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## New Insights Into Cancer-Associated Thrombosis

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### Abstract

Venous thromboembolism (VTE) is an increasingly frequent complication of anti-cancer therapy. The underlying mechanisms are not completely understood, but are related in part to oncogene activation and tissue factor (TF) expression. Several risk factors have been identified including site and stage of cancer, patient comorbidities and specific therapeutic agents. Candidate biomarkers such as blood counts, TF and P-selectin have recently been identified. A risk model predictive of chemotherapy-associated VTE has been validated. Thromboprophylaxis with low molecular weight heparin (LMWH), unfractionated heparin (UFH) or fondaparinux is recommended for hospitalized medical and surgical cancer patients. Long-term anticoagulation with LMWH is safe and effective in reducing recurrent VTE in cancer. The role of thromboprophylaxis in ambulatory cancer patients receiving chemotherapy is an area of active investigation.

### Keywords

Thrombosis; Risk Factors; Cancer

### Introduction

Cancer is a prothrombotic state, and cancer treatments are often complicated by thromboembolism. Venous events are the most common, presenting as either deep venous thrombosis (DVT) or pulmonary embolism (PE), together described as venous thromboembolism (VTE). Indeed, cancer patients account for as much as 20% of the total burden of VTE<sup>1</sup>. Arterial events, including stroke and myocardial infarction, are also more prevalent in cancer patients<sup>2</sup>.

The prothrombotic state of cancer is driven by specific oncogenic events<sup>3, 4</sup>. Activation of the coagulation cascade appears integrally linked to the processes of tumor growth, metastasis and angiogenesis. Elegant preclinical studies have shown, for instance, that defects in fibrinogen and platelet activation can decrease metastatic potential<sup>5-7</sup>. This has led to a renewed interest in studying the anti-cancer effects of interrupting the coagulation cascade.

Several other factors have contributed to an increasing awareness of the impact of VTE in cancer. The incidence of VTE in cancer is on the rise<sup>8</sup>. Novel anti-cancer drugs, particularly anti-angiogenic agents, may be contributing to this increase<sup>9, 10</sup>. VTE is the second leading cause of death in cancer patients<sup>11</sup> and the most common cause of death in the postoperative period<sup>12</sup>. VTE in cancer is associated with a 21% annual risk of recurrent VTE, a 12% annual risk of bleeding complications, requirement for long-term anticoagulation and interruption of chemotherapy<sup>13, 14</sup>.

This brief review will focus on new insights into the pathophysiology of cancer-associated thrombosis, risk factors and candidate predictive biomarkers for VTE as well as appropriate strategies for the prevention and treatment of VTE in cancer.

## Mechanisms of Thrombosis

The pathophysiology of cancer-associated thrombosis is not entirely understood. Rather than one unifying mechanism, the etiology is likely multifactorial with different factors assuming lesser or greater degrees of importance depending on the clinical setting.

Much of the research in this area has focused on the intrinsic properties of tumor cells that lead to a prothrombotic state. The role of tissue factor (TF) has gathered the most attention. TF, a transmembrane glycoprotein, is the prime physiologic initiator of coagulation and is expressed in a variety of human cancers, induced by activation of oncogenes or inactivation of tumor suppressor genes<sup>4</sup>. Overexpression of TF in tumor cells or elevated TF levels in association with microparticles in the systemic circulation may contribute to systemic hypercoagulability<sup>15-19</sup>. Much of this work has focused on selected cancers, particularly pancreas, and whether TF is equally important in other cancers remains to be seen. Activation of the MET oncogene has been shown in a mouse model of hepatocarcinogenesis to result in a thrombohemorrhagic state mediated by upregulation of plasminogen activator inhibitor type 1 (PAI-1) and cyclooxygenase-2 gene activity<sup>3</sup>. However, the applicability of this model to other cancers and to the clinical setting is not known. Carcinoma mucins, glycosylated molecules that act as ligands for the selectin family, may also play a role in thrombosis<sup>20</sup>. Finally, the role of tumor hypoxia and inflammatory cytokines has also been speculated to contribute to the prothrombotic state in cancer but firm experimental evidence is awaited<sup>21-23</sup>.

Extrinsic factors are also important but, unfortunately, are not accounted for by the various experimental models discussed above. Chemotherapy can result in activation of hemostasis within a few hours of administration<sup>24</sup>. This occurs via a variety of mechanisms, including induction of TF in tumor cells<sup>25</sup> and monocytes<sup>26</sup>, downregulation of anticoagulant proteins such as protein C and S<sup>27, 28</sup>, damage to vascular endothelium<sup>29</sup> and platelet activation<sup>30</sup>. Anti-angiogenic agents also contribute to thrombosis, perhaps through endothelial cell and platelet activation<sup>31</sup>.

