Secondary prophylaxis of venous thromboembolism (VTE) in cancer patients

HOT SPOT

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Background

Deep vein thrombosis and/or pulmonary embolism (VTE) is a common and important complication in patients with cancer

- Occurs in 4% to 20% of cancer patients in course of their disease
- Second most common cause of death in cancer patients
- Risk of VTE is four to seven times higher in cancer patients compared to general population
- Cancer therapy: surgery, chemotherapy, supportive therapy (e.g. Erythropoietin), etc., adds additional risk burden of VTE
- Cancer patients with VTE have a worse survival than cancer patients in general (One-year survival: Cancer in general ~36%, Cancer and VTE ~12% [Sorenson et al., NEJM 2000])

Treatment of acute VTE: Two phases

- **Initial treatment:** to reduce clot activity and risk of further clot extension and embolism: for 5 to 7 days until switched to Secondary Prophylaxis (see below).
  - Therapeutic dose low molecular weight heparin (LMWH) subcutaneously (preferred)

    or

  - Intravenous unfractionated heparin (UFH) in therapeutic doses: Target aPTT: 1.5–2.5 times mean normal lab control value or upper limit of normal range
- **Secondary Prophylaxis:** Prevention of VTE recurrence: for three months ➔ indefinite duration
  - Therapeutic dose low molecular weight heparin (LMWH) s.c. (recommended)

    or

  - Warfarin or other Vitamin K antagonist (VKAs): Target INR 2.0–3.0

Risk of recurrent VTE and bleeding on warfarin (VKA) anticoagulation

• Cancer patients on oral anticoagulants (VKAs) for secondary prophylaxis have:

- Higher risk of recurrent VTE: 21% in cancer patients compared to 7% in noncancer patients
  Hazard Ratio 3.2
- Higher risk of major bleeding: 12% in cancer patients compared to 5% in noncancer patients
  Hazard Ratio 2.2 (Prandoni et al., 2002)

Warfarin (VKA) therapy in cancer patients is problematic

- Higher VTE recurrence and bleeding risks
- Cancer and chemotherapy: Drug interactions, vomiting, malnutrition, liver dysfunction, etc., leads to unstable INRs = unpredictable anticoagulation
- Need for frequent laboratory testing for repeat INRs + poor venous access = poorer quality of life
- Difficulties with rapid reversing and resuming anticoagulation for repeated interventional procedures for cancer management

Advantages of LMWH for secondary prophylaxis

- Stable therapeutic levels on fixed daily dosing (weight based)
- Few drug interactions, no dependence on nutritional status or dietary influence
- No need for routine lab monitoring
- Rapid reversal and resumption of anticoagulant effect accommodates repeated interventional procedures or thrombocytopenia
- Effective in cancer patients with "warfarin failure" (~ 20% recurrence rate)

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Secondary prophylaxis studies in cancer patients with VTE LMWH versus oral Vitamin K antagonists (VKA)—Warfarin

CLOT study: Lee et al., *NEJM, 2003*, LMWH—Dalteparin

- VTE recurrence rate: Warfarin 17% versus LMWH 9% p=.002 Risk Reduction 49%
- Major bleeding rates: Warfarin 4% versus LMWH 6%—equivalent rates

LITE study: Hull et al., *Am J Med, 2006*, LMWH—Tinzaparin

- VTE recurrence rate: Warfarin 16% versus LMWH 7% p=.044 Risk Reduction 56%
- Major bleeding rates Warfarin 7% versus LMWH 7%—equivalent rates

CANTHENOX study: Meyer, *Arch Int Med, 2002*

- small study showed no difference in VTE recurrence rates, but more bleeding in warfarin group

Drug agency approval

- **U.S. Food and Drug Administration approval—May 2007:** Dalteparin Sodiun injections for extended treatment (6 months) of symptomatic VTE to reduce the risk of recurrence of VTE in cancer patients
- **Canadian Health Protection Branch approval—October 2004:** Fragmin (Dalteparin Sodium injection) is approved for: Extended treatment of symptomatic venous thromboembolism (6 months) to prevent recurrence of venous thromboembolism in patients with cancer

Guideline recommendations for secondary prophylaxis/ extended treatment of VTE in cancer patients

- **American Society of Clinical Oncology—***J Clin Oncol, Dec. 2007*
  - LMWH is the preferred approach for the initial 5 to 10 days of anticoagulant treatment of cancer patients with VTE
  - LMWH given for at least 6 months is also the preferred approach for long-term anticoagulant therapy. Vitamin K antagonists (Target INR 2.0–3.0) are an acceptable alternative if LMWH is not available
  - After 6 months, indefinite anticoagulant therapy should be considered for patients with active cancer (metastatic disease or receiving chemotherapy)
  - Insertion of an inferior vena caval filter (IVCF) is only indicated for patients with contraindications to anticoagulant therapy or with recurrent VTE despite adequate long-term LMWH
- **American College of Chest Physicians 8th ACCP Guidelines**—*CHEST, June 2008*
  Patients with DVT and cancer:
  Recommendations:
  - LMWH for the first 3 to 6 months of long-term anticoagulants (Grade 1A recommendation)
  - Subsequent anticoagulant therapy with VKA or LMWH indefinitely or until the cancer is resolved (Grade 1C)
  - For patients with DVT, routine insertion of a vena caval filter in addition to anticoagulants is not recommended (Grade 1A)
  - For patients with acute proximal DVT, inferior vena caval filter (IVCF) insertion is recommended, if anticoagulation is contraindicated because of increased bleeding risk (Grade 1C)
  - For patients with acute DVT who have IVCF inserted as alternative to anticoagulation, therapeutic anticoagulation should subsequently be given once bleeding risk has resolved (Grade 1C)

Recurrent VTE despite adequate anticoagulant therapy

Usually indicates aggressive or extensive cancer

- If patient had recurrence on Warfarin ("warfarin failure"), then switch to LMWHs
- If recurrence occurs while on weight based LMWH then:
  - LMWH—adjusted to achieve target anti Factor Xa level taken 4 to 6 hours after LMWH injection. Target anti Factor Xa: 0.6–1.0 IU/ml for bid dosing
    1.0–2.0 IU/ml for od dosing

    or
  - Unfractionated heparin subcutaneously in bid dosing, adjusted to achieve therapeutic target aPTT: 1.5–2.5 times mean normal lab control value or upper limit of normal range, taken 6 hours after a.m. dose of UFH is given
- Inferior Vena Cave Filter may prevent clinically important PE on short-term basis only, but may predispose hypercoaguable cancer patient to increased morbidity and mortality from further recurrent DVT and PE (IVC thrombosis and IVC filter thrombosis) and should not be used without concomitant therapeutic anticoagulation (see above) if not contraindicated.