Thromboprophylaxis in the Cancer Patient

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Introduction

It has long been recognized that thrombosis is associated with malignant disease [1]. In his original description, Trousseau links the occurrence of a spontaneous thrombophlebitis with the presence of underlying malignant disease. Patients with established cancer are also at greater risk for the development of thromboembolic disease secondary to the malignancy itself, part of the intervention they are receiving for treatment of their cancer, and the debilitation and immobility associated with the advancing stage of their disease.

The hypercoagulable state is often recognized in patients with malignant disease. This condition appears to be secondary to tumor elaboration of the physiological initiator of blood coagulation tissue factor [2]. Patients with solid tumor malignancy have higher circulating levels of tissue factor associated with a marked elevation in levels of factor VIIa, indicating extrinsic pathway activation. They also have evidence of excessive systemic thrombin generation [3].

Cancer Interventions

Although it is recognized that thrombosis may complicate the course of a number of different cancers, the impact of tumor type on the frequency of thromboembolic complications is poorly understood. The clinical manifestation of venous thromboembolism in the cancer patient extends from asymptomatic distal deep vein thrombosis to fatal pulmonary embolism.
Kakkar et al. in 1970 demonstrated that cancer patients undergoing surgical intervention had a higher risk for the development of deep vein thrombosis compared to noncancer patients [3]. Since that time, numerous other studies have confirmed these original findings and have also demonstrated that fatal pulmonary embolism after major surgery in cancer patients is significantly higher that in noncancer patients (1.6% vs. 0.4%) [4]. Evidence suggests that in patients with malignant disease venous thromboembolism is the second most common cause of death [5,6]. Overall, some 15% of cancer patients will experience symptomatic thromboembolic disease during the course of their disease [7–9].

There have been more limited studies that have assessed the risk of thromboembolic complications associated with chemotherapeutic intervention. The best investigated population of patients are women with breast cancer receiving either adjuvant or palliative chemotherapy. In a study of postmenopausal women receiving adjuvant therapy for breast cancer, the combination of Tamoxifen with cytotoxic chemotherapy was associated with an increase in risk from 1.4% for Tamoxifen alone to 9.6% for the combination ($P = 0.0001$) [8]. Cancer patients receiving cytotoxic chemotherapy for management of breast cancer appear to be at greatest risk for the development of thrombosis while they are actively receiving their anticancer treatment [9]. Beyond the use of chemotherapy, intervention with radiotherapy also appears to increase the risk of thrombosis in certain cancer populations. For instance, in patients with rectal cancer receiving neoadjuvant radiotherapy, there is an increase in risk for the development of subsequent postoperative venous thromboembolism from 3.6% to 7.5% ($P = 0.001$) [10].

**Prevention of Venous Thromboembolic Disease in Cancer Surgical Patients**

The frequency of thromboembolic complications in cancer patients is of sufficient magnitude, and the consequences in terms of symptomatic thrombosis and fatal pulmonary embolism in particular are so devastating, that mandatory thromboprophylaxis is recognized to be essential in cancer patients undergoing major surgical intervention.

A number of methods are available including mechanical and pharmacological approaches. In terms of mechanical methods of prevention of thromboembolic disease in cancer patients, there is limited evidence for their benefit. Small studies have indicated that intermittent compression of the calf can reduce the frequency of postoperative deep vein thrombosis from 21% to 12% [11]. However, this form of prophylaxis has never been demonstrated to be effective in reducing the frequency of pulmonary embolism in cancer patients.
Pharmacological methods such as aspirin and dextran have not been adequately assessed in cancer patients, and no recommendation can be made about their use in this population.

Unfractionated low-dose subcutaneous heparin has been extensively evaluated for the prevention of thromboembolic disease in high-risk surgical populations. In a meta-analysis of low-dose heparin studies in which its efficacy was compared against controls or placebo, data from 919 patients with cancer demonstrated that low-dose unfractionated heparin, administered perioperatively, reduced the frequency of postoperative deep vein thrombosis from 30.6% in the control group to 13.6% in the heparin group \((P = 0.001)\) [12]. Low-dose unfractionated heparin has also been shown to reduce the frequency of fatal pulmonary embolism in high-risk surgical patients, including those with malignant disease [13].

More recently, the low molecular weight heparins have replaced low-dose unfractionated heparin. The benefits of low molecular weight heparins include a more predictable bioavailability after subcutaneous administration, a longer plasma half-life, and a lower frequency of thrombocytopenia and osteoporosis when compared to unfractionated heparin. It is for this reason that low molecular weight heparins have replaced low-dose unfractionated heparin for thromboprophylaxis. Low molecular weight heparins have been extensively investigated for thromboprophylaxis for a large number of surgical patients. However, there are very few studies that have specifically investigated their benefit for venous thromboembolism prophylaxis in patients with cancer. Bergqvist et al. [14] randomized more than 2000 patients, 65% of whom were undergoing operation for malignant disease, to receive prophylaxis with a standard- or higher-risk prophylactic dose of low molecular weight heparin (Dalteparin). He was able to demonstrate that increasing the dose of perioperative low molecular weight heparin reduced the frequency of postoperative deep vein thrombosis from 14.9% in the standard-dose group to 8.5% in the higher-dose group, without any significant increase in bleeding complications.

Further data about the safety of low molecular weight heparins in cancer surgical patients have been provided by studies in neurosurgical patients, many of whom have undergone operations for intracranial malignancy. In a study of some 300 patients [15], many of whom were undergoing operation for intracranial malignancy, patients were randomized to receive low molecular weight heparin or placebo in combination with graduated lower limb compression stockings. The addition of low molecular weight heparin reduced the frequency of postoperative thromboembolic complications in this high-risk group without any significant increase in bleeding complications.

More recently, dermatan sulfate (glycosaminoglycan), which inhibits heparin cofactor II and thus achieves an antithrombotic effect, has been
assessed in more than 800 patients randomized to receive this agent or low-dose unfractionated heparin. The patients were undergoing operation for cancer. The frequency of deep vein thrombosis in the heparin group was 22%, reduced to 15% in that group of patients receiving dermatan sulfate [16].

The duration of thromboprophylaxis has recently been assessed in cancer surgical patients. Current recommendations indicate the patients undergoing operation for malignant disease should receive at least 7 to 10 days of thromboprophylaxis with low-dose or low molecular weight heparin while in the hospital. A recent study randomized patients at the time of hospital discharge to continue with placebo or low molecular weight heparin for a further 3 weeks with venographic screening for thrombosis at the end of this period. The frequency of deep vein thrombosis was reduced from 12% in the group of patients who received prophylaxis in hospital to only 4% when prophylaxis was continued into the postdischarge period [17].

**Thromboprophylaxis in Nonsurgical Cancer Patients**

There are many fewer data available in the published literature with regard to the efficacy and safety of routine thromboprophylactic intervention in nonsurgical cancer patients. Only one randomized trial has assessed the benefits of such intervention in women with advanced breast cancer receiving cytotoxic chemotherapy. In this trial, more than 300 women receiving chemotherapy were randomized to low-dose Warfarin or placebo. The international normalized ratio was maintained at between 1.3 and 1.9 in the Warfarin group. The frequency of thrombotic complications was reduced by 85%, from 4.4% in the control group to 0.6% in the Warfarin group \((P = 0.003)\) [18].

Another group of patients who have historically been considered to be at high risk for the development of thromboembolic complications are cancer patients with indwelling central venous catheters. Two studies in the early 1990s [19, 20] evaluated 1 mg Warfarin or 2500 units low molecular weight heparin Dalteparin, respectively, in the prevention of central venous catheter-associated thrombosis. In the first study, with Warfarin rates of thrombosis were reduced from 37% to 9% when screened using upper limb venography [19]. In the second study, rates of thrombosis were reduced from more than 60% to 6% with the use of Dalteparin [20]. However, contemporary studies assessing the value of these interventions in patients receiving modern central venous catheters suggest that the rates of thrombosis are now much lower, and it is difficult at this stage to recommend routine antithrombotic therapy in this population.
Low Molecular Weight Heparin Therapy in Survival in Cancer

An intriguing recent observation has been that chronic administration of low molecular weight heparin may be associated with enhanced survival in cancer patients. A meta-analysis of deep vein thrombosis treatment studies undertaken in the early 1990s suggested that cancer patients who received low molecular weight heparin for initial treatment of their deep vein thrombosis had a lower mortality after 3 months than those who received intravenous unfractionated heparin [21, 22].

Recently, the Fragmin Advance Malignancy Outcome Study (FAMOUS), the first prospective randomized placebo-controlled trial, has assessed the value of up to 1 year of low molecular weight heparin therapy with Dalteparin sodium in patients with advanced malignant disease [23]. Three hundred and eighty-five patients with advanced cancer were randomized to receive Dalteparin in a dose of 5000 units or placebo injection. The study failed to detect a significant difference in overall survival between the two populations. However, in a subgroup of patients, identified post hoc, there was an increase in median survival from 23 to 43 months in favour of Dalteparin.

In a further study of 302 patients who were randomized to receive either low molecular weight heparin for 6 weeks or placebo [24], those receiving the low molecular weight heparin Nandroparin demonstrated a significant survival advantage at up to 84 months of follow-up. Similarly, in a trial of 84 patients with small cell lung cancer [25] who were all receiving chemotherapy but were additionally randomized to receive the low molecular weight heparin Dalteparin or no antithrombotic therapy, there was an increase in both overall survival and disease-free survival for those patients with lung cancer receiving the low molecular weight heparin.

Although the mechanism for these apparent survival benefits associated with the low molecular weight heparin treatment in cancer patients remains unclear, further trials are warranted to investigate their potential benefit.

Conclusions

Thrombosis is an important complication in cancer patients. Cancer surgical patients receiving thromboprophylaxis with either low-dose or low molecular weight heparin are protected against thrombosis, this intervention has been validated in terms of efficacy and safety. In non-surgical cancer patients, those with breast cancer may receive low-dose oral anticoagulation with vitamin K antagonists. The benefit of routine thromboprophylaxis in other ambulant cancer populations receiving medical therapy for their cancers...
remains to be established by way of prospective clinical trials. For cancer patients with central venous catheters, no recommendations can be made about routine antithrombotic therapy, although certain patients at high risk could be considered for either vitamin K antagonists (Warfarin, 1 mg) or low molecular weight heparin (Dalteparin, 2500 units). The intriguing observation that low molecular weight heparin therapy may be associated with enhanced survival has become more plausible with the evidence generated from contemporary prospective clinical trials. However, further clinical trials in specific cancer populations are required before low molecular weight heparins may be used for this exciting indication.

References


