Venous Thrombosis in Patients with Solid Tumors: Determination of Frequency and Characteristics

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Deep venous thrombosis, pulmonary embolism, cancer, solid tumors, malignancy

Summary

Deep venous thrombosis (DVT) and pulmonary embolism (PE) are well recognized complications of cancer. However, our current knowledge of this association is derived from studies conducted more than a decade ago. In light of the changes in medical practice and the improvement in cancer care in recent years, a re-evaluation of the relationship between malignancy and venous thrombosis is in order. Of a total of 1041 patients with solid tumors admitted to 3 major medical centers, there were 81 (7.8%) diagnosed with DVT/PE. Patients were more likely to develop DVT/PE during chemotherapy (p = .0001). Advanced malignancies (p = .001), renal carcinoma (p = .005), pancreatic (p = .001), gastric (p = .014) and brain tumors (p = .001) were independent variables strongly associated with the occurrence of venous thrombosis. The occurrence of thrombotic events in the population tested in this study did not adversely affect survival (p = .082).

The study identifies subset of patients with cancer at high risk for venous thrombosis. Early prophylaxis with anticoagulants in these patients may be warranted. Most importantly, further clinical trials are desperately awaited to detect possible new trends in the frequency and types of thrombotic events and to better define prevention strategies in cancer patients at risk for thrombosis.

The association between venous thromboembolic disease (VTD) and malignant neoplastic disorders is well known and has been the subject of several reports for more than a century (1-8). There is a general agreement among investigators that thrombotic complications in patients with cancer occur at a rather high frequency, and that other circumstantial factors such as surgery or chemotherapy potentiates this risk (9,10). However, several important considerations pertaining to cancer and thrombosis continue to be shrouded in controversy. For example, there are inexplicable differences in the proportion of patients with cancer diagnosed with deep venous thrombosis (DVT) or pulmonary embolism (PE) reported in the literature (2, 4, 5, 11). In the absence of large well-controlled studies, one may only postulate on the reasons that contributed to these differences. The inclusion of different types of VTD such as superficial, venous, arterial or vascular access device-induced thrombosis may have led to overestimation of the incidence of these events in patients with underlying malignancy. Another possible explanation for this discrepancy relates to the use of a variety of diagnostic and methodological criteria ranging from observation and clinical suspicion to more invasive procedures resulting in considerable differences in the rate of reported clotting events (12). Along the same line of discussion, one may argue whether VTD is a random event or constitutes a complication that occurs more commonly in patients with distinct characteristics and certain tumor types. To further investigate the association between malignancy and thrombosis, we evaluated 1041 patients with solid tumors for the risk of DVT/PE. The main objectives of the study were to determine the frequency of DVT/PE based on validated diagnostic criteria and to identify patients with cancer at high risk for developing these thrombotic episodes. Also, we evaluated the impact of VTD on the survival of these patients.

Patients and Methods

Between 1993 and 2000, we retrospectively evaluated the occurrence of venous thrombotic disease in patients with solid tumors. Patients were referred to hematology/oncology services in 3 tertiary medical centers; University of Tennessee Health Science Center; University of North Carolina at Chapel Hill and East Carolina University. All patients had histologic confirmation of malignancy and underwent complete staging evaluation. Stage I and II tumors were considered as early while stages III and IV were defined as advanced malignancies. Patients were included in the study regardless of their performance status. Every effort was made to assure analysis of consecutive patients. However, a small number of patients with early stage tumors treated with surgery or radiotherapy alone, i.e., early prostate cancers, were not considered in the final analysis unless they were referred and cared for by the above services.

The diagnosis of deep venous thrombosis was confirmed by duplex ultrasonography and/or venography while high-probability ventilation-perfusion lung scan and/or positive angiography were required to establish the diagnosis of pulmonary embolism. Computed tomography scan or magnetic resonance imaging were used to confirm the presence of intra-abdominal or pelvic vein thrombosis. The following thrombotic events were excluded from the analysis; vascular access-induced thrombosis, superficial thrombophlebitis and thrombosis related to direct extension or compression by malignant tumor and thrombosis occurring in the setting of disseminated intravascular coagulation. The temporal association between venous thromboembolic disease and chemotherapy or surgery was recorded and compared with the type of treatment received by patients who did not develop thrombosis.
Statistical Analysis

In order to compare the patients with thrombosis to the patients without thrombosis, two-sample t-test was used for continuous variables such as age; otherwise the two-way contingency table methods such as chi-square test and Fisher’s exact test were used when the variable of interest was categorical. Cox regression was used to adjust for confounders such as stage and type of malignancy. The time to survival was also compared between the two groups with and without thrombosis. Because time to survival was subject to censoring, Kaplan-Meier method was used followed by log-rank test.