## Risk Factors

Multiple recent studies have evaluated risk factors for VTE in cancer patients in the general population, in hospitalized patients and in registries of outpatients receiving chemotherapy. Overall, these risk factors for VTE can be categorized according to patient characteristics and comorbidities, malignancy-related characteristics and therapeutic interventions for cancer (Table 1). Comorbid conditions such as infection, obesity, anemia, pulmonary and renal disease particularly add to the risk of VTE<sup>8</sup>. The primary site of cancer is an important risk factor, with highest rates observed in patients with brain, pancreas, gastric, kidney, ovary and lung cancers and hematologic malignancies, particularly lymphomas<sup>8, 32-34</sup>. In a population-based study, the risk of VTE was greatest in the first three months after the diagnosis of cancer (OR 53.5, 95% CI 8.6 – 334.3)<sup>32</sup>. Hospitalization increases the risk of VTE in cancer patients<sup>35</sup>. Major surgery has long been known to be associated with an increased risk of VTE; more recent data indicates that this risk extends for a prolonged period after the procedure, with 40% of all VTE events in one registry occurring later than 21 days from surgery<sup>12</sup>. Chemotherapy is associated with a 2- to 6-fold increased risk of VTE as compared to the general population<sup>36, 37</sup>. VTE is also associated with the use of central venous catheters<sup>38</sup>. Erythropoiesis-stimulating agents (ESAs) has been found to increase the risk of VTE; unfortunately, red blood cell transfusions may have a similar association<sup>39, 40</sup>. Novel therapeutics such as the anti-angiogenic class of

agents are also associated with VTE. Thalidomide and lenalidomide-containing regimens increase the risk several-fold in patients with myeloma<sup>41</sup>. Regimens containing bevacizumab, a monoclonal antibody directed against the pro-angiogenic vascular endothelial growth factor, are associated with high rates of both arterial and venous events<sup>10, 42</sup>.

## Candidate Biomarkers

Research conducted primarily in cancer outpatients has resulted in the identification of novel candidate biomarkers that may be predictive of cancer-associated VTE. In an observational study, VTE occurred in 4% of patients with a pre-chemotherapy platelet count  $\geq 350,000/\text{mm}^3$  as compared to 1.25% for those with counts  $<200,000/\text{mm}^3$ <sup>34</sup>. An elevated pre-chemotherapy leukocyte count (defined as  $>11,000/\text{mm}^3$ ) was also significantly and independently associated with an increased risk of VTE<sup>43</sup>. High grades of TF expression in tumor cells and elevated levels of circulating TF have been associated with the risk of VTE in pancreatic and ovarian cancers<sup>19, 44</sup>. In a prospective cohort study, elevated levels of soluble P-selectin levels ( $>53.1 \text{ ng/mL}$ , representing the 75th percentile) were predictive of VTE (HR 2.6, CI 1.4-4.9)<sup>45</sup>. Markers of hemostatic activation, particularly D-dimer, have been observed to be elevated in cancer patients and predictive of recurrent VTE in cancer patients<sup>46</sup>. In an observational study of 507 cancer patients, an elevated C-reactive protein ( $>400\text{mg/dL}$ ) was associated in multivariate analysis with VTE<sup>35</sup>.

## A Predictive Risk Model

VTE in cancer is a multifactorial disease and various risk factors, as is evident from the preceding discussion. A risk model for chemotherapy-associated VTE has recently been published and is based on scores assigned to five predictive variables identified in a development cohort of 2,701 ambulatory cancer patients initiating chemotherapy (Table 2)<sup>43</sup>. The score was then validated in an independent cohort of 1,365 patients from the same study. Rates of VTE in the development and validation cohorts, respectively, were 0.8% and 0.3% in the low-risk category (score=0), 1.8% and 2% in the intermediate-risk category (score=1-2), and 7.1% and 6.7% in the high-risk category (score  $\geq 3$ ) over a median period of 2.5 months<sup>43</sup>. Rates of VTE in this high-risk subgroup are comparable to hospitalized patients for whom prophylaxis is safe and effective. The National Heart, Lung and Blood Institute has recently funded a study of outpatient prophylaxis in cancer patients identified as high-risk based on this model.

## Prevention of VTE

### Hospitalized Medical Cancer Patients

Three large randomized controlled trials studied either enoxaparin, dalteparin or fondaparinux for thromboprophylaxis in acutely ill hospitalized medical patients and reported relative risk reductions in VTE ranging from 45 to 63% with anticoagulation<sup>47-49</sup>. Unfortunately, none of these were cancer-specific study populations and cancer patients formed only a minority (ranging from 5 to 15%) of study patients. Furthermore, bleeding complications, a major concern with anticoagulation in cancer, were not separately reported for cancer patients. Unfractionated heparin (UFH) is an acceptable alternative to low-molecular-weight heparins (LMWHs) as thromboprophylaxis in this setting<sup>50</sup>. Despite the lack of cancer-specific data, the American Society of Clinical Oncology (ASCO) guidelines recommend that hospitalized cancer patients should be considered for VTE prophylaxis with anticoagulants in the absence of bleeding or other contraindications to anticoagulation<sup>51</sup>.

