THE CHALLENGE OF CANCER AND THROMBOEMBOLIC DISEASE

Current trends and recommendations

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Abstract

It has been known for nearly 200 years that people with cancer are more prone to venous thromboembolic disease (VTE). The most common form of VTE is deep vein thrombosis (DVT), which can lead to potentially fatal pulmonary embolus. Almost 20% of all DVTs occur in people with cancer, and an estimated 10% of patients presenting with unprovoked DVT are diagnosed with cancer within the next few years. Arterial thrombotic events, including myocardial infarction and thromboembolic stroke, also occur in cancer patients. VTE is more common in certain types of cancer, especially multiple myeloma, other hematologic malignancies, adenocarcinomas (especially of the pancreas, ovary, colon, stomach, lung and kidney) and malignant brain tumours. Other risk factors for VTE in cancer patients are advanced age, immobility, having a central venous catheter, surgery and other cancer treatments including radiation and some chemotherapeutic agents. VTE is difficult to prevent, diagnose and treat in cancer patients. Anticoagulation agents including warfarin, heparin and low-molecular-weight heparin can be given for prophylaxis of VTE, but these (especially warfarin) are complicated to administer and may cause bleeding. Low-molecular-weight heparin prophylaxis should be considered in selected cancer patients undergoing surgery and in those with multiple risk factors.

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access devices and type of cancer treatment, such as surgery, radiation therapy, hormonal therapy, cytotoxic chemotherapy and some targeted anti-cancer agents. The location of the tumour mass and presence of bulky adenopathy may also contribute to venous stasis. Recent evidence showing that the risk of thrombosis is highest during the first six months after cancer diagnosis suggests that treatment contributes significantly to the burden of thrombotic disease.6,10

The most common malignancies seen in industrialized countries — lung, breast, colon and prostate cancer — are all associated with DVT. Other malignancies with high risk of VTE are malignant brain tumours, adenocarcinomas (especially of the pancreas, ovary, colon, stomach, lung and kidney) and hematologic malignancies such as lymphoma, acute myeloid leukemia and especially myeloma and other plasma cell dyscrasias.11-13 With a relative risk of VTE ranging from 1.02 to 4.34, patients with metastatic disease have been reported to have a 20-fold increased risk of VTE compared to those without metastases.7 Cancer patients who present with an episode of VTE or who develop an episode of VTE within a year of their cancer diagnosis are prone to recurrent VTE, and have a shorter life expectancy than those with cancer and no VTE.14,15

SCREENING FOR OCCULT MALIGNANCY IN IDIOPATHIC VTE
Patients presenting with an unprovoked episode of VTE have a 10% chance of being diagnosed with a malignancy within the next few years, with the highest risk in the first 6–12 months.6,10,37 Compared to patients who develop thromboembolism secondary to a known trigger, patients with an unprovoked episode of idiopathic thromboembolic disease have a 3–4-fold higher risk of an occult malignancy.4 However, current evidence does not support performing extensive screening to look for occult cancer in patients with unprovoked VTE; they should be carefully evaluated by history and undergo age- and gender-appropriate standard cancer screening protocols. Further followup is indicated if a suspicious history, physical findings or abnormal routine blood work are found.18,19

PREVENTION OF VTE IN CANCER PATIENTS
The American College of Chest Physicians’ Prevention of Venous Thromboembolism,20 the foremost international consensus guideline on this topic, strongly recommends that every care institution develop a formal, active strategy to address prevention of VTE.20 Although preventive therapy for VTE in cancer patients admitted to hospital has not been formally studied,20 it should be seriously considered in those who are immobilized and/or have other risk factors for thrombosis.

Prophylaxis following surgery for cancer is strongly recommended, and continuing prophylaxis beyond hospital discharge in selected patients after surgery should also be considered.21 It is important that all oncology professionals and patients be aware of the risk of thrombosis and apply appropriate prophylaxis when indicated. Although the evidence for these measures is weak, it may help to avoid dehydration, use antiembolism stockings and follow a gentle exercise program.

