Clinical Guide - Cancer & Thrombosis (January 2007)

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Cancer and Venous Thrombo-Embolic Disease – A Significant Issue

- Active cancer accounts for almost 20% of all new venous thromboembolic events occurring in the community.
- Most common cancers in patients with VTE are lung, breast, colorectal and prostate.
- Patients presenting with unprovoked venous thromboembolism (VTE) have a 10% risk of developing cancer within the next two years.
- Occult malignancy is 3-4 times higher in patients who present with idiopathic thromboembolic disease versus patients with a secondary venous thromboembolic event.
- Patients who receive a diagnosis of cancer at the same time or within one year of an episode of a venous thromboembolic event have a shorter life expectancy than patients with cancer who do not have VTE.
- In cancer patients who undergo surgery, the risk of a post-operative deep vein thrombosis (DVT) is twice that of patients without cancer and the risk of fatal pulmonary embolism (PE) is 3-fold higher than patients having surgery for benign conditions.
- In-hospital mortality is 2- to 3-fold higher in cancer patients who experience venous or arterial thrombotic events compared with cancer patients without these complications.
- While on warfarin therapy, the risk of bleeding is six times higher and the risk of recurrent VTE is 2-3 times higher in cancer patients than in non-cancer patients.There is a very strong association between cancer and venous thromboembolism. This association was first suggested in 1865 by Dr. Armand Trousseau, who later developed unexplained DVT and then died of a gastric carcinoma.

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The malignancies most frequently seen in patients with DVT or PE are lung, breast, colon and prostate cancer, the commonest malignancies seen in industrialized countries. However, certain malignancies are particularly associated with a high risk of venous thromboembolic disease. These include malignant brain tumours and adenocarcinoma, including ovary, pancreas, colon, stomach, lung and kidney. Risk factors for venous thromboembolic disease in patients with cancer include immobility, use of central venous access devices, hormonal therapy, chemotherapy and surgery.

Screening for Occult Malignancy in Idiopathic Venous Thromboembolic Disease

Potentially 10% of patients who present with unprovoked or idiopathic thrombosis are diagnosed with cancer within two years of their initial thrombotic event. The incidence of cancer is highest in the first 6-12 months and approximately 40% of patients already have metastatic disease when their cancer becomes clinically evident. Because there is no evidence that invasive screening in asymptomatic patients improves survival, we recommend that appropriate investigations for malignancy be performed only if indicated by history (e.g., unexplained weight loss), the presence of suspicious physical findings or abnormal routine blood work.

<u>Prevention of Venous Thromboembolic Disease in Cancer Patients</u>

Central Venous Access Devices – The presence of a central venous access device alters the blood flow in the upper venous system and is an independent risk factor for upper extremity DVT. Low dose warfarin or low dose LMWH prophylaxis has been used for prevention of catheter-related thrombosis but contemporary randomized studies have failed to show any reduction in symptomatic catheter-related thrombosis with these regimens compared to placebo. A large randomized trial in fact showed that low dose warfarin is associated with an increase in bleeding. Furthermore, the risk of symptomatic catheter-related thrombosis in adults is approximately 5%, which is much lower than previously reported. The risk of clinically relevant VTE is likely higher in children. It is possible that improvements in the manufacture of central venous access devices and better insertion techniques have decreased the risk of catheter-related thrombosis. The optimal prevention of catheter-related thrombosis remains unclear and we cannot recommend low dose anticoagulation for routine prophylaxis.

Chemotherapy – Although one RCT has shown that low dose warfarin can safely reduce symptomatic VTE in women with stage IV breast cancer who are receiving chemotherapy, there is no recommendation for routine primary prophylaxis in ambulatory medical oncology patients. Prophylaxis may be considered in patients who have additional risk factors, such as previous history of VTE or known thrombophilia, if their risk of bleeding is low. Cancer patients who are hospitalized and who are immobile should receive prophylaxis according to guidelines appropriate for hospitalized medical patients. The optimal strategy to prevent thrombosis in myeloma patients receiving thalidomide/dexamethasone remains controversial.

Hormonal Therapy – Hormonal manipulation also affects venous thromboembolic risk. The risk of venous thromboembolic disease is increased 2-6 times among women with breast cancer receiving adjuvant tamoxifen therapy compared to patients taking placebo. When tamoxifen is used for the primary prevention of breast cancer, it is associated with an increased relative risk of DVT and PE of 1.6 and 3.0, respectively. Other selective estrogen receptor modulators, like raloxifene, are also associated with an increased thrombo-embolic risk. Aromatase inhibitors have a lower risk of VTE than tamoxifen and are a reasonable alternative in postmenopausal women with other risk factors for VTE. Studies have not been done to evaluate the efficacy or safety of primary prophylaxis in cancer patients receiving hormonal therapy.