## Surgical Cancer Patients

Multiple clinical trials have established the safety and efficacy of thromboprophylaxis in the perioperative period for cancer patients undergoing major surgical procedures. More recently, two studies (including one cancer-specific study) have suggested that extending the duration of post-operative LMWH prophylaxis for 2-4 weeks after hospital discharge reduces the incidence of late venographic VTE<sup>52, 53</sup>. Both the ASCO and the National Comprehensive Cancer Network (NCCN) guidelines support either UFH, LMWH or fondaparinux in the surgical cancer patient for VTE prophylaxis and suggest using prolonged prophylaxis in high-risk patients<sup>54, 55</sup>.

## Ambulatory Cancer Patients

The treatment of cancer has now primarily moved to the outpatient setting. Several clinical trials have been conducted to evaluate the benefit of thromboprophylaxis for cancer outpatients, with varying inclusion criteria and contradictory results<sup>56-58</sup>. Data from the most recent and largest study found fewer thromboembolic events (venous and arterial combined) occurred in the nadroparin arm than in the placebo arm (2.0% vs 3.9% P = 0.033, NNT = 53.8)<sup>59</sup>. Current guidelines do not recommend prophylaxis for cancer outpatients, although data from more targeted approaches such as the risk model described above are awaited. One exception to this is patients with multiple myeloma receiving thalidomide/lenalidomide-based regimens for whom prophylaxis is recommended with either LMWH or warfarin based on data from non-randomized studies<sup>51</sup>.

## Treatment of VTE in Cancer Patients

Warfarin has previously been the standard for chronic anticoagulation but in the cancer population is associated with increased rates of bleeding, recurrent VTE and dietary and drug-related interactions. In the CLOT trial, 672 cancer patients with documented VTE were randomized to receive either dalteparin or dalteparin followed by a vitamin K antagonist (control group) for a total of 6 months<sup>60</sup>. Recurrent VTE at six months occurred in 9% of patients in the dalteparin group compared to 17% in the control group. These findings are consistent with data from multiple other smaller studies and a meta-analysis<sup>61</sup>. These data have established LMWH for at least 3-6 months as the standard of care for treatment of VTE in cancer, as recommended by the ASCO, NCCN and other guidelines<sup>51, 55</sup>. The optimal duration of anticoagulation in cancer patients with VTE remains unknown. Given that cancer patients remain at risk for VTE, it is recommended that patients with active cancer be considered for indefinite anticoagulation. It is important to note in this context preclinical and clinical data (albeit conflicting) suggesting that anticoagulants, particularly LMWHs, may impact cancer processes such as angiogenesis and tumor cell adhesion and, therefore, clinical outcomes<sup>62-64</sup>.

## Conclusions

Ongoing areas of investigation include understanding the pathophysiology of cancer-associated thrombosis in ways that can impact tumor biology, targeted prophylaxis in cancer outpatients and studying the impact of anticoagulation on survival in cancer. While many new beginnings have been made in the field of cancer-associated thrombosis in the past decade, much learning awaits.

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**Table 1**  
**Risk factors and candidate biomarkers for VTE**

<b>Patient-related factors</b>
Older age
Female gender
Race
Higher in African Americans
Lower in Asians/Pacific Islanders
Comorbidities
Infection, renal disease, pulmonary disease, obesity
Inherited prothrombotic mutations
Prior history of VTE
<b>Cancer-related factors</b>
Primary site of cancer
Brain, pancreas, kidney, stomach,
lung, gynecologic, lymphoma, myeloma
Advanced stage of cancer
Initial period after diagnosis of cancer
<b>Treatment-related factors</b>
Major surgery
Hospitalization
Cancer therapy
Chemotherapy
Hormonal therapy
Anti-angiogenic agents
Thalidomide, lenalidomide, bevacizumab
Erythropoiesis-stimulating agents
Transfusions
Central venous catheter
<b>Candidate Biomarkers</b>
Pre-chemotherapy platelet count $\geq 350,000/\text{mm}^3$
Pre-chemotherapy leukocyte count $> 11,000/\text{mm}^3$
Tissue factor (TF)
High grade of TF expression by tumor cells
Elevated TF plasma levels
Soluble P-selectin
D-dimer
C-reactive protein

**Table 2**  
**A Validated Predictive Model for Chemotherapy-Associated VTE<sup>65</sup>**

Patient Characteristic	Risk Score
<b>Site of Cancer</b>	
-Very high risk (stomach, pancreas)	2
-High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
<b>Pre-chemotherapy platelet count <math>\geq 350,000/\text{mm}^3</math></b>	1
<b>Hemoglobin <math>&lt; 10\text{g/dL}</math> or use of red cell growth factors</b>	1
<b>Pre-chemotherapy leukocyte count <math>&gt; 11,000/\text{mm}^3</math></b>	1
<b>Body mass index <math>\geq 35 \text{ kg/m}^2</math></b>	1