Results

Characteristics of Patients

Of a total 1041 patients identified, 81 (7.8%) were diagnosed with venous thrombosis. Table 1 depicts demographics and distribution of sites and stages of solid tumors in the patients with and without venous thrombosis. The median age of the 565 men and 476 women was 60 years (range, 26-89 years). The median follow-up for all patients was 26 months (range, 1-76 months). Chemotherapy as the primary

<table>
<thead>
<tr>
<th>Number of Patients</th>
<th>Patients with Thrombosis</th>
<th>Patients without Thrombosis</th>
<th>P value</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex M/F</td>
<td>81/960</td>
<td></td>
<td>.809</td>
<td>1.06</td>
<td>.67, 1.67</td>
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<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td>.141</td>
<td></td>
<td></td>
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<td>Median/Range</td>
<td>59/57.9/31-74</td>
<td>60/59.7/26-88</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I/II</td>
<td>33/546</td>
<td></td>
<td>.005</td>
<td>1.92</td>
<td>1.21, 3.04</td>
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<tr>
<td>III/IV</td>
<td>48/414</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Tumor Site</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Breast</td>
<td>13/128</td>
<td></td>
<td>.493</td>
<td>1.24</td>
<td>.67, 2.31</td>
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<tr>
<td>Lung</td>
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<td>.749</td>
<td>1.11</td>
<td>.59, 2.11</td>
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<tr>
<td>Colon</td>
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<td>.312</td>
<td>1.43</td>
<td>.71, 2.88</td>
</tr>
<tr>
<td>Kidney</td>
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<td>.002</td>
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<td>1.54, 8.85</td>
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<td>2.18</td>
<td>.89, 5.35</td>
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<tr>
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<td>.836</td>
<td>.91</td>
<td>.35, 2.32</td>
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<td>.207</td>
<td>1.85</td>
<td>.70, 4.87</td>
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<td>Brain</td>
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<td>.143</td>
<td>2.21</td>
<td>.74, 6.59</td>
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<td>Ovarian</td>
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<td>.519</td>
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<td>.47, 4.09</td>
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<td>Testicular</td>
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<td>.46, 3.33</td>
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<td>Head/Neck</td>
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<td>.11, 1.16</td>
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<td>Others</td>
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<td></td>
<td></td>
<td></td>
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<td>Chemotherapy alone</td>
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<td>1.80, 4.60</td>
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<td></td>
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<td>Others</td>
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<td></td>
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Table 1 Comparison of the characteristics and tumor sites between the patients with and without venous thrombosis

Table 2 Distribution of thrombotic episodes in all 1041 patients
modality for cancer treatment was administered to 282 patients while surgical resection of the tumor without further treatment was performed in 315 patients. A combined modality approach (surgery/chemotherapy/radiation/hormonal manipulation) was considered in 297 patients. Other therapeutic options such as radiation, immune response modifiers or hormonal treatment were offered to 96 patients. A total of 57 patients received supportive or palliative care only without any treatment of the underlying tumor.

Venous Thrombotic Episodes

Table 2 shows the types of thrombotic events observed in the patients included in the current analysis. Of the 1041 patients, 81 (7.8%) developed 114 venous thrombotic episodes as defined by the study. Of the 81 patients who developed venous thrombotic episodes, 11 were diagnosed with PE and lower extremity DVT and 8 patients with bilateral extremity DVT. Therefore, a recurrence rate of DVT/PE of 17% was observed in the current study. In 40 patients, VTD occurred during chemotherapy cycles, while in 31 patients thrombosis was detected during the postoperative period. When compared to the modality of treatment received by the patients without DVT/PE, patients were more likely to develop DVT/PE during chemotherapy alone (p = .0001). In the majority of patients, the clotting episodes occurred between weeks 9 and 17 of chemotherapy. Fig. 1 depicts the number of patients with DVT/PE at different week midpoints of chemotherapy cycles. Patients with DVT/PE were more likely to have advanced cancers when compared to patients without thrombosis (p = .005).

At multivariate analysis, advanced tumor stage was an independent variable in terms of its association with thrombotic events (p = .001; relative risk [RR] 3.2; 95% confidence interval [CI] 1.9, 5.2). Also, renal carcinoma (p = .005; RR 3.1; 95% CI 1.4, 6.8), pancreatic (p = .001; RR 8.8; 95% CI 3.5, 22.4) gastric (p = .014; RR 3.3; 95% CI 1.3, 8.5), and brain tumors (p = .001; RR 9.0; 95% CI 3.1, 26.4) were all independent risk factors for venous thrombosis.

In 92 patients, there were a total of 119 venous thrombotic events related to indwelling venous catheters or induced by direct extension of tumor. These thrombotic events are shown in table 2. Patients diagnosed with DVT/PE in the setting of disseminated intravascular coagulation have been reported previously (13).

Fig. 2 shows Kaplan-Meier survival curves for the patients with and without DVT/PE (p = .082).