Anti-angiogenic or Targeted Therapy – Novel agents aimed at inhibiting angiogenesis appear to be associated with an increased risk of thrombosis. Thalidomide or lenalidomide in combination with chemotherapy significantly increases the risk of symptomatic VTE in patients with multiple myeloma. Prophylaxis with low dose anticoagulant therapy has not been formally evaluated in these patients.

Surgery – Cancer patients who require surgery are twice as likely as non-cancer patients to develop post-operative DVT and more than three times as likely to develop fatal PE. Patients with cancer are also more likely to develop VTE despite prophylaxis. There is good evidence that low dose unfractionated heparin (5000 U three times a day) or LMWH once a day will reduce DVT and fatal PE following cancer surgery. Two recently published clinical trials have shown that continuation of LMWH prophylaxis for a total of 1 month in patients who underwent cancer surgery reduced the risk of late venous thromboembolic disease by 62% based on venography. Further studies are necessary to evaluate whether extended prophylaxis will reduce symptomatic VTE. Patients who had protracted surgery, experience prolonged immobilization or have other risk factors for VTE are likely to benefit.

Management of Patients with Venous Thromboembolic Disease

Diagnosis – The diagnosis of a venous thromboembolic event in a patient with cancer is more challenging than in a non-cancer patient. Standard objective investigations (compression ultrasonography, ventilation-perfusion lung scanning, spiral computed tomography) are all useful for diagnosing VTE in cancer patients. However, D-dimer tests are less reliable and less useful for excluding DVT in cancer patients as the D-dimer level is often raised in these patients. For patients presenting with suspected DVT, compression ultrasonography should be the first investigation of choice. For patients presenting with suspected PE, spiral CT is preferred over ventilation-perfusion scanning because it is readily available and can provide an alternative diagnosis in many cases.

Treatment – LMWH should be considered as first-line treatment for acute VTE. LMWH is preferred over unfractionated heparin for initial therapy because it can be given on an outpatient basis and is associated with a lower risk of heparin-induced thrombocytopenia. Based on recent evidence from randomized clinical trials that showed LMWH is more effective and as safe as warfarin for prevention of recurrent VTE in cancer patients, LMWH should be considered also as first-line therapy for long term treatment. LMWH also obviates laboratory monitoring and has fewer drug interactions. In patients with significant GI disturbance and poor nutrition, LMWH also avoids the unpredictable anticoagulant responses associated with warfarin. Cost is frequently a problem.

There is little or no evidence on the efficacy or safety of vena caval filters in cancer patients. In patients with active bleeding, or in those requiring urgent surgery, the use of a temporary or long-term inferior vena cava filter (IVC) may prevent PE in those with recently diagnosed proximal DVT. However, IVC filters may increase the risk of recurrent DVT in the lower limbs and the risk of post-phlebitic syndrome. Filters are therefore contraindicated in cancer patients unless there is a recent history of proximal DVT and an absolute contraindication to therapeutic anticoagulation. Specifically filters should not be used for treating first episode or recurrent VTE, unless there is an absolute contraindication for therapeutic anticoagulation.

Anticoagulant therapy should be continued while the patient is on active cancer therapy or has any evidence of active cancer. However, discontinuation should be considered when patients develop potentially life-threatening bleeding or has a very short life expectancy.

Catheter-related Thrombosis – Randomized controlled trials have not been done to evaluate optimal treatment of catheter-related thrombosis. Anticoagulant therapy following the regimens for VTE is a reasonable approach. Removal of the catheter has not been shown to improve outcome and is associated with more morbidity and cost if another catheter has to be inserted to provide ongoing central venous access. A Canadian study has shown that treatment of upper extremity DVT's secondary to central venous catheters in cancer patients with standard dalteparin/warfarin can allow the line to stay in with little risk of recurrence/ extension of the DVT.

Summary of Recommendations

1. We recommend that appropriate investigations for malignancy be performed in patients with unprovoked VTE only if indicated by history, the presence of suspicious physical findings or abnormal routine blood work.
2. Cancer patients who are hospitalized for medical reasons and who are immobile should receive prophylaxis according to guidelines appropriate for hospitalized medical patients.
3. Studies have not been done to evaluate the efficacy or safety of primary prophylaxis in ambulatory cancer patients receiving anti-cancer therapy.
4. Aromatase inhibitors have a lower risk of VTE than tamoxifen and are a reasonable alternative in postmenopausal women with other risk factors for VTE.
5. Cancer patients undergoing surgery should receive LMWH prophylaxis while in hospital. Patients with additional risk factors may benefit from extended prophylaxis until 1 month after surgery.
6. Standard objective testing is essential to confirm or refute a diagnosis of DVT or PE. D-dimer tests are less reliable and less useful for excluding DVT in cancer patients.
7. Monotherapy with LMWH should be considered as first-line therapy for acute treatment and secondary prevention of VTE.
8. The optimal prevention of catheter-related thrombosis remains unclear and we cannot recommend low dose anticoagulation for routine prophylaxis.
9. Catheter-related thrombosis should be treated with anticoagulant therapy. Removal of the catheter does not appear to be necessary.

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