

Cancer Related Thrombophilia: Clinical Importance and Management Strategies

MADHUCHANDA KAR

INTRODUCTION

The incidence of various thrombosis in the general population is 117 per 100,000 people per year¹. Cancer is an important risk factor for deep venous thrombosis (DVT) with one population-based study indicating that its presence leads to a 6 fold increase in risk for venous thromboembolism². However, thrombophilia in each cancer patient depends on the tumor type, extent of cancer, type of anticancer therapy, presence of extrinsic factors (like surgery and immobilization) and previous history of thrombosis. The best evidence on the incidence of thrombosis in a particular type of cancer comes from clinical trials of systemic therapy of women with early breast cancer^{3,4}.

RELATION WITH CANCER THERAPEUTICS

Therapeutic interventions in cancer have also been associated with thrombophilia like concurrent chemotherapy with radiation or use of erythropoietin as supportive care⁵. Interestingly, the enigma of thrombogenicity of anticancer agents has been rekindled because of unexpectedly high venous thromboembolism (VTE) episodes in patients receiving novel anticancer agents aimed at specific molecular targets in the cancer cell, for example anti-vascular endothelial growth factor, anti-epidermal growth factor receptor agents and thalidomide⁶.

PROGNOSIS OF PATIENTS WITH CANCER AND VTE

Patients with cancer who develop VTE have a shorter life expectancy². In a population based study, mortality rate in cancer patients was approximately 2-3 folds higher in patients with VTE^{7,8}. The exact reasons for the

bad prognosis are unknown but possible explanations include:

- Premature death from fatal pulmonary embolism,
- Thrombosis is a marker of aggressive malignancies,
- Activation of coagulation is inherently involved in tumor growth and metastatic spread.

PATHOGENESIS

In 1865, Professor Armand Trousseau first reported on the association between cancer and thrombosis⁹. It involves a complex interaction between tumor cell, the patient and the hemostatic system. All three mechanisms of Virchow's are at play in patients with malignant disease i.e. stasis, activation of blood coagulation and vascular injury¹⁰.

- Stasis results from patient's immobility or from extrinsic venous compression from tumor masses and lymph nodes.
- Blood coagulability results from tumor cell production of procoagulant molecules that activate coagulation directly or indirectly by initiating an inflammatory response. The two best characterized procoagulants associated with tumor cells are tissue factor (TF) and cancer procoagulant^{11,12}. At present TF seems to play a more important role in the pathogenesis of clinical thrombosis than cancer procoagulant.
- The third mechanism is vascular injury.
- Extrinsic factors like surgery, chemotherapy drugs and vascular access catheters can all damage the vessel wall. Mechanism of chemotherapy induced thrombosis is unclear but is likely to be multifactorial¹³.

- In patients receiving tamoxifen, thrombosis may be due to its partial estrogen agonist effect¹⁵.
- It is likely that chemotherapy causes endothelial cell damage or change¹⁴.

PREVENTION OF THROMBOSIS

1. Prophylaxis in surgical patients with cancer: Postoperative thrombosis is higher in cancer compared to noncancer patient¹⁵. In a trial by Mismetti, et al once daily low molecular weight heparin (LMWH) demonstrated equal efficacy to unfractionated heparin (UFH) in high risk major surgery¹⁶. The once daily injection is attractive because of comfort of patients, convenience for medical staff and lower risk of drug error. There are also some studies like that of Bergqvist, et al of extended prophylaxis in cancer patients beyond postoperative period¹⁷. These findings were later corroborated by dalteparin and enoxaparin studies which reached statistical significance in reduction in DVT¹⁸.

Extended prophylaxis in cancer surgery is potentially an important advance in the care of patients with cancer undergoing surgery. However, further research is required to show that continuing anticoagulant therapy beyond hospitalization will also reduce the risk of clinically important VTE.

2. Prophylaxis in medical patients with cancer: There are two main clinical situations when considering prevention of VTE in the medical patients with cancer.

The first involves the ambulatory patient who is receiving chemotherapy or radiotherapy and the second involves patients who are bed-ridden for prolonged periods. There are not enough data on primary prevention of thrombosis in ambulatory patients with cancer and oncologists do not routinely use oral anticoagulants for patients receiving chemotherapy.

