Thrombophilia in Malignancy: A Review of the literature

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Abstract

Hypercoagulable state is a well recognized complication of malignancy. Venous thrombosis manifests mainly as deep venous thrombosis or pulmonary embolism. Autopsy studies have reported increased rates of pulmonary embolism among cancer patients as compared to patients without malignancy.[1] The risk of recurrence is also high among the cancer patients.[2] Patients who present with an unprovoked venous thromboembolism (VTE) are more likely to have an underlying cancer than those patients with an identifiable risk factor.[3, 4] Concurrent VTE and cancer also increases the risk of death. The increased risk for deep venous thrombosis in cancer patients is often not considered while planning treatment.

INTRODUCTION

Armand Trousseau made the first observation of the association of malignancy and thrombosis. “Trousseau, in 1861, stated that if the diagnosis of a suspected carcinoma of an internal organ could not be verified, the sudden and spontaneous appearance of thrombophlebitis in a large vein afforded necessary proof for diagnosis”. In 1865, he described “phlegmasia alba dolens” as a presenting symptom of occult cancer. Since then a series of clinical observations has confirmed venous thrombosis, a clinical complication of acute leukemia. Bleeding and thrombosis are well recognized complications of acute promyelocytic leukemia. A majority of patients with solid tumors and leukemias may have only laboratory abnormalities of coagulation profiles without manifest thrombosis. The basic research and clinical studies has improved our knowledge in this field only in the last few decades. This review article illustrates the magnitude of the problem of VTE in cancer patients, the effect of VTE in cancer patients, the possible mechanism of VTE in cancer, and prophylaxis and treatment for VTE in malignancy.

EPIDEMIOLOGY

Thrombosis is a common complication in cancer patients. VTE significantly influences the morbidity and mortality in cancer patients. It still remains under diagnosed and under treated in cancer patients.5, 6 At least 50 percent of cancer patients are found to have VTE in autopsy studies.7, 8 The assessment of true incidence of VTE in cancer patients is difficult because most of these patients receive chemotherapy and hormonal therapy apart from other comorbid conditions like indwelling central venous access which increases the risk for thrombosis.9, 10 In the course of their illness 15 percent of all cancer patients develop clinically apparent thrombosis.11, 12 In a multivariate logistic analysis of potential risk factors for DVT or PE, the first life time episode of venous thromboembolism diagnosed in the community showed a 4 fold increase in the risk among cancer patients.13 The risk was even more when the cancer patients were treated with chemotherapy when compared with control.13

Incidence rates of thrombosis have been determined in prospective clinical trial for women with breast cancer receiving different hormonal and other therapeutic agents. The risk of thrombosis increases with advanced stage at diagnosis. The analysis also found that the risk of VTE was greatest in patient receiving hormonal and chemotherapeutic agents.14, 15, 16 The incidence rate ranges from 0.1 percent in early stage breast cancer to 17percent in advance stage breast cancer patients on chemotherapyd17. The incidence was also higher among post menopausal patients on treatment.18

A retrospective analysis of 493 NSCLC patients to determine the incidence and predictors of VTE has revealed a high incidence of DVT in NSCLC. In this study the advance stage and male sex are independent predictors of DVT. NSCLC patients with DVT have 1.7 fold increase risk of dying as compared to those who are not diagnosed with VTE. Age, type of NSCLC, and chemotherapy did not

predict DVT.19 In another observation the incidence of DVT was higher among multiple myeloma patients who were treated with chemotherapy and thalidomide.20

Studies have shown a significant association between initial deep venous thrombosis, pulmonary embolism and subsequent development of cancer.21 The incidence of cancer is also higher among patients with recurrent VTE. The risk of developing cancer was particularly higher in patients less than 60 years of age and almost entirely during the first year of follow up for the VTE or pulmonary embolism.22 The detection of cancer in patients presenting with an initial VTE or PE often requires an extensive work up. It is not clear whether extensive screening of these patients with thromboemolism for malignancy would be either cost effective or change the outcome.23, 24 The diagnosis of cancer at the time or within a year of an episode of VTE is associated with an advanced stage of cancer and a poor prognosis 6.

PATHOGENESIS

Hypercoagulable state of malignancy is a clinical spectrum where patients can present with abnormal coagulation tests with no clinically apparent thromboembolism to arterial and venous thrombosis, migratory thrombophlebitis , thrombotic non bacterial endocarditis ,thrombotic microangiopathy and or, DIC.

