Review Article

Cancer Related Thrombophilia: Clinical Importance and Management Strategies

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Abstract

Acquired thrombophilic state associated with a significant risk of thrombosis is frequently encountered in malignancy. Venous and arterial thromboembolism is a common complication and patients with cancer, also present with a hypercoagulable state, even in the absence of thrombosis. Furthermore, clotting activation may play a role in tumor progression. The pathogenesis of thrombosis in cancer is multifactorial; however, a relevant role is attributed to the tumor cell capacity to interact with and activate the host hemostatic system. Among other factors, the prothrombotic action of antitumor therapies is also important. Thrombotic events can influence the morbidity and mortality of the underlying disease. Therefore, preventing these complications in cancer patients is a clinically relevant issue. Recently, new approaches to the prevention and cure of thrombosis in cancer have been investigated, and the hypothesis that the strategies to inhibit clotting mechanism may favorably affect malignant disease is gaining increasing interest. In this article, the various aspects of the complex relationship between thrombosis and cancer, from pathophysiology to therapy, are reviewed.

INTRODUCTION

Patients with cancer are exposed to a significant risk of thrombosis. The interrelationship between hemostasis and cancer although widely accepted but remains poorly understood. However this interrelationship goes beyond thrombosis. Hemostasis is deeply involved in tumor growth, angiogenesis and metastasis and modulation of these pathways may yield interesting and promising future treatment options.

It has been estimated that approximately 15% of all cancer patients develops thrombosis during the course of their disease. Thrombotic disorders in cancer patients include venous and arterial thrombosis, migratory thrombophlebitis, thrombotic nonbacterial endocarditis, and systemic syndromes such as, thrombotic microangiopathy and disseminated intravascular coagulation (DIC). Severe DIC is generally associated with acute promyelocytic leukemia (AML – M3) and is characterized by life-threatening hemorrhages and concomitant thrombotic complications.

Most patients with solid tumors and leukemias commonly suffer from chronic compensated DIC and have abnormalities in laboratory coagulation tests, without manifest thrombosis. This subclinical hypercoagulable condition is characterized by varying degrees of blood clotting activation. The results of laboratory tests in these patients demonstrate that a process of fibrin formation and lysis is continuously ongoing during the course of malignancy.

The aim of this review is to summarize the recent advances in the understanding of the relationship between thrombophilia and cancer, particularly the pathophysiologic mechanisms of blood clotting activation in malignancy and the current concepts in the prevention and treatment of the thrombosis in cancer.

CANCER ASSOCIATED HYPERCOAGULABILITY

Different tumors of different extent, with a different comorbidities, and different inherited hypercoagulable states may promote the development of thrombosis by different combinations of tumor and non – tumor associated procoagulant mechanisms. Solid tumor mediated extrinsic vascular compression and invasion can obstruct venous return, resulting in blood flow stasis, and promote endothelial cell injury, resulting in coagulation activation. Tumor cells promote thrombin generation directly by producing tissue factor; expressing the coagulation factor X activator known as cancer procoagulant; displaying surface sialic acid residues that can support nonenzymatic factor X activation and indirectly by eliciting tissue factor.
expression from monocytes and endothelial cells.\textsuperscript{5,6}

It is widely recognized that the majority of cancer patients present with one or more abnormalities of laboratory coagulation tests. The most frequent abnormalities include increased levels of fibrinogen, factors V, VIII, IX, X, fibrinogen(ogen) degradation products (FDPs) and thrombocytosis.\textsuperscript{7}

Recently, the development of newer, more sensitive laboratory tests have enabled the detection of markers of ongoing activation of blood coagulation in vivo. These tests measure the final products of clotting reactions in plasma and are listed in Fig. 1. Studies of the plasma levels of these parameters have provided a biochemical definition of the hypercoagulable state in humans. However, little or no information is available on the clinical utility of any of them in the single patient. No large prospective studies have been conducted to assess the predictive value of these laboratory tests for thrombosis in cancer patients. In a small series of cancer patients enrolled in a trial of perioperative heparin prophylaxis versus placebo, the study of biological markers showed that preoperative thrombin – antithrombin complex (TAT) values > 3.5 ng/ml were significantly predictive for post – operative deep vein thrombosis (DVT), with a relative risk of 7.5 (p<0.05).\textsuperscript{8} However, subsequent studies in patients with colorectal cancer or ovarian cancer have reported conflicting results.\textsuperscript{9}

**PATHOGENESIS OF INCREASED RISK OF THROMBOSIS IN CANCER**

Activation of blood coagulation and thrombotic diathesis is a complex phenomenon and that it involves different hemostatic pathways in patients with cancer, and many factors which contribute includes non – specific factors, tumor-specific factors, and anticancer therapy-related factors.\textsuperscript{4} Non - specific causes such as immobilization causing stasis; effects of damaged or necrotic normal or tumor tissues, associated inflammation or infection, entry of mucin into the circulation, and foreign body effects of venous access devices all aids in thrombus formation.

