% of pt with VTE have concomitant cancer, higher with idiopathic, often advanced ca
- Numerous articles suggest – hx, O/E, lab tests and basic imaging are sufficient and cost effective (~80%)
- In patients with malignancy – second leading cause of death
- Compared with non-cancer patients risk of symptomatic VTE, 6-7 x higher in cancer pt with similar risks
- Until recently incidence and time course unknown, small cohort studies incidence ~4% among various pt groups

Determinants of Risk of VTE in Cancer

1. Tumour stage
2. Tumour type
3. Anticancer therapy
4. Surgery
5. Prothrombotic abnormalities

Chew HK, Arch Int Med, Feb 2006

- California Cancer registry, assessed incidence and timing of VTE within 1-2 years after after diagnosis in 12 different malignancies
- 1.6% pt developed VTE within 2 yr (12% at time of diagnosis, 88% subsequently)
- Metastatic disease at diagnosis strongest prediction of VTE (56% of concurrent) 5-20x higher than local disease
- Pancreatic > stomach > bladder > uterine > renal > lung
- After adjustment for age, race, stage at time of diagnosis: within 1 yr – VTE diagnosis significant predictor of death

Blom et al, JAMA, Feb 2005

- Netherlands - 3220 consecutive pt with VTE
- 7x ↑ risk of VTE with malignancy
- Pt with hematologic malignancies highest risk > lung > GI
- Risk highest in first few months, those with mets
- Factor V Leiden 12x risk
4. Surgery
- 2x greater risk in cancer/non-cancer patients
- Some studies up to 3-4% cystectomy, neurosurgery

5. Prothrombotic abnormalities
- immobilization, age, hypercoag states
- FVL had 12x risk in cancer versus non-cancer pt, same for prothrombin mutation

Recurrence clots
- after discontinuing warfarin, 2x risk of recurrence in cancer patients
- cancer pt who have DVT – 3x ↑ risk of recurrence in first 12 months compared to those without
- Prandoni (2002 – 6.8% recurrence in non-cancer pt versus 21% in those with cancer)

**Prognosis**
- Developing VTE predicts worse prognosis
- 1 yr survival 12% in pt with cancer and VTE, compared to 36% without VTE (Danish Registry)
- Other studies more than 2 fold higher mortality

**Anticancer Agents and Thrombosis**
- Chemotherapy well established as an independent risk factor for thrombosis and presently the most changing determinant
- Annual incidence ~11% of VTE in ca pt on chemo, climb as high as 20% depending on type (cancer pt 4x ↑ risk VTE, 6x when chemo)
- **Breast cancer**
  - Best evidence for role of chemo in VTE
  - DVT early breast ca – 1%, if adjuvant chemo 2-10%
  - Levine (Thromb Hemost 97)
  - stage II breast ca – CMFVP + doxorubin + tamoxifen
  - 7% during chemo none while off. Stage IV disease 18%
  - more recent Epirubin/Cyclo – 10%

**Tamoxifen**
- Women risk ↑ 2-3x N (similar to BCP/HRT)
- In early stage postsurgery 1.5 – 7 ↑ risk (post menopausal 3x higher than pre)
- When taken with chemo risk 3-8x ↑ than tamoxifen alone, 3-5x greater than chemo alone and 20x greater than no Rx
- Aromatase inhibitors – 1-2% incidence DTE, risk lower than tamoxifen

**Thalidomide**
- Monotherapy - ~5% risk, with dexamethasone 10-20% and with concurrent chemo – 20-40%
- Prophylactic LMWH may reduce risk, not low dose warfarin, ? role ASA
- Thalidomide analogues – Revlimid
  - ? thrombogeneity appears ↑ with dexamethasone, several studies suggest ASA works – need for randomized
• Cisplatinum - germ cell tumors – 8.4%, lung cancer 17.6%, cervical cancer 16.7%
• L-asparaginase 4-14% in adults
• Bevacizomib colorectal 9% vs 19% (FU/LU)
  - other studies no ↑
EPO – definitely ↑ risk esp ↑ Hb
Radiation – theoretical but no reliable studies

Treatment Protocol - UHN
• Cancer patients often ↑ risk of bleeding, VTE additional negative impact in quality of life, overall ↑ mortality compared to ca patient without VTE
• TGH Thrombosis Unit, cancer pt ~50% of new pt
• Symptomatic verses asymptomatic

Risk of Recurrence
• Initial studies IV hep/LMWH, retrospective analysis of 3 months Rx → recurrence 27/100 pt years in cancer verses 9/100 pt years non-cancer, bleeding risk 6x ↑, 13/2 per 100 pt year
• Prandoni - cohort 842 pt - recurrence 20% / 7% (cancer/non-cancer), bleeding 12.5%/5%

Initial Rx
• LMWH (outpatient) – standard initial Rx for all DVT/PE pt except renal failure/high bleeding risk (up to 80%)
  - some evidence twice daily LMWH better in cancer but no formal studies
  - no role for IVC filters in most pt

Long Term Therapy
• Several previous studies – not specifically on cancer pt, no definite conclusion
• 2 more recent studies – changed dramatically the way we treat pt
  Meyer et al. Arch Int Med 2002
  - warfarin verses enoxaparin daily x3 months
  - Warfarin – 21% major outcome events verses 10% LMWH
  - 6 deaths due to warfarin verses 0 in LMWH

