Identifying cancer patients at risk for venous thromboembolism

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Keywords
Thrombosis, risk factors, malignancy

Summary
Venous thromboembolism (VTE) is a known complication of cancer which impacts on patient mortality and quality of life. Despite the known deleterious effects of VTE, the benefits of thromboprophylaxis have not been fully established. Identification of patients at highest risk of VTE could lead to better targeting of thromboprophylaxis. Several risk factors have been identified as contributing to VTE such as site and stage of cancer, age, comorbidities, obesity, and acquired prothrombotic states. Anti-cancer agents as well as the use of growth factor support have also been implicated in VTE. Recent data have identified biomarkers such as blood counts, tissue factor and P-selectin. In this review, we briefly summarize the risk factors for VTE as well as candidate biomarkers for VTE in cancer patients. We also review a validated risk score that can identify cancer patients at high risk for VTE. Risk stratification of cancer patients will allow clinicians to identify those patients at highest risk for VTE, who may derive the most benefit from thromboprophylaxis.

Patient characteristics and comorbidities

Several patient characteristics are associated with a high incidence of VTE and include among others (9):
- age greater than 65 years,
- female gender,
- obesity,
- immobility and infection.

The risk of VTE (9) may also substantially be increased by
- acquired prothrombotic states such as factor V Leiden,
- prothrombin gene mutation in addition to a prior VTE.

Risk factors

Risk factors for VTE can be categorized as those related to patient characteristics including comorbidities, to the type of malignancy and to the therapeutic interventions for cancer (Tab. 1).

Malignancy-associated risk factors

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. The extent of metastatic spread further adds to the risk. VTE is not simply a complication of solid organ tumors since recent data suggest that hematologic malignancies also have a high rate of VTE. In a recent population-based study, hematologic malignancies had the highest risk of VTE, followed by lung, and gastrointestinal cancers (3). Furthermore, the initial three months following diagnosis carried the highest risk for VTE (3). In a study of ambulatory cancer patients receiving chemotherapy, the highest risk of VTE was found in gastrointestinal cancers followed by lung cancer and lymphoma (10).

Venous thromboembolism (VTE) is increasingly frequent in cancer patients and is associated with (12)
- worsened short-term mortality,
- decreased long term survival as well as
- a significant impact on quality of life.

A recent analysis of causes of death obtained from the Awareness of Neutropenia in Chemotherapy (ANC) Study Group indicated that thrombosis was the second leading cause of death in cancer patients (12, 21). To further complicate matters, several novel anti-cancer agents have been associated with VTE, thereby bringing this topic to the forefront of cancer medicine.

Despite the known adverse consequences of VTE, it is not common prac-
Chemotherapy is associated with a 2-to 6-fold increased risk of VTE compared to the general population (4, 9). This risk is further augmented by the use of central venous catheters in chemotherapy delivery. Several studies have demonstrated a direct link between the use of chemotherapy and the incidence of thromboembolic disease (8, 15, 24). In a randomized study of stage II breast cancer patients, approximately 7% developed thromboembolic events during chemotherapy as compared to no events when not actively receiving chemotherapy (15). A similar study of stage IV breast cancer patients found the rate of thrombosis to be 17.4% while receiving chemotherapy, higher than the rate of thrombosis in cancer patients not on therapy (8). VTE can occur as a result of non-chemotherapeutic agents as well. Breast cancer patients treated with 5 years of tamoxifen have a 1.5-fold to 7.1-fold increased risk of VTE. However, the risk appears to be lower with newer hormonal agents such as the aromatase inhibitors (2).