### Table 1: Malignancies often associated with thrombosis

<table>
<thead>
<tr>
<th>Cancer Stage</th>
<th>Malignancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>Gall bladder</td>
</tr>
<tr>
<td>Gastric</td>
<td>Lung (any cell type)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Myeloproliferative syndrome</td>
</tr>
<tr>
<td>Ovary</td>
<td>Pancreas</td>
</tr>
<tr>
<td>Lymphomas / Primary bone tumors</td>
<td>Paraprotein disorders</td>
</tr>
</tbody>
</table>

### Table 2: Cancer – specific mechanisms of activation of blood coagulation

1. **Tumor cell activities**
   - Procoagulant
   - Fibrinolytic proteins
   - Pro inflammatory and proangiogenic cytokine production
   - Direct interaction with host vascular and blood cells (platelets, leukocytes and endothelial cells)

2. **Neovascularization**

3. **Antitumor therapies**
   - Chemotherapy, radiotherapy, hormone therapy, antiangiogenic therapy
have focused on the procoagulant activities expressed by leukemic cells.\textsuperscript{3,15} Interestingly, the rapid resolution of the severe coagulopathy observed in patients with APML receiving all-trans-retinoic acid therapy is strictly associated with the loss of procoagulant activity from bone marrow blast cells.\textsuperscript{3}

(ii) Fibrinolytic system

The presence of inhibitors of fibrinolysis was observed in cancer patients long before the plasminogen activator inhibitor type I (PAI – 1) was identified. Tumor cells can express all proteins of the fibrinolytic system, including the urokinase-type (u-PA) and tissue type (t-PA) plasminogen activators, and their inhibitors PAI-1 and PAI-2.\textsuperscript{16} An impaired plasma fibrinolytic activity has been described repeatedly in patients with solid tumors, representing an additional tumor – associated prothrombotic mechanism. Recent data strongly suggests that fibrinolytic proteins play a major role in tumor invasion, tumor cell proliferation , and metastasis. In addition, these factors are under evaluation as potential predictors of disease-free interval and long-term survival in malignant disease.\textsuperscript{17}

(iii) Cytokines

Tumor cells synthesize and release inflammatory cytokines, including TNF-\(\alpha\) and IL-1\(\beta\), which can induce the expression of TF procoagulant activity by endothelial cells and monocytes.\textsuperscript{18} These cytokines also downregulate the expression of endothelial cell thrombomodulin (TM), a potent anticoagulant factor. TF upregulation and TM downregulation lead to a prothrombotic condition of the vascular wall. The same cytokines stimulate endothelial cells to produce the fibrinolysis inhibitor PAI-1, which depresses fibrinolysis and further favors a prothrombotic phenomenon.\textsuperscript{18}

In addition, the production of vascular endothelial growth factor (VEGF) by malignant cells may significantly affect the functions of micro vessels in proximity of the tumor and play an important role in tumor neo-angiogenesis. Furthermore, VEGF is chemotactic for macrophages and can induce TF procoagulant activity by monocyte and endothelial cells. Interestingly, the expression of TF by tumor cells upregulates the transcription of VEGF in the same cells. Regulation of VEGF synthesis by TF in malignant cells and vascular cells provides an important link between thrombosis, inflammation, and tumor growth and metastasis.

(b) Direct Interaction of Tumor cells with Host cells

The presence of cell adhesion molecules on the surface of tumor cells provides the possibility for direct interaction with host cells. During the hematogenous spread, this interaction occurs with endothelial cells, platelets, and leukocytes.

The tumor cell capacity to adhere to the endothelium and the underlying matrix is well described and adhesion molecule pathways specific to different tumor cell types have been identified.\textsuperscript{19,20} Endothelial cells activated by IL-1\(\beta\) or TNF-\(\alpha\) increase the exposure on their membranes of counter-receptors for the tumor adhesion molecules. The malignant cells attached to the vessel wall may play a key role in promoting localized clotting activation and thrombus formation by releasing their cytokine content and favoring the adhesion and arrest of other cells, including leukocytes and platelets.

The adhesion of tumor cells to leukocytes or to vascular walls may also facilitate cell migration and extravasation.

(c) Prothrombotic Mechanisms of Antitumor Drugs

Increasing evidence has accumulated that anticancer therapy may significantly affect the thrombotic risk in cancers. Several mechanisms related to anticancer drugs have been identified. One mechanism relies on the release of procoagulants and cytokines by tumor cells damaged by chemotherapy. The role of these mediators to increase the thrombotic risk in cancer patients has been documented.\textsuperscript{21}

Another mechanism involves the direct damage exerted by chemotherapy and radiotherapy on vascular endothelium. In animal studies, bleomycin has been demonstrated to cause morphological damage to the vascular endothelium of the lung, resulting in pulmonary thrombosis and fibrosis. A new class of substances with endothelial toxic activity is represented by the antiangiogenic drugs, such as thalidomide and SU5416, an anti-VEGF receptor. In patients with multiple myeloma, an increased rate of venous thromboembolism (VTE) is associated with thalidomide therapy, especially in combination with chemotherapy.\textsuperscript{22}

**CLINICAL CONDITIONS**

A wide spectrum of clinical manifestations of thrombosis may be observed in cancer, ranging from asymptomatic with laboratory coagulation abnormalities alone, to massive life-threatening venous thrombosis. Patients of cancer presenting with acute VTE detection have a greater likelihood of distant metastases at the time of diagnosis as compared to individuals without concomitant VTE.\textsuperscript{23} VTE presentations in the cancer patients include symptomatic DVT, pulmonary embolism, superficial thrombophlebitis, central venous access device thrombosis, arterial thrombosis and non bacterial thrombotic endocarditis. In cancer, syndromes of a systemic involvement of the clotting system, such as DIC or thrombotic microangiopathy have also been described.

Some malignancies are associated with a higher incidence of thrombosis than others (Table 1). Although the incidence of thrombosis in malignancy is about 15%, but in certain tumors such as pancreatic carcinoma, it may be seen in more than 50% of patients.\textsuperscript{24} Mucinous adenocarcinomas have been the most commonly
associated with thrombus formation. Evidences have shown that the sialic acid moiety of mucin secreted by these malignancies can initiate coagulation by the non-enzymatic activation of factor X to Xa.

Importantly, thrombosis can represent the earliest clinical manifestation of an occult cancer, as shown by a prospective clinical trial demonstrating patients with idiopathic VTE have a 4- to 7-fold increased risk of being diagnosed with cancer in the first year after thrombosis, as compared with patients of VTE secondary to known causes such as, surgery, congenital thrombophilia, oral contraceptives, pregnancy, immobilization, etc. This risk is 10-fold greater in case of idiopathic recurrent VTE. However, the question of whether aggressive diagnostic screening for cancer in patients with idiopathic DVT may improve the outcome of the disease remains to be answered. In a report from the Danish Epidemiology Science Center examined registry data from 1977 through 1992 of 15,348 patients with DVT and 11,305 patients with pulmonary embolism. The risk of underlying cancer was approximately 3 times the expected for each cohort examined. This increased risk existed for the first six months which declined to 2.2 at one year, and thereafter only marginal at 1.1. Another study, demonstrated that an extensive screening of patients with DVT with no apparent risk factors is ineffective in identifying an occult malignancy compared with routine clinical practice.

VTE: Management Strategies In Cancer Patients

DVT and pulmonary thromboembolism (PTE) warrant prompt institution of antithrombotic therapy in order to effectively ameliorate symptoms; prevent thrombus propagation; embolization; recurrence and allow for thrombus organization, plasmin mediated lysis and restoration of venous patency. Specific therapy and duration of therapy will depend on thrombus location (i.e., ileofemoral DVT versus calf DVT), thrombus extent (i.e., massive PE versus subsegmental PE), and underlying thrombosis “trigger” (i.e., major abdominal surgery versus congenital antithrombin deficiency).

The natural history of VTE in the cancer patient differs remarkably from that in the non-cancer patient. Cancer patients are more likely to present with proximal DVT, with a greater initial thrombus burden, experience greater clinical deterioration despite anticoagulant therapy and to have less venographic improvement in response to standard treatment. In addition, the risk of recurrences is significantly increased in cancer versus non cancer patients, even during treatment for VTE. The fact that cancer patients have a higher recurrence rate while reportedly “therapeutically” anti-coagulated suggests that the usual target international normalized ratio (INR) range of 2.0 to 3.0 may not be therapeutic at all. The greatest risk of recurrent VTE was observed in patients with genito-urinary tract, gastrointestinal tract and lung cancers and predominantly during the first month of anticoagulation.

(i) Heparin Resistance

Cancer patients, like others with a acute illness and inflammatory processes, have a propensity towards heparin resistance. “True” heparin resistance manifests as inadequate anticoagulant and antithrombotic responses from what would otherwise be perceived as adequate dose of heparin. Requirement of very high dose of heparin (>35,000 units in 24 hours) may reflect this form of heparin resistance. True heparin resistance most likely results from the non-specific binding of heparin to mononuclear white cells, vascular endothelial cells and acute phase proteins such as histidine rich glycoprotein, vitronectin, and platelet factor 4, resulting in an inadequate quantity of free or antithrombin bound heparin. Another potential cause of heparin resistance in the cancer patients is compensated DIC – associated antithrombin deficiency. True heparin resistance, can be detected by activated partial thromboplastin test (APTT) and the anti-factor Xa activity assay.

