Unresolved problems in venous thromboembolism treatment in cancer

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A B S T R A C T

Venous thromboembolism (VTE) is a common complication in cancer patients. Prevention and treatment of VTE are major issues in cancer patients. For prophylaxis in the surgical setting, once-daily subcutaneous injections of low molecular weight heparin (LMWHs) are as effective and safe as multiple doses of unfractionated heparin (UFH). Extending prophylaxis with LMWH beyond hospital discharge reduces the risk of postoperative thrombosis after abdominal surgery for cancer. The clinical benefit from antithrombotic prophylaxis in medical cancer patients remains uncertain. For the initial treatment of VTE, LMWHs are effective and safe. For the long-term treatment of VTE, LMWHs have been shown to be more effective than the vitamin K antagonists in preventing recurrent VTE in cancer patients. The preliminary observations that LMWHs are associated with reduction in cancer mortality deserve further interest.

Cancer and its treatment are well-recognized risk factors for venous thromboembolism (VTE). About 15% of patients with cancer develop a clinically overt VTE during their disease. These patients are hospitalized more frequently than VTE patients without cancer, are sicker and more prone to develop treatment side-effects. Patients with cancer have more frequently an extensive or bilateral DVT of the lower limbs and venous thrombosis in unusual sites. Although patients with cancer may have a VTE at any stage of their disease, this complication is particularly common in association with surgery for cancer, chemotherapy and use of a central vein catheter (CVC).

Primary prevention of VTE in cancer patients

Postoperative VTE

For a similar type of surgery, post-operative VTE occurs 3-5-time more frequently in cancer patients than in non-cancer patients.[1] In cancer patients undergoing surgery without prophylaxis, the incidence of deep vein thrombosis (DVT), as shown by screening procedures, is 40-80% and that of proximal DVT 10-20%. In a large multicenter study including patients undergoing abdominal surgery, the incidence of fatal pulmonary embolism (PE) was 1.6% in cancer patients and 0.5% in those without cancer (p=0.05).[2] A recent prospective study focused on the incidence of clinically overt VTE in patients undergoing surgery for cancer and found an incidence of 2.1% at the 30th post-operative day despite most of the patients were on pharmacological prophylaxis. About 40% of VTE events occurred beyond three weeks after surgery. The 30-day mortality was 1.72% and approximately half of deaths were due to pulmonary embolism.[3] Extensive abdominal or pelvic surgery, age older than 60 years, obesity, previous VTE episodes and prolonged immobility place patients with cancer at particularly high risk of post-operative VTE complication.

The most commonly used prophylactic regimen consists in a single pre-operative injection of heparin (UFH or LMWH), followed by subcutaneous injections starting within 12-24 hours after surgery. Typically, UFH is given two or three times daily while LMWH is given once-daily.

Based on the meta-analysis by Mismetti *et al.*,[4] once-daily LMWH is as safe and effective as multiple daily-injections of UFH in reducing the incidence of post-operative VTE. The largest randomized, controlled trial that compared LMWH (enoxaparin 40 mg once-daily) with UFH (5000 U three times a day) given for 10 days showed a non significant risk reduction in favour of enoxaparin (14.7% versus 18.2%, respectively).[5] The benefit of extended prophylaxis for VTE after cancer surgery has been demonstrated by the ENOXACAN II study.[6] This study reported a statistically significant reduction from 12% to 4.8% in the rate of DVT in associ-

ation with extended prophylaxis (4 weeks) as compared with shorter prophylaxis (first post-operative week). In the PEGASUS study, fondaparinux was associated with a 40% risk reduction of VTE in the subgroup of patients undergoing abdominal surgery for cancer.[7]

Chemotherapy

While receiving chemotherapy and/or hormone therapy, cancer patients have an increased risk of developing a VTE. Data on radiotherapy are less clear. The risk of VTE associated with chemotherapy is dependent on many contributing factors including cancer stage, age, co-morbidities, bed rest, type and intensity of therapeutic regimens. Most of the data on the incidence of chemotherapy-associated VTE derive from studies in women with breast cancer. In these patients, the risk of VTE ranges from 4% to 15% and is even higher in patients with metastatic cancer. An incidence of VTE of approximately 10% per year has been recently reported in patients with a variety of cancer including cancer of the colon, lung, breast and genitourinary.[8]

Warfarin 1 mg a day has been reported to be safe and effective in reducing VTE complications in patients with stage IV breast cancer.[9] However, the available evidence to recommend routine antithrombotic prophylaxis in whatever type of cancer is modest. More data about this issue will be available after the completion of several ongoing studies designed to assess the clinical benefit of antithrombotic prophylaxis to prevent chemotherapy associated VTE.

Central vein catheters

Currently, most of the cancer patients have a long-term CVC inserted for chemotherapy. CVC offers to cancer patients advantages that are potentially overweighed by complications as CVC-related DVT and infections. The incidence of asymptomatic CVC-related DVT is estimated to be about 20%, while the rate of clinically overt DVT of upper limbs is ranging between 2 and 4%. Some features of the catheter may influence the occurrence of VTE complications.[10] The role of antithrombotic prophylaxis in the prevention of CVC-related thrombosis is controversial. Although some open label studies[11,12] demonstrated a benefit in the prevention of CVC-related complications with both LMWH and warfarin, more recent randomized, placebo controlled trials[13-15], where either symptomatic or venography-detected thrombosis was measured, did not confirm this benefit.

Recently, a multicenter, randomized, double-blind, placebo-controlled study assessed the efficacy and safety of enoxaparin, given for 6 weeks, for the prevention of VTE in 385 cancer patients with CVC. In this study, a 22% not statistically significant risk reduction in the rate of CVC-related VTE was detected between patients receiving enoxaparin and those receiving placebo.[15]

Treatment of VTE in cancer patients

When VTE is objectively confirmed, anticoagulant therapy is required. The traditional anticoagulant regimen (adjusted-dose UFH or fixed dose LMWH for 5 to 7 days followed by oral anticoagulation) is highly effective and safe in most patients with VTE. However, in cancer patients the unfavourable natural history of VTE and the high risk of adverse events can complicate the management of VTE. Recurrence of VTE is more common in cancer patients than in non-cancer patients[19,20] and can occur despite an appropriate anticoagulation. In the other hand, cancer patients are particularly prone to develop bleeding complications while receiving anticoagulant treatment. LMWHs have been reported to be associated with a lower risk of adverse events compared with warfarin. A study of 146 cancer patients with VTE who received 3 months of treatment with LMWH or warfarin demonstrated a higher risk of major bleeding or recurrent of VTE in the warfarin group (21.1% versus 10.5% respectively), although this difference was non statistically significant.[16]

Recently, a randomized, controlled study in cancer patients showed that long-term administration of LMWH may be an improved treatment option for this group of patients. In the CLOT study,[17] patients were randomized to receive an initial treatment with once-daily dalteparin (200 UI/kg), followed by either dalteparin or warfarin. The results of the study demonstrated a significant reduction in recurrent of VTE in patients who received dalteparin in comparison to patients who received heparin and warfarin. This benefit was obtained without any increase of the risk of bleedings.

The optimal duration of antithrombotic treatment in cancer patients remains to be defined. The seventh ACCP consensus conference recently recommended an indefinitely or *as long as cancer is active* anticoagulation for VTE occurring in cancer patients.[18]

Conclusions

Because few clinical trials have focused on the prevention and treatment of VTE in patients with cancer, many questions on these issues remain open. Currently, LMWHs are emerging as the agents of choice for the prevention and treatment of VTE in patients with cancer, offering advantages over unfractionated heparin and warfarin.

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