Novel medications such as the anti-angiogenic class of agents, particularly thalidomide and lenalidomide, have been associated with a 7-fold increase in the rate of DVT when given in combination with multi-agent chemotherapy (25). In a pooled analysis of randomized clinical trials, bevacizumab-containing regimens have also been associated with increased risk for arterial thromboembolic events, but not for VTE (20). However, individual non-randomized studies have reported high rates of VTE in association with bevacizumab. High rates of both venous and arterial events have been observed in clinical trials of other anti-angiogenic agents as well, suggesting this toxicity may be a class effect. In addition to increased risk related to chemotherapy, there is also added risk in the use of erythropoiesis-stimulating agents (ESA). Patients receiving ESAs have significantly greater VTE events as compared to untreated controls and this may, in part, account for the increased mortality associated with these agents in some studies (5).

### Biomarkers

Recent research conducted primarily in the ambulatory cancer population has resulted in the identification of novel biomarkers that may be predictive of cancer-associated VTE in this setting (Tab. 2).

### Tissue factor

Tissue factor (TF), a transmembrane glycoprotein, is the prime physiologic initiator of coagulation and is commonly expressed in a variety of solid tumors and hematologic malignancies. It has been reported that malignancy associated VTE portends a worse prognosis. Further research has demonstrated a relationship between hypercoagulability and increased angiogenesis suggesting that hypercoagulability confers a growth advantage (22). This may be secondary to the upregulation of vascular endothelial cell growth factor (VEGF) expression, a potent mediator of angiogenesis by tissue factor (17). In turn, VEGF expression leads to up-regulation of TF expression.

In a recent retrospective analysis, normal pancreas did not express TF. In contrast, TF expression was observed in a large majority of both noninvasive and invasive pancreatic neoplasms. TF expression in resected pancreatic cancers correlated with expression of VEGF, supporting a linkage with angiogenesis. Of particular note, pancreatic cancer patients with high TF expression in resected tumor specimens had a VTE rate of 26.3% compared with 4.5% in patients with low TF expression ($p=0.04$) (11). Similar
data have been reported in ovarian cancer as well (23).

TF expression has also been demonstrated in circulation in the form of microparticles (MP), membrane vesicles released from cells. Measurements of MP-TF activity in metastatic pancreatic cancer patients were found to be elevated in comparison to patients without malignancy (p<0.004). The finding of VTE in those with metastatic cancer was associated with a MP-TF activity level up to eighteen-fold greater than in metastatic cancer patients without VTE (p<0.001) (22). In a recent analysis, elevated or rising TF levels, measured by both antigen and activity, were predictive of subsequent VTE in a small series of patients with advanced pancreatic cancer (11).

**Platelet and leukocyte counts**

In an analysis of data from the ANC Study Group Registry, a prospective observational study of patients initiating chemotherapy, elevated pre-chemotherapy platelet counts were strongly associated with VTE (10). Over a 2.5 month period, the incidence of VTE was nearly 4% for patients with a pre-chemotherapy platelet count ≥ 350 000/mm³ as compared to 1.25% for patients with pre-chemotherapy platelet count of < 200 000/mm³ (for trend p = 0.0003). This association between pre-chemotherapy platelet counts and increased risk of VTE continued while patients were on chemotherapy. Patients who developed VTE had significantly elevated mean platelet counts prior to each cycle of chemotherapy when compared to patients who did not develop VTE (p = 0.001). In an expanded analysis of this registry, a pre-chemotherapy leukocyte count > 11 000/mm³ was found to be significantly and independently associated with an increased risk of subsequent VTE (13).

**P-selectin**

P-selectin is a cell adhesion molecule found in endothelial cells and platelet granules that has been implicated in leukocyte adhesion, growth of metastasis and most notably thrombosis. Upon cell activation, P-selectin is rapidly expressed on the cell surface. Emerging evidence from animal studies suggests that P-selectin fosters thrombus development via interaction with P-selectin glycoprotein ligand-1 leading to platelet aggregation, recruitment of TF-positive monocytes, and release of procoagulant microparticles (6). A recent prospective cohort study of 687 patients sought to determine the relationship between P-selectin plasma levels and risk of VTE (1). According to this study, P-selectin levels were significantly higher in cancer patients with VTE as compared to those without (1) (HR 2.6, CI 1.4–4.9). Of note, P-selectin levels were not significantly associated with the type of malignancy or with platelet counts.