Surgery
Surgery is a major risk factor for VTE: compared to non-cancer patients, those with cancer have at least twice the risk of postoperative DVT and three times the risk of a fatal pulmonary embolism.20 One analysis found that an average of 29% of surgically treated cancer patients who did not receive antithrombotic prophylaxis later developed DVT.22

Hence, The American College of Chest Physicians consensus guidelines strongly endorse chemoprophylaxis against VTE in cancer patients undergoing surgery.20 The Thrombosis Interest Group of Canada (TIGC, a group of Canadian health professionals in fields related to thrombosis who collaborate to write evidence- and consensus-based clinical guides on the investigation, management, and diagnosis of thrombotic disorders, www.tigc.org) recommends that hospitalized cancer patients undergoing surgery receive low-molecular-weight heparin (LMWH) prophylaxis.23 Warfarin is not recommended because it is difficult to use in the postoperative setting and may be associated with higher risk of bleeding from unstable international normalized ratio (INR). Two randomized trials have shown that continuing LMWH prophylaxis for a month in patients undergoing cancer surgery reduces the incidence of late VTE by 60%, based on venography,24,25 but no study has yet demonstrated that prophylaxis extended to a month will reduce symptomatic thromboembolism. However, a recent prospective cohort study showed that roughly half of all symptomatic thrombotic events occurred after hospital discharge and that 46% of all postoperative deaths in cancer patients are due to fatal pulmonary embolus.26 Consequently, patients who have complex surgery or who experience long-term immobilization or other risk factors for VTE must be evaluated for risk after they leave hospital, and are likely to benefit from extended (one-month) LMWH prophylaxis.

Central venous access devices
The presence of a central venous catheter alters blood flow in the upper venous system and is an independent risk factor for upper extremity DVT. The risk is somewhat related to design and insertion technique — further improvements could potentially decrease this risk.27 The incidence of symptomatic catheter-related thrombosis is currently estimated to be about 5% in adults, and is likely higher in children.28
Prophylaxis against catheter-related VTE is not recommended for cancer patients with a central venous catheter unless warranted by additional risk factors. Low-dose warfarin and low-dose LMWH prophylaxis have been tested for preventing catheter-related thrombosis, but large randomized trials have failed to show any reduction in symptomatic catheter-related thrombosis with these regimens as compared to placebo in cancer patients. Furthermore, low-dose warfarin is associated with an increased risk of bleeding in cancer patients with central venous catheters.

Chemotherapy and supportive therapies
Cancer chemotherapy is a risk factor for VTE. Apart from the chemotherapeutic agents themselves, use of cytokines such as granulocyte-colony stimulating factor (G-CSF) and erythropoietin-stimulating agents are associated with increased risks of VTE and the latter are also associated with higher risk of both venous and arterial thromboembolic events and death. A multivariate analysis of cancer patients receiving chemotherapy found the following risk factors to be significantly associated with development of symptomatic VTE: upper gastrointestinal or lung malignancy, pre-chemotherapy platelet count ≥ 350 x 10^9/L, use of white cell growth factors, and hemoglobin < 100 g/L or use of red-cell growth factors.

Hormonal agents
The selective estrogen receptor modulator agent tamoxifen, used to treat hormone receptor-positive breast cancer, is estimated to increase the risk of vascular thrombotic events two- to five-fold while patients remain on treatment, especially in postmenopausal women also receiving chemotherapy. The aromatase inhibitors anastrozole, letrozole and exemestane are associated with about half the likelihood of VTE compared to tamoxifen, and hence are reasonable alternatives for postmenopausal women with risk factors for VTE. Estrogen therapy for menopausal symptoms increases venous thromboembolic risk approximately three-fold.

Androgen deprivation therapy to treat men with prostate cancer is associated with an increased risk of cardiac and vascular disease, including DVT.