Discussion

Several studies have demonstrated the presence of hemostatic defects in patients with malignancy. These abnormalities range from laboratory evidence of coagulation activation to clinically significant bleeding, DIC or life-threatening pulmonary embolism (3-6, 13-15). Because of the inherent difficulty in evaluating different types and stages of tumors, there has been a number of inconsistent observations among investigators with respect to frequency, demographics and sites of tumors in patients with cancer and venous thrombotic disease (4, 5, 7, 16-18). It is also important to remember that few recent studies have attempted to rechallenge certain concepts pertaining to the nature of the relationship between clotting and malignant disorders. It is plausible that advances in cancer diagnosis and management transpiring during the past few years might have influenced the appearance of thrombotic complications in patients being diagnosed and treated in current health care facilities. In the current study, we provided a re-evaluation of the
association between malignancy and thrombosis in patients admitted or cared for in three major cancer centers.

The frequency of DVT/PE in this study was 7.8%; a rate considerably lower than the 10% and up to 50% figures quoted usually in the literature (3-6, 8, 17, 18). The explanation of this controversy may be in what constitutes a clotting event. We used a definition of DVT/PE based on objective and well-validated methods of diagnosis, instead of evaluating all types of thrombotic episodes (superficial, deep, arterial, vascular access-induced) collectively. Also, the smaller observed frequency in this study may be a reflection of the changes in medical practice behavior that took place over the past years. Emphasis now is given on outpatient treatment and shorter hospital stays with adequate prophylaxis with anticoagulants as opposed to old medical traditions that subjected patients to longer and frequent admissions which might have allowed a higher frequency of thrombosis (19).

In multivariate analysis, the stage of solid tumors, renal, pancreatic, gastric and brain tumors were independent variables significantly related to the occurrence of venous thrombotic disease. The association between advanced tumors and thrombosis observed in the current study is in accordance with findings by other investigators addressing the impact of tumor burden on the hemostatic system (5, 7, 8, 17, 18). Patients with more extensive tumors are more likely to have poor functional performance and to suffer from more complications related to the underlying malignancy. Although supportive care may lead to small increase in survival in some patients with advanced malignancies, this advantage may be counterbalanced by greater opportunities to develop thrombotic complications.

The increased incidence of venous thrombosis in patients with renal, pancreatic, gastric and brain cancers is not a unique finding of our study, but is an observation that has been made by other investigators addressing the impact of tumor burden on the hemostatic system (5, 7, 11, 17, 18, 20-22). The exact mechanisms by which these tumors predispose to thrombosis remain a matter of great debate. A combination of factors inherent to the biology of tumor and the treatment of these patients are likely to account for this form of hypercoagulability. The spectrum of such factors may include: increased ability of these cancers to invade adjacent major vessels; high potential for local and distant metastases; secretion of cancer pro-coagulant and, thrombogenic effect of chemotherapy and of other agents used in the treatment of these malignancies (5, 21-25).

Some of our other findings are also noteworthy. In particular, the high number of thrombotic events occurring during chemotherapy. This is consistent with the general experience that this modality of treatment constitutes a risk factor for clotting in cancer patients (9, 10). Equally important, was the lack of negative effect of thrombosis on survival as estimated by the Kaplan-Meier formula. This may be a reflection of the relatively small number of patients with thrombosis in this study or possibly due to the improved management of both DVT and the underlying malignancy (26).

A potential flaw of our analysis is the inclusion of patients with different types of solid tumors and the possible bias in patient selection. It is conceivable that these patients are heterogeneous in terms of their management and prognosis and therefore, they are exposed to variable degrees of risk for thrombosis. Conversely, the impact of a given clotting event may vary according to the underlying malignancy and the performance status of the patient. These problems may be circumvented by studying VTD in patients with single tumor type under similar circumstantial risks. This approach, however, requires an enormous number of patients and a considerable cooperative effort. Nonetheless, the findings from this study are of some significance. On a practical level, identification of patients at high risk for DVT/PE provides rationale for more targeted prophylactic anticoagulant strategies. This comes at an era where the role of heparins in improving the survival of cancer patients is being evaluated on a continuous basis (27, 28). On a historical level, we are unaware of any studies examining covariates related to VTD in cancer patients in an independent manner as opposed to direct description of this complication. For example, previous studies have given strong emphasis on thrombosis occurring in patients with adenocarcinoma, especially, of the lung, colon and pancreas. One should bear in mind, that such higher reported frequency does not denote necessarily particular association but rather reflects a larger absolute number of adenocarcinomas in the general population.

Given our data, and in light of the progress that has been achieved in the field of cancer treatment in the past decade, we believe that large scale clinical studies are needed to re-evaluate the clinical association between malignancy and VTD, and to address changing trends in the frequency of thrombotic complications in cancer patients.

References

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