Venous Thromboembolism: Mechanisms, Treatment, and Public Awareness

New Insights Into Cancer-Associated Thrombosis

Tarek Sousou, Alok A. Khorana

Abstract—Venous thromboembolism (VTE) is an increasingly frequent complication of anticancer 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. (Arterioscler Thromb Vasc Biol. 2009;29:316-320.)

Key Words: thrombosis ■ risk factors ■ cancer

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. Arterial events, including stroke and myocardial infarction, are also more prevalent in cancer patients.

The prothrombotic state of cancer is driven by specific oncogenic events. 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. This has led to a renewed interest in studying the anticancer 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. Novel anticancer drugs, particularly antiangiogenic agents, may be contributing to this increase. VTE is the second leading cause of death in cancer patients and the most common cause of death in the postoperative period. 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.

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 physiological initiator of coagulation and is expressed in a variety of human cancers, induced by activation of oncogenes or inactivation of tumor suppressor genes. Overexpression of TF in tumor cells or elevated TF levels in association with microparticles in the systemic circulation may contribute to systemic hypercoagulability. Many 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 thrombomorragic state mediated by upregulation of plasminogen activator inhibitor type 1 (PAI-1) and cyclooxygenase-2 gene activity. 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. 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.

Extrinsic factors are also important but, unfortunately, are not accounted for by the various experimental models dis-
Table 1. Risk Factors and Candidate Biomarkers for VTE

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Candidate Biomarkers</th>
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<tbody>
<tr>
<td>Patient-related factors</td>
<td>Prechemotherapy platelet count ≥350 000/mm³</td>
</tr>
<tr>
<td>Older age</td>
<td>Prechemotherapy leukocyte count &gt;11 000/mm³</td>
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<tr>
<td>Female gender</td>
<td>Tissue factor (TF)</td>
</tr>
<tr>
<td>Race</td>
<td>High grade of TF expression by tumor cells</td>
</tr>
<tr>
<td>Advanced stage of cancer</td>
<td>Elevated TF plasma levels</td>
</tr>
<tr>
<td>Initial period after diagnosis of cancer</td>
<td>Soluble P-selectin</td>
</tr>
<tr>
<td>Treatment-related factors</td>
<td>D-dimer</td>
</tr>
<tr>
<td>Major surgery</td>
<td>C-reactive protein</td>
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<tr>
<td>Hospitalization</td>
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<td>Cancer therapy</td>
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<tr>
<td>Chemotherapy</td>
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<td>Antiangiogenic agents</td>
<td></td>
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<tr>
<td>Thalidomide, lenalidomide, bevacizumab</td>
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<tr>
<td>Erythropoiesis-stimulating agents</td>
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<tr>
<td>Transfusions</td>
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<tr>
<td>Central venous catheter</td>
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<tr>
<td>Candidate biomarkers</td>
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<tr>
<td>Prior history of VTE</td>
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</tr>
<tr>
<td>Cancer-related factors</td>
<td>Brain, pancreas, kidney, stomach, lung, gynecologic, lymphoma, myeloma</td>
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<tr>
<td>Primary site of cancer</td>
<td>Advanced stage of cancer</td>
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<tr>
<td>Initial period after diagnosis of cancer</td>
<td>Treatment-related factors</td>
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<td>Advanced stage of cancer</td>
<td>Hospitalization</td>
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<td>Prior history of VTE</td>
<td>Candidate biomarkers</td>
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<tr>
<td>Brain, pancreas, kidney, stomach, lung, gynecologic, lymphoma, myeloma</td>
<td>Prediagnosis of recurrent VTE in cancer patients</td>
</tr>
</tbody>
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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 to 2), and 7.1% and 6.7% in the high-risk category (score ≥ 3) over a median period of 2.5 months. 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

Hospitals 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. 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. 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.

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 postoperative LMWH prophylaxis for 2 to 4 weeks after hospital discharge reduces the incidence of late venographic VTE. 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.

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.

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% versus 3.9% P = 0.033, NNT = 53.8). 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 nonrandomized studies.

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. Recurrent VTE at 6 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. These data have established LMWH for at least 3 to 6 months as the standard of care for treatment of VTE in cancer, as recommended by the ASCO, NCCN, and other guidelines. 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.

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. Although many new beginnings have been made in the field of cancer-associated thrombosis in the past decade, much learning awaits.

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References