Targeted agents
In addition to the heightened danger of VTE faced by patients with multiple myeloma, many of the antiangiogenic agents used in treatment further increase the risk. Thalidomide and lenalidomide are associated with increased likelihood of VTE, especially in combination with anthracycline-based chemotherapy and/or high-dose dexamethasone. The risk of VTE in multiple myeloma is lower with lenalidomide. Bortezomib, another agent used to treat multiple myeloma and relapsed or refractory mantle cell lymphoma, increases the risk of DVT, although thrombocytopenia is a much more prominent adverse effect of this drug. L-asparaginase is a very effective treatment for acute lymphoblastic leukemia, however it carries a major chance of thrombotic complications, requiring monitoring of blood clotting factors and replacement when indicated. The vascular endothelial growth factor (VEGF) inhibitor bevacizumab may increase the incidence of thromboembolic complications as well as of bleeding events. Other antiangiogenic agents have been reported to be associated with VTE, but the exact risk and the excessive risk above what would be expected in specific cancer populations have not been established.

Thrombosis Interest Group of Canada recommendations

- 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.
- Cancer patients who are hospitalized for medical reasons and who are immobile should receive prophylaxis according to guidelines appropriate for hospitalized medical patients.
- Not enough studies have been completed to evaluate the efficacy and safety of primary prophylaxis in ambulatory cancer patients receiving anti-cancer therapy.
- Aromatase inhibitors have a lower risk of VTE than tamoxifen and are a reasonable alternative in postmenopausal women with other risk factors for VTE.
- Cancer patients undergoing surgery should receive LMWH prophylaxis while in hospital. Patients with additional risk factors may benefit from extended prophylaxis until one month after surgery.
- Standard objective testing is essential to confirm or refute a diagnosis of DVT or pulmonary embolus. D-dimer tests are less reliable and less useful for excluding DVT in cancer patients.
- Monotherapy with LMWH should be considered as first-line therapy for acute treatment and secondary prevention of VTE.
- The optimal prevention of catheter-related thrombosis remains unclear and we cannot recommend low-dose anticoagulation for routine prophylaxis.
- Catheter-related thrombosis should be treated with anticoagulant therapy. Removal of the catheter does not appear to be necessary.
Chemoprophylaxis

While a benefit of prophylactic use of low-dose warfarin was shown in the 1990s, using this drug in patients receiving chemotherapy is very difficult. Warfarin has a long half-life, dosage is difficult to stabilize and it is particularly problematic in cancer patients with potential multiple drug interactions. Their higher baseline risk of significant bleeding also discourages the use of primary chemoprophylaxis. Until recently, investigations of thromboprophylaxis with LMWHs for patients on chemotherapy had not been positive for preventing VTE.

For multiple myeloma patients treated with antiangiogenic agents (thalidomide, lenalidomide or bortezomib), prophylaxis with LMWH, or warfarin or aspirin has been recommended by some experts to reduce the risk of thromboembolic events. However, no clinical trial evidence supports such recommendations. Administration of a LMWH may reduce the incidence of DVT in patients receiving L-asparaginase in acute lymphoblastic leukemia.

New evidence comes from the Prophylaxis of Thromboembolic Events in Cancer Patients Receiving Chemotherapy trial (PROTECHT), presented at the American Society of Hematology 2008 Annual Meeting. This trial randomized 1166 patients with metastatic or locally advanced cancer in a 2:1 fashion to receive the LMWH nadroparin (3800 anti-Xa IU) or placebo, both administered once daily by subcutaneous injection started on the day of initiation of the first cycle or a new course of chemotherapy, and planned for chemotherapy duration up to a maximum of four months. The average time on nadroparin in both groups was about three months. Patients had a variety of solid tumours: 279 lung, 235 colon, 165 breast, 143 ovarian, 98 stomach, 87 rectal, 53 pancreatic, 56 head and neck, and 54 other. The primary outcome was a clinically overt venous or arterial thromboembolic event, including DVT of the upper or lower limbs, visceral and cerebral venous thrombosis, pulmonary embolus, myocardial infarction, ischemic stroke, acute peripheral thromboembolus or unexplained death of possible thromboembolic origin. In 769 patients receiving nadroparin, there were 16 events (2.1%). In 381 placebo patients there were 15 events (3.9%). The relative risk reduction was 49.6% with an interim adjusted p-value of 0.024. The incidence of minor bleeding was similar in both groups: 7.4% for nadroparin and 7.9% for placebo.