Pathogenesis of thrombosis in cancer is multifactorial. Cancer cells can contribute to activation of the clotting system by their capacity to produce and release procoagulant, fibrinolytic substances and inflammatory cytokines, and by their interaction with host cells. Chemotherapy, hormonal therapy and radiotherapy can also increase the risk of thromboembolic complications in cancer patients by release of procoagulants by tumor cells, through endothelial damage, or stimulation of tissue factor production by host cells.25 Intact tumor cells also possess tumor specific clot promoting mechanism. The best studied among them are tissue factor and cancer procoagulant.26

Tissue factor (TF) is a transmemberane glycoprotein that forms a complex with factor VII to activate factor IX and factor X by proteolysis. Thus TF primarily activates the intrinsic blood coagulation pathway. TF is a cellular procoagulant found in normal cells, including endothelial cells and monocyte – macrophages but not expressed in the resting condition. In healthy vascular cells, expression of the tissue factor is induced by inflammatory stimuli such as the cytokines interleukin 1 and tumor necrosis factor (TNF) as well as bacterial endotoxin.27 TF is consistently expressed in malignant cells and its expression inversely correlates with the degree of differentiation of the tumor.

Cancer procoagulant (CP) is calcium dependent cysteine protease found in malignant cells but not in normally differentiated tissue.28 CP can directly activate factor X independently of factor VII and tissue factor complex.29 CP and TF have been identified in several human and animal tumor tissues. Myeloid precursors in the bone marrow do not possess procoagulant activity. Hypercoagulopathy in acute promyelocytic leukemia resolves with disappearance of leukemic blast cells in the bone marrow. The procoagulant properties of blast promyeloyte from APL patients appear to be down regulated by ATRA. The resolution of severe coagulopathy in acute promyelocytic leukemia parallel with blast cell procoagulant activities supports the role of tumor procoagulant in promoting clotting complications.30

Malignant cells also express proteins that regulate fibrinolysis. Increase in the plasma concentration of plasminogen-activator inhibitors and impairment in plasma fibrinolytic activity in patients with solid tumors indicates another tumor associated prothrombotic mechanism.31 Tumor cells induce platelet activation and aggregation by direct cell-cell contact or by releasing soluble factors, such as ADP, thrombin and other proteases 32. Endothelial cells may become procoagulant under the influence of inflammatory cytokines and other peptide products. TNF is able to dramatically enhance the procoagulant and suppress the anticoagulant properties of cultured vascular endothelial cells.33 At the same time studies have not shown consistent and significant elevation of TNF in all patients with malignancy.34, 35

The pathogenesis of cancer-associated VTE is a complex phenomenon. Various components of haemostatic host cells directly interact with tumor cells with the help of adhesion molecules on the surface of the tumor cells. Recent evidences from tumor biology indicate that the activation of haemostasis in malignant disease contributes to tumor growth and progression by stimulation of intracellular signaling pathways. The interaction of tissue factor, thrombin and other coagulation factors with protease activated receptor (PAR) proteins expressed by tumor cells and host vascular cells leads to the induction of genes related to the processes of angiogenesis, cell survival and cell adhesion and migration.36

ANTICOAGULATION PROPHYLAXIS

The role of primary prophylaxis in ambulatory or hospitalized cancer patients who are actively receiving chemotherapy outside the perioperative setting is not well understood. There is only a limited number of studies of the value of anticoagulation in cancer patients have been conducted. The lower survival rates among the cancer patients with VTE support the value of thromboprophylaxis in this patient population. In contrast to surgical cancer patients the routine use of thromboprophylaxis in medical cancer patients was substantially lower in a worldwide survey of practice pattern of thromboprophylaxis among cancer patients.37

Large clinical trials have demonstrated the routine use of VTE prophylaxis with low molecular weight heparin (LMWH) or unfractionated heparin (UFH) in cancer patient undergoing surgery.38 Patients who had surgery for abdominal cancer are known to have significant risk for VTE. The enoxaparin and cancer study evaluated subcutaneous enoxaparin 40mg daily versus low dose UFH 5000 unit administered three times daily for 8-12 days in more than 600 patients requiring abdominal or pelvic surgery for their malignancies.39 Enoxaparin and UFH were equally effective in reducing early onset of VTE and were associated with similar risks of major bleeding complications. The overall rate of DVT was 14.7 percent for enoxaparin group and 18.2 percent for UFH group.39 The combination thromboprophylaxis by mechanical graded compression stockings and UFH increases the efficacy in colorectal surgery patients.40 There are no studies available presently using LMWH and mechanical device in prophylaxis for cancer patients. Combination thromboprophylaxis is generally recommended for patients with multiple risk factors.41