• Lee et al. NEJM, 2003 (Clot Study)
  - Fragmin verses warfarin x 6 months
  - 15.7% recurrent DVT in warfarin verses 8.0 on LMWH
  - major bleeding 3.6% warfarin, 5.6% LMWH (not significant)
Therefore LMHW – standard Rx for cancer pt
  - reduces recurrence, no ↑ risk bleeding
### ACCP Guidelines

- 3-6 months of LMWH, grade 1A
- Consider therapy indefinitely or until cancer resolved (grade 1C)

### ASCO Guidelines (2007)

1. LMWH – preferred for initial 5-10 days
2. LMWH – for 6 months preferred over OA (INR 2-3)
3. After 6 months – continue Rx for those with metastatic disease or those on chemotherapy
4. IVC filter only for those with contraindication to anticoagulants or recurrent DVT despite adequate therapy
5. CNS malignancy – watch for bleeding
6. Elderly same as young

### TGH

- All cancer pt offered LMWH x 6 months
- Monitor platelet count weekly x3 then monthly
- Dose reduction – for creatine clearance <30
- After 6 months, ? based on risk of bleeding verses recurrence
- No clinical trials – but definitely ↑ risk of recurrence
- Recurrence depends on presence of disease, chemo, level of mobility, if clot still present
- Recommend ongoing Rx for at least 6 months after chemo/radiation depending if any disease present. If no disease – suggest stop Rx. If disease still present – offer ongoing LMWH or oral anticoagulants
- ? Value of hypercoag workup

### Prevention of DVT

- ACCP Guidelines
  1. Cancer & surgery – guidelines as relevant to surgery itself
  2. Bedridden with acute illness – routine medical prophylaxis
  3. Indwelling catheters, not use prophylactic LMWH (1B) or minidose warfarin (1B)
  4. Chemo/hormone therapy – recommend against routine prophylaxis
  5. Survival – recommend against routine use

### Prevention of DVT – cont’d

- ASCO Guidelines
  1. Anticoagulants are not recommended to improve survival
  2. Hospitalized pt should be given VTE prophylaxis
  3. Surgical pt at least 7-10 days post-op prophylaxis
  4. Routine prophylaxis not recommended, but thalidomide/lenolidomide with chemo or dex should receive LMWH or warfarin (INR 1.5)

### Asymptomatic DVT/PE

- At UHN asymptomatic DVT/PE up to 25% of patients seen in clinic
- Am J Roentgent, July 2007
  - 435 elective screening CT scans
  - prevalence of 6.8% unsuspected iliofemoral DVT, 1.2% unsuspected common iliac, 0.3% IVC DVT, 3.3% PE, overall 6.3%
  - more common in inpatients and RR 1.6 with advanced disease
  - other studies – unsuspected PE 1.5% routine CT chest with rates 2.6 – 3.4% in malignancies
• JCO, Oct 2006
  - 59 pt unsuspected PE
  - up to 75% had symptoms – fatigue and SOB
  - 20% had previous VTE
  - no diff if chemo; central line or EPO

Asymptomatic PE

• ACCP Guidelines
  1. Review CT scans to see if findings are convincing
  2. Recommend same treatment as with symptomatic PE (1C)
     - In Toronto variable approaches, especially to subsegmental PE’s. (Options)
       1. Full dose treatment
       2. Dopplers – if negative, no treatment
       3. Role for prophylaxis

Newer Antithrombotic Agents

Present Medications
- Warfarin/LMWH

Newer Medications
Indirect AT-Mediated
- Fondaparinux (sc)
- Idraparinux(sc)
- Dabigatran Extilate (oral)

Direct(Factor Xa)
- Rivaroxaban
Central Venous Catheters

- Initial small studies suggested coumadin 1 mg daily or LMWH prophylaxis reduced thrombosis
- Recent meta analysis for cancer and central lines – low dose warfarin 6.34% verses 7.5%
- Cochrane Database Systemic Review 2007
  - LMWH trend to reducing DVT – not statistically significant
  - Warfarin not significant

Central line thrombosis – up to 37% venography, lower in ultrasound
- ? how long to treat
- Remove line or not?
- Risk of embolization?

Cancer Survival and anticoagulants

- Theoretical evidence that anticoagulants exert negative impact on tumour angiogenesis by interfering with thrombin activity or tissue factor activation
- Meta analysis of early studies – UFH/LMWH suggested survival benefit of LMWH independent of PE/bleeding
- FAMOUS study – J Clin Onc 2004
  - 385 pt – Fragmin 5000 unit/placebo x 1 yr
  - Placebo group 41%/18%/12%: 1, 2, 3 yr
  - Survival verses fragmin 46%/27%/21% - not significant
  - 2 further studies variable results

Cancer Survival and anticoagulants – cont’d

- Recent lung cancer – J Thromb Hemost 2004
  - Chemo ± LMWH in small cell lung ca significant
  - ↑ progression free and overall survival
- Cochrane Review – Sept 2007
  - LMWH – 8% reduction in 1 yr mortality, warfarin 3%, bleeding 1% in LMWH, higher in warfarin