PROTECHT is the first randomized controlled trial to show a benefit of LMWH thromboprophylaxis of patients on active chemotherapy. However, many chemotherapeutic protocols are already intensive and may be associated with a risk of severe thrombocytopenia (and thus of bleeding). Other disadvantages of adding anticoagulation are also significant, particularly with a subcutaneous injection, including inconvenience, cost and pain. Many oncologists are concerned that the addition of anticoagulants may increase the chance of bleeding and add to discomfort for patients who may not want the extra burden of a daily subcutaneous injection, especially ambulatory patients who do not have additional risk factors such as immobility or the need for surgery.

Fondaparinux, a synthetic Factor Xa inhibitor, is approved for marketing in Canada for surgical patients at high risk of VTE and for treatment of VTE. It is currently being evaluated in Phase I and II preventive clinical trials for patients with gynecologic and lung cancer. While further studies are needed, it appears to have good potential for prevention of VTE in cancer patients who require surgery.

Vena cava filters, used to prevent pulmonary embolus in patients with proximal DVT, are generally contraindicated in cancer patients because of the increased risk of recurrent lower limb DVT and of post-phlebitic syndrome (chronic pain, swelling, heaviness and sometimes venous ulcers). They can be used in patients for whom anticoagulants are contraindicated, such as those with active bleeding or who require urgent surgery.

DIAGNOSIS AND MANAGEMENT

It is more challenging to diagnose DVT in a patient with cancer than in a non-cancer patient. The simple, minimally invasive diagnostic blood test to measure D-dimer (a small protein fragment present in the blood after a blood clot is degraded by fibrinolysis) yields a higher rate of false positives in cancer patients (false-positive rates are also higher in the elderly and in the presence of infection). Some researchers have suggested that D-dimer levels may be useful to predict risk of thromboembolic disease in cancer patients and may eventually be helpful in stratifying patients and preventing this condition, but studies are needed to address this hypothesis.

Treatment of VTE in cancer patients differs from the general population in that warfarin should be avoided due to the excessive risk of bleeding. First-line treatment is with a LMWH for three to six months. After four weeks the dose may be reduced to 80% of the original dose. Treatment should be reassessed and possibly continued in patients with metastatic disease. Several oral anticoagulants are already approved for use in orthopedic prophylaxis and are in final phases of clinical development for atrial fibrillation and VTE treatment, including and dabigatran and rivaroxaban, but research specific to cancer patients is only in the preliminary stage.

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References

10


10. Wun T, White RH. Venous thromboembolism (VTE) in patients with cancer:


13. Srkalovic G, Cameron MG, Rybicki L et al. Monoclonal gammopathy of undeter-


23. Scully MF, Geerts W, Kovacs M, Lee A. American Society of Clinical Oncology


29. Masci G, Magagnoli M, Zucali PA Minidose warfarin prophylaxis for catheter-


19. Cornu J, Pearson SD, Creager MA et al. Importance of findings on the initial


guideline: recommendations for venous thromboembolism prophylaxis and


22. Geerts WH, Bergqvist D, Pineo GF et al. Prevention of venous thromboembolism:

American College of Chest Physicians Evidence-Based Clinical Practice Guide-


20. Rasmussen MS, Jørgensen LN, Wille-Jørgensen P et al. Prolonged prophylaxis


guideline: recommendations for venous thromboembolism prophylaxis and


20. Rasmussen MS, Jørgensen LN, Wille-Jørgensen P et al. Prolonged prophylaxis


guideline: recommendations for venous thromboembolism prophylaxis and


Thrombosis Interest Group of Canada. Available at www.tigc.org/pdf/cancer06.pdf


guideline: recommendations for venous thromboembolism prophylaxis and


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