The optimum duration of thromboprophylaxis in high risk patients undergoing surgery remains controversial. The results from a multicenter, double blind, placebo controlled ENOXACAN II trial showed a definite evidence of reduction of VTE in patients treated with enoxaparin for long term postoperatively. The patients who had curative abdomen-pelvic surgery for cancer and treated with enoxaparin 40 mg once daily for 3 additional weeks had significantly less incidence of VTE as compared to patients who were treated only for 6-10 days of thromboprophylaxis postoperatively.42

There have been no well conducted, randomized controlled trials focused specifically on the efficacy and safety of anticoagulants among cancer patients hospitalized for medical conditions. MEDNOX (prophylaxis of VTE in medical patients with enoxaparin) study, evaluated LMWH for prophylaxis in acutely ill medical patients who are admitted to hospital.43 Approximately 12 to 15 percent of the patients among this group had documented malignancy. In this study 2 different doses of enoxaparin 20 mg and 40 mg subcutaneous once daily were compared to each other and compared with a placebo over 6-14 days in more than 1100 acutely ill medical patients. Those who received enoxaparin 40 mg had 6 percent incidence of VTE detected by bilateral venography as compared to 15 percent in the placebo group ($P<0.001$).43 Symptomatic VTE was detected in 2.1% of patients in the enoxaparin group and 5.6% in placebo group. This represent a significant reduction of VTE incidence among patients treated with enoxaparin. There was no significance difference identified in the incidence of VTE among Placebo group and low dose enoxaparin injection group (20 mg).

A prospective evaluation of efficacy of daltaparin for the prevention of VTE in immobilized patients (PREVENT) demonstrated substantially reduced incidence of VTE among medical patients who received prophylactic anticoagulant with daltaparin 5000 IU subcutaneously daily for 14 days compared with placebo. Five percent of these general medical patients were diagnosed with cancer. The combined primary end point of the trial was VTE and or sudden death. The incidence was 2.77% in daltaparin group as compared to 4.96% in placebo group ($P<0.0015$).44

The role of prophylactic anticoagulant in cancer patients receiving outpatient chemotherapy has been evaluated. In a double blind randomized controlled trial, 311 women receiving chemotherapy for metastatic breast cancer were randomly assigned to either very-low-dose warfarin or placebo. The warfarin dose was 1 mg daily for 6 weeks and was then adjusted to maintain the prothrombin time at an international normalised ratio (INR) of 1.3 to 1.9. Study treatment continued until 1 week after the end of chemotherapy (average 6 months). The mean time at risk of thrombosis was 126 days for warfarin-treated patients and 137 days for placebo recipients ($p = 0.45$). There were 7 VTE events in the placebo group and one in the warfarin group during the follow up. The relative risk reduction was 85% ($p = 0.031$). Major bleeding occurred in 2 placebo recipients and 1 warfarin-treated patient. There was no detectable difference in survival between the treatment

groups. This study proves a very-low-dose warfarin is a safe and effective method for prevention of thromboembolism in ambulatory patients with metastatic breast cancer who are receiving chemotherapy.44 There was no difference in the incidence of major bleeding in placebo versus the LMWH group in all these studies.

Recent studies have also reported higher incidence of VTE in patients receiving thalidomide or lenalidamide for multiple myeloma. Incidence is much higher in combination with chemothapy drugs.46 No randomized controlled trials are available to optimize thromboprophylaxis in these high risk patients. Based on observational data antithrombotic therapy is well tolerated among these groups.47 Based on available data primary prophylaxis may be recommended in cancer patients admitted to hospital with acute medical illness. Saftey and efficacy of routine thromboprophylaxis in ambulatory cancer patient is not well understood. Thromboprophylaxis after major surgey in certain cancer patients is justified. ACCP recommends post hospital thromboprophylaxis with LMWH or UFH.48

SECONDARY PROPHYLAXIS FOR VTE IN CANCER PATIENTS.

