Venous Thromboembolism and Cancer: Risks and Outcomes

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Abstract—Cancer and its treatments are well-recognized risk factors for venous thromboembolism (VTE). Evidence suggests that the absolute risk depends on the tumor type, the stage or extent of the cancer, and treatment with antineoplastic agents. Furthermore, age, surgery, immobilization, and other comorbid features will also influence the overall likelihood of thrombotic complications, as they do in patients without cancer. The role of hereditary thrombophilia in patients with cancer and thrombosis is still unclear, and screening for this condition in cancer patients is not indicated. The most common malignancies associated with thrombosis are those of the breast, colon, and lung, reflecting the prevalence of these malignancies in the general population. When adjusted for disease prevalence, the cancers most strongly associated with thrombotic complications are those of the pancreas, ovary, and brain. Idiopathic thrombosis can be the first manifestation of an occult malignancy. However, intensive screening for cancer in patients with VTE often does not improve survival and is not generally warranted. Independently of the timing of cancer diagnosis (before or after the VTE), the life expectancy of cancer patients with VTE is relatively short, because of both deaths from recurrent VTE and the cancer itself. Patients with cancer and acute VTE who take anticoagulants for an extended period are at increased risk of recurrent VTE and bleeding. A recent randomized trial, the Randomized Comparison of Low Molecular Weight Heparin versus Oral Anticoagulant Therapy for Long-Term Anticoagulation in Cancer Patients with Venous Thromboembolism (CLOT) study, showