Venous Thromboembolism and Cancer: Prevention and Therapy

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Summary: Venous thromboembolism (VTE) is a common problem in patients with cancer that complicates management and predicts for a worse prognosis. Hence, effective methods to prevent and treat VTE can reduce morbidity and mortality. Low molecular weight heparins have simplified and improved management of VTE and recent studies suggest these agents may improve survival in cancer patients. This review will provide an update on the primary prevention and treatment of VTE, as well as prophylaxis for central venous catheters, in patients with malignancy.

Key words: venous thromboembolism – cancer

Introduction
It has long been recognized that venous thromboembolic events are common in patients with cancer. Venous thromboembolism (VTE) can also complicate and potentially compromise their cancer treatment and it also predicts for shortened survival. Furthermore, the morbidity of acute thrombotic events, the limitations of traditional anticoagulant therapy, and the high frequency of anticoagulant treatment failure in this population also make VTE an important quality of life issue. Low-molecular weight heparins (LMWH) have simplified and improved management of VTE in cancer patients and may improve survival in patients with limited or early stage disease. This review will summarize the recent clinical studies in the primary prevention and treatment of VTE and the prevention of catheter-related thrombosis (CRT) in patients with malignancy.

Prophylaxis of VTE

Major Surgery
Patients undergoing major surgery for benign or malignant disease require routine anticoagulant prophylaxis because the risk of post-operative thrombosis is substantial. Unfractionated heparin (UFH) and LMWH are comparable in efficacy and safety in this setting although few clinical trials have studied prophylaxis specifically in patients undergoing surgery for cancer. The ENOXACAN investigators conducted the first randomized trial that compared LMWH with UFH in patients undergoing abdominal surgery for cancer [1]. No difference in efficacy was detected between enoxaparin 40 mg injected once a day and UFH 5000 U administered three times daily in preventing venographically detected DVT and symptomatic VTE. Differences in major bleeding and mortality were not observed. Subgroup analyses of cancer patients from other trials are consistent with these findings [2].

Extending prophylaxis beyond hospitalization to further reduce the risk of VTE has also been examined in cancer patients [3]. In a multicentre, double-blind, placebo-controlled trial, patients undergoing elective, curative abdominal surgery for cancer received enoxaparin 40 mg once daily for the first 6–10 days after surgery and then were randomized to continue with enoxaparin 40 mg once daily or placebo injections until...
Mandatory bilateral venography was performed between 25-31 days after surgery. During the treatment period, 12.0% (20/167) of the placebo patients compared with 4.8% (8/165) of the enoxaparin patients had a confirmed thrombotic event (P = 0.02). Therefore, extended prophylaxis with enoxaparin significantly reduced the rate of VTE by 60% and this benefit was maintained at 3 months. The absolute risk reduction of 7% found in this trial means that 14 patients must be treated to avoid one case of venographic DVT. Overall, there was no detectable difference in any or major bleeding during the treatment period and no difference in mortality up to 1 year of follow-up.

Similar results were also reported in an open-label randomized trial in which patients having abdominal surgery were randomized to receive dalteparin 5000 U once daily and stockings for 21 days after hospital discharge or to stockings alone [4]. All patients received dalteparin for the first 7 days after surgery. A subgroup analysis of the 198 patients with cancer showed that prolonging prophylaxis with dalteparin significantly reduced the incidence of DVT on venography from 19.6% to 8.8% (P = 0.03) as well as that of proximal DVT from 10.4% to 2.2% (P = 0.02). Accordingly, 9 patients must be treated to avoid 1 episode of DVT while 12 must be treated to avoid 1 episode of proximal DVT.

Fondaparinux, a selective inhibitor of activated factor X that is approved for prophylaxis in orthopedic surgery, has been evaluated in a phase III, double-blind, double-dummy trial (PEGASUS trial) in patients undergoing high-risk abdominal surgery [5]. Patients with and without cancer were randomized to receive once daily injections of fondaparinux 2.5 mg or dalteparin 5000 U. Based on a composite outcome of DVT detected with bilateral venography performed on day 5–10 after surgery and symptomatic VTE up to day 10, a difference in thromboembolic events was not observed (4.6% vs. 6.1%, respectively; P = 0.14). Major bleeding was also comparable between the groups. However, in the subgroup of 1408 patients with cancer, fondaparinux was associated with a statistically significant reduction in VTE (4.7% vs 7.7%; P = 0.02). Given the potential for bias in subgroup analyses, further studies are required to examine the relative efficacy of fondaparinux and LMWH in cancer surgery prophylaxis.

Central Venous Catheters
Contemporary prospective cohort studies and randomized trials now provide evidence that low-dose anticoagulant therapy with either warfarin or LMWHs are ineffective in reducing symptomatic CRT. In a randomized, double-blind, placebo-controlled study, 255 cancer patients with central venous catheters were assigned to 1 mg of warfarin daily or placebo [6]. Clinically evident CRT occurred in 5 of 124 (4%) patients in the placebo group and in 6 of 130 (4.6%) patients in the warfarin group. There was also no difference in the incidence of major or minor bleeding between the two groups. A recent larger trial evaluating a fixed dose of warfarin (1 mg daily) or low-dose warfarin (international normalized ratio – INR – adjusted to 1.5 to 1.9) also failed to demonstrate a reduction in symptomatic CRT with warfarin (5% vs. 6%; p = 0.84), but found that warfarin was associated with a higher risk of major bleeding (2% vs. 0.2%; p = 0.07) [7]. This observation is consistent with the results from a prospective cohort study in which one-third of patients receiving fluorouracil-based chemotherapy and 1 mg warfarin daily had a prolonged INR, while 19% had an INR of more than 3.0 and 7% had an INR of more than 5.0 during follow-up [8].