Venous thromboembolism is a frequent complication of active malignancy and has been identified as a marker of poor outcome in patients with cancer. Patients with cancer and venous thromboembolism have a lower survival at 1 year than patients with cancer who do not have venous thromboembolism. The increased mortality rate observed in cancer patients with venous thromboembolism may result from a more advanced cancer state or may be related to venous thromboembolism itself. Most of the small trials comparing low-molecular-weight heparins with warfarin for the secondary prophylaxis of venous thromboembolism did not find a difference in the risk of recurrent thrombosis.

In the CLOT trial patients with cancer who had acute, symptomatic proximal deep-vein thrombosis, pulmonary embolism, or both were randomly assigned to receive low-molecular-weight heparin (dalteparin) at a dose of 200 IU per kilogram of body weight subcutaneously once daily for five to seven days and a coumarin derivative for six months (target international normalized ratio, 2.5) or dalteparin alone for six months (200 IU per kilogram once daily for one month, followed by a daily dose of approximately 150 IU per kilogram for five months). During the six-month study period, 27 of 336 patients in the dalteparin group had recurrent venous thromboembolism, as compared with 53 of 336 patients in the oral-anticoagulant group (hazard ratio, 0.48; P=0.002). The probability of recurrent thromboembolism at six months was 17 percent in the oral-anticoagulant group and 9 percent in the dalteparin group. No significant difference between the dalteparin group and the oral-anticoagulant group was detected in the rate of major bleeding (6 percent and 4 percent, respectively) or any bleeding (14 percent and 19 percent, respectively). The mortality rate at six months was 39 percent in the dalteparin group and 41 percent in the oral-anticoagulant group.49 The CLOT trial concluded that patients with cancer and acute venous thromboembolism, dalteparin was more effective than an oral anticoagulant in reducing the risk of recurrent thromboembolism without increasing the risk of bleeding.

In another randomized, open-label multicenter trial, compared subcutaneous enoxaparin sodium (1.5 mg/kg once a day) with warfarin given for 3 months in 146 patients with venous thromboembolism and cancer.50 Among the 71 evaluable patients assigned to receive warfarin, 15 (21.1%; 95% confidence interval [CI], 12.3%-32.4%) experienced one major outcome event compared with 7 (10.5%) of the 67 evaluable patients assigned to receive enoxaparin (95% CI, 4.3%-20.3%; P = .09). There were 6 deaths owing to hemorrhage in the warfarin group compared with none in the enoxaparin group. In the warfarin group, 17 patients (22.7%) died (95% CI, 13.8%-33.8%) compared with 8 (11.3%) in the enoxaparin group (95% CI, 5.0%-21.0%; P = .07). No difference was observed regarding the progression of the underlying cancer or cancer-related death among the two groups. The results of this study suggest that the long-term use of enoxaparin may be an effective and safe treatment for secondary prevention of venous thromboembolism in patients with cancer and venous thromboembolism.

A prospective evaluation of the effectiveness and safety of long-term subcutaneous dalteparin in a series of consecutive patients with symptomatic VTE and metastatic cancer showed a fixed dose 10 000 IU subcutaneous dalteparin once daily for 3 months was not associated with more complications in patients with disseminated cancer.51

Primary prophylaxis for VTE is recommended for hospitalized patients with cancer in the absence of specific contraindications such as active bleeding. The recommendations for VTE prophylaxis in hospitalized patients with cancer are based on clinical trials that enrolled only a small proportion of patients with cancer. Although the low complication rates with thromboprophylaxis in most clinical trials justify the use of VTE prophylaxis in

hospitalized patients with cancer. None of the randomized clinical trials have reported any major bleeding in the subgroup of patients with cancer. There are only a few data available on the prevention of VTE in ambulatory patients with cancer. Some of the observational data suggests the use of LMWH or adjusted-dose warfarin in patients who are recognized with high risk for VTE such as patients receiving thalidomide with chemotherapy or dexamethasone. More randomized controlled trials are required to evaluate the potential risk of VTE and the value of primary prophylaxis in patients receiving novel targeted therapies, like antiangiogenic agents. Primary prophylaxis should be considered for all patients undergoing major surgical intervention for malignant disease for at least 7 to 10 days postoperatively. Prolonged prophylaxis for up to 4 weeks may be considered in patients undergoing major abdominal or pelvic surgery for cancer with high-risk features. LMWH is the preferred approach for both initial and long-term anticoagulant therapy for documented VTE in patients with malignant disease. Indefinite anticoagulant therapy may be considered for patients with active cancer, including those with metastatic disease or those continuing to receive systemic chemotherapy.

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