Cancer patients can also manifest an “apparent” heparin resistance characterized by dissociation between the APTT and heparin assays. In these patients, the APTT may be normal or near normal while the anti – factor Xa activity assay reveals a therapeutic heparin activity level between 0.3 and 0.7 IU / ml. Simply escalating the dose of heparin to achieve the desired APTT without checking a heparin assay may result in a pronounced bleeding risk. Dissociation between the APTT and heparin concentration likely reflects elevated levels of factor VIII that can shorten the in vitro APTT without affecting the anti thrombotic actions of the drug.

(ii) Warfarin Failure

Warfarin failure is suspected if a patient develops an objectively documented recurrent VTE, despite an apparently stable INR between 2.0 - 3.0 and suggests that this degree of anticoagulation was insufficient to neutralize the sum of hypercoagulable stimuli in a given individual. Underlying cancer, because of its potent prothrombotic nature, is often suspected in the setting of warfarin failure. This may reflect cancer associated hypercoagulability in excess of warfarin induced anticoagulation or inability to keep cancer patients within the target therapeutic INR range.

(iii) Cancer Patient Response to LMWH

Several prospective, randomized, controlled trials have demonstrated the efficacy and safety equivalency of intravenous, APTT adjusted, unfractioned heparin (UFH) and subcutaneous, weight based low molecular weight heparin (LMWH) for the initial treatment of acute lower extremity DVT. Since LMWH can be self-administered at home without the need for therapeutic monitoring, thus reducing the mean hospital length of
stay compared with UFH, which may be of particular importance in immunocompromised cancer patients who are prone to nosocomial infections. LMWH does not require frequent phlebotomy for therapeutic monitoring in most patients.

LMWHs are associated with less heparin induced thrombocytopenia (HIT), than UFH, especially in heparin naïve patients. This makes LMWHs useful for VTE prevention and treatment in cancer patients with disease and/or chemotherapy – related thrombocytopenia in whom detection of HIT may be hindered by preexistent low platelet counts.

LMWHs display less non-specific binding to acute phase plasma proteins, platelets, mononuclear leukocytes, and endothelial cells. Active cancer patients treated with LMWHs are therefore, theoretically, less likely to experience true heparin resistance. Besides these LMWHs promote thrombus regression and restoration of venous patency. Disadvantages of LMWHs include the inability to be completely reverse the anticoagulant effect by protamine sulfate in the event of bleeding or unanticipated surgery and accumulation in patients with severe renal insufficiency thereby precluding its use in cancer patients with renal failure.

(iv) Duration of anticoagulation

With regard to the optimal duration of anticoagulation in patients with VTE in the setting of cancer, it seems prudent to treat for 6 months or at least until all cancer therapy has been completed and the patient has been deemed to have no residual malignancy. Residual malignancy constitutes a persistent hypercoagulable state that typically warrants long term anticoagulant treatment. Warfarin therapy itself has been shown to improve survival in patients with extensive stage small cell lung carcinoma, and a longer duration of oral anticoagulation (6 months versus 6 weeks) following acute VTE has been shown to reduce the risk of developing recurrence of genitourinary tract cancers.

**CONCLUSIONS**

Cancer patients are at significantly high thrombotic risk. The pathogenesis of thrombosis in cancer is different and reflects the activation of the various components of the hemostatic system, triggered by tumor cell-associated prothrombotic properties. The laboratory coagulation parameters show that patients with cancer very commonly present with a hypercoagulable state, however the clinical utility of laboratory testing for thrombotic markers is not yet established.

Idiopathic VTE can be the earliest manifestation of an occult cancer; therefore, patients with idiopathic VTE, in which all other causes have been carefully excluded, should be observed closely for the development of cancer, particularly during the 6 to 12 months immediately following the VTE episode. On the other hand, patients with known cancers have an increased risk of secondary VTE, particularly when surgery or medical therapies are undertaken.

Management of VTE in cancers has shown increased recurrence rates off warfarin, increased VTE recurrence rates on warfarin, increased bleeding rates on warfarin, and greater difficulty maintaining an INR between 2.0 and 3.0. Even brief exposure to LMWH can have a positive impact on cancer patient survival.

**REFERENCES**


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**Announcement**

**11th Asia Pacific Congress of Doppler Echocardiography (APCDE)** to be hosted by the Escorts Heart Institute and Research Centre, New Delhi on 26th – 27th November 2005.

The theme of this two days meeting is “Echocardiography in Clinical Decision Making”.

For Details and Online Registration visit our Website at www.ehirc.com

For details contact Dr. RR Kasliwal, President, XI APCDE, Director Cardiology, DNB Program and Community Outreach Escorts Heart Institute & Research Centre, Okhla Road, New Delhi-110 025.

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