Similarly, low-dose LMWH does not appear to be effective in reducing symptomatic CRT. In a randomized, double-blind, placebo-controlled study, 439 cancer patients were assigned in a 2 to 1 fashion to receive 5000 U dalteparin or placebo for 16 weeks starting within 5 days of catheter insertion [9]. In this study, the primary outcome was clinically overt catheter-related complications including thrombotic events requiring anticoagulant or thrombolytic therapy, clinically overt PE and catheter obstruction requiring catheter removal. Dalteparin did not reduce the incidence of catheter-related complications compared with placebo (3.7% vs. 3.4%, p = 0.09). In another placebo-controlled trial, enoxaparin 40 mg once daily was assessed for prophylaxis in 321 cancer patients with central venous catheters [10]. The primary outcome was CRT detected with routine screening venography at 6 weeks. No difference was found between treatment groups; 14.1% of patients who received enoxaparin and 18.0% in those who received placebo developed CRT. There was also no difference in symptomatic events.

Treatment of VTE
Anticoagulants are the mainstay therapy for the prevention and treatment of acute VTE. Although these agents are highly efficacious and have an acceptable safety profile in most patients, cancer patients have a higher risk of recurrent VTE and anticoagulant-related bleeding compared with patients without cancer [11]. These complications likely reflect the heightened hypercoagulable state associated with malignant diseases and the multiple co-morbidities in cancer patients that may alter their response to anticoagulant therapy and their risk of bleeding. LMWHs are convenient, efficacious and safe compared with UFH and vitamin K antagonists (VKAs) and
are becoming the anticoagulant class of choice in treating VTE in oncology patients.

**Initial Therapy**

To-date, multiple randomized trials and meta-analyses of these trials have confirmed that for initial therapy, LMWHs are at least as efficacious as UFH in reducing recurrent thrombosis and are associated with a lower risk of major bleeding [12]. Furthermore, LMWHs can be given safely in an outpatient setting without the need for laboratory monitoring and has a lower risk of heparin-induced thrombocytopenia. However, whether LMWHs and UFH perform comparably in patients with cancer and acute VTE has not been formally investigated.

**Long-term Therapy**

Despite their pharmacological and practical limitations, coumarin derivatives have been the mainstay of long-term anticoagulant treatment for VTE. Although VKAs are highly effective in reducing recurrent thrombosis in the general population, treatment failures, serious bleeding and difficulties with maintaining the INR within the therapeutic range are common problems in patients with cancer. A prospective cohort study reported that the 12-month cumulative incidence of recurrent VTE in cancer patients was 20.7 %, versus 6.8 % in patients without cancer, while the corresponding estimate for major bleeding was 12.4 %, versus 4.9 %, respectively [13]. Patients with cancer also experience recurrent VTE despite having therapeutic INR levels and suffer serious bleeding complications without receiving excessive anticoagulation [14].

To-date, two published clinical trials have examined the use of long-term LMWH as an alternative to warfarin therapy in cancer patients with acute VTE. Two other similar trials have not been published. A number of other randomized studies also have compared LMWH with oral anticoagulant therapy for long-term treatment but they included primarily patients without cancer. The CANTHANOX trial compared 3 months of standard warfarin therapy with enoxaparin therapy in cancer patients with proximal DVT, PE or both [15]. All patients were treated initially for at least 4 days with therapeutic doses of enoxaparin at 1.5 mg/kg once daily and were randomized to either continue with enoxaparin at the same dose or warfarin therapy. By 3 months, 15 of 75 patients had recurrent VTE or major bleeding in the warfarin group compared with 7 of 71 patients assigned to enoxaparin. The difference was not statistically significant (P = 0.09). Major bleeding was reported in 17 patients; of these, 6 patients in the warfarin group died of bleeding.

In a similar patient population, the CLOT trial evaluated the use of long-term dalteparin [16]. In this multicentre, randomized, open-label study, 676 cancer patients with proximal DVT, PE or both were randomized to usual treatment with dalteparin initially followed by 6 months of therapy with either VKA or dalteparin alone. In the dalteparin group, patients received therapeutic doses at 200 U/kg once daily for the first month and then 75–80 % of the full dose for the next 5 months. The cumulative risk of recurrent VTE at 6 months was reduced from 17 % in the VKA group to 9 % in the dalteparin group, resulting in a statistically significant risk reduction of 52 % (P = 0.002). Accordingly, 1 episode of recurrent VTE is prevented for every 13 patients treated with dalteparin. Overall, there were no differences in major or any bleeding between the groups. By 6 months, 39 % of the patients had died in each group; 90 % were due to progressive cancer. A post-hoc subgroup analysis showed that among patients who had no known metastatic disease at randomization, those who were randomized to dalteparin had better survival compared with those who had received a VKA [17]. Whether this was due to an anticoagulant or an anticancer cancer effect remains uncertain.

**Summary**

The recent advances in the management of VTE in cancer patients are exciting. Randomized controlled trials have shown that extended prophylaxis with LMWH following major abdominal surgery for cancer reduces the risk of VTE without significantly increasing the risk of bleeding. In contrast, strong evidence has emerged that low-dose anticoagulant therapy with warfarin or LMWHs do not reduce the risk of symptomatic CRT. The CLOT trial presents compelling evidence that LMWHs should become the standard of care as monotherapy for the treatment of VTE in cancer patients. There are still many unanswered clinical questions in management of VTE in oncology patients, but LMWHs have taken us a step forward in improving and simplifying both prophylaxis and treatment regimens.

**References**