On the other hand, patients who are hospitalized with acute complications related to his or her cancer (e.g. pain crisis, infection or hypercalcemia) should receive prophylaxis with low dose UFH or LMWH¹⁹.

3. Central vein catheter thrombosis. Thrombosis associated with central vein catheters can be particularly problematic in the patient with cancer. There have been only 2 randomized trials in this regard for primary prevention with warfarin (1 mg/d) and LMWH (dalteparin 2500 μ /d) which have shown significant reduction in thrombosis compared with

control arm^{20,21}. However there have been many recent trials where the rates of central venous catheter related thrombosis have been rather low possibly due to use of newer generation catheters and improved catheter care^{22,23}. Presently, there is not robust evidence to routinely use antithrombotic prophylaxis in such patients.

TREATMENT

- a. *Initial Therapy*: Management of venous thrombosis in cancer patients is complicated because they are at increased risk for recurrent VTE and anticoagulant associated bleeding compared with patients who do not have cancer²³. LMWHs have largely replaced UFH because they are as effective and safe, can be used at home and do not need laboratory monitoring²⁴.
- b. *Long Term Therapy*: In the past cancer patients with thrombosis have been treated with long term anticoagulant therapy, but this requires laboratory monitoring to maintain target INR. This has some difficulties like drug interactions with use of concomitant medications, alterations in impaired hepatic functions and need for temporary cessation to accommodate chemotherapy-induced thrombocytopenia or during invasive procedures.

LMWH is a good alternative to Vit K as they do not require laboratory monitoring and is potentially associated with less bleeding than warfarin. Two trials recently have examined long-term LMWH in patients with cancer and compared with oral anticoagulants. In the trial by Meyer, et al, composite outcome event rate (major bleeding and recurrent VTE) was 21% in the warfarin arm compared to 10.5% in the LMWH (enoxaparin) arm contributed by 16.4% bleeding in warfarin arm compared to 7.5% in LMWH arm²⁴. In the trial by Lee, et al [Randomized Comparison of Low Molecular Weight Heparin Versus Oral Anticoagulant Therapy for Long Term Anticoagulation in Cancer with Venous thromboembolism (CLOT) trial] LMWH (dalteparin) was compared to oral anticoagulant²⁵.

The probability of VTE was reduced from 17.4% in the oral anticoagulant group to 8.8% in the dalteparin group but no statistically significant difference in major bleeding was noted. However the rate of any bleeding (major and minor) was 18.5% in the oral anticoagulant group compared with 13.6% in the dalteparin group. So these trial results make LMWH an important advance in the treatment of patients with cancer associated acute VTE²⁷.

In general, duration of long term treatment of VTE is based on patient's risk of recurrent thrombosis and bleeding. But there are no trials in cancer patients and data regarding duration of anticoagulation have to be extrapolated from trials of patients with idiopathic thrombosis. Usually it is individualized e.g. in metastatic setting anticoagulation needs to be continued indefinitely or until contraindications develop. On the other hand, in presence of active (but non-metastatic) disease it should be administered for at least 6 months or as long as there is evidence of cancer or while patient is receiving chemotherapy. Lastly, in patients without active cancer but with a strong risk factor (e.g. surgery) a minimum of 3 months anticoagulation is probably reasonable.

ANTINEOPLASTIC EFFECTS OF ANTICOAGULANTS

In 1984, a large Veterans Affairs Cooperative trial reported a survival advantage for patients with small cell lung cancer who were randomly assigned to receive either warfarin in addition to multiagent chemotherapy or chemotherapy alone.²⁸

Interest in potential for antithrombotics to impact on survival waned until a number of metaanalysis of trials of LMWH compared with UFH for the initial treatment of acute VTE demonstrated a reduction in mortality in favor of LMWH^{29,30}. The observed reduction was as a result of the effect in the subgroup of patients with cancer. But none of these trials were designed with survival as the primary outcome. Recent trials in these regard are also encouraging as LMWHs can have effects on angiogenesis, apoptosis and tumor cell invasion³⁰.

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