**Risk model-based approach**

It is clear from the extensive list of risk factors and biomarkers discussed here that VTE in cancer is a multifactorial disease, and various risk factors can interact in the same patient. Identifying subgroups of patients at low or high risk for VTE requires construction of a risk model that incorporates multiple known risk factors, and their relationships. A validated risk model for chemotherapy-associated VTE has recently been developed based on data obtained from the ANC Study Group Registry (Tab. 3) (13).

Risk factors for VTE were studied in a development cohort of 2701 ambulatory cancer patients from the ANC registry. A risk score for VTE was derived using regression coefficients estimated in the multivariate model. The score was then validated in an independent cohort of 1365 patients from the same study. Five predictive variables were identified in a stage-adjusted multivariate model in the development cohort: site of cancer, hemoglobin < 10 g/dL, pre-chemotherapy leukocyte count > 11 000/mm³, pre-chemotherapy platelet count ≥ 350 000/mm³ and/or use of erythropoietin and body mass index ≥ 35. Rates of development of VTE (14). Markers of hemostatic activation, particularly D-dimer, have been observed to be elevated in cancer patients and predictive of recurrent VTE in cancer patients (7). Data from a variety of sources suggests that elevated D-dimer levels may be predictive of primary VTE as well although this requires prospective confirmation.

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**Tab. 2** Potential predictive biomarkers for cancer-associated thrombosis

<table>
<thead>
<tr>
<th>biomarker</th>
<th>measure</th>
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<tbody>
<tr>
<td>pre-chemotherapy</td>
<td>platelet count ≥ 350 000/mm³</td>
</tr>
<tr>
<td></td>
<td>leucocyte count &gt; 1 000/mm³</td>
</tr>
<tr>
<td>tissue factor (TF)</td>
<td>high grade of TF expression by tumour cells</td>
</tr>
<tr>
<td></td>
<td>elevated TF plasma levels</td>
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<tr>
<td>P-selectin</td>
<td></td>
</tr>
<tr>
<td>D-dimer</td>
<td></td>
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<tr>
<td>C-reactive protein</td>
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**Tab. 3** A validated predictive model for chemotherapy-associated VTE

<table>
<thead>
<tr>
<th>patient characteristics</th>
<th>risk score</th>
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</thead>
<tbody>
<tr>
<td>site of cancer</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>very high risk (stomach, pancreas)</td>
</tr>
<tr>
<td></td>
<td>high risk (lung, lymphoma, gynaecologic)</td>
</tr>
<tr>
<td>pre-chemotherapy platelet count ≥ 350 000/mm³</td>
<td>1</td>
</tr>
<tr>
<td>haemoglobin &lt; 10 g/dL or use of red cell growth factors</td>
<td>1</td>
</tr>
<tr>
<td>pre-chemotherapy leucocyte count &gt; 11 000/mm³</td>
<td>1</td>
</tr>
<tr>
<td>body mass index ≥ 35 kg/m²</td>
<td>1</td>
</tr>
</tbody>
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Hämostaseologie 1/2009
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 ≥ 3) over a median period of 2.5 months (13).

The high rate of VTE observed in the high-risk subgroup of patients is similar to that seen in hospitalized patients and is higher than the rates of symptomatic VTE published in prior studies (15). Given that prophylactic anticoagulation in hospitalized patients is safe and effective, similar assumptions can be made for cancer patients identified to be at high risk. A model-based approach incorporating biomarkers may be the most efficient way to identify cancer patients at highest risk for VTE and to study prophylaxis strategies in those patients.

Acknowledgement:
Dr. Khorana is supported by grants from the National Cancer Institute K23 CA120587, National Heart, Lung and Blood Institute 1R01HL095109-01 and the V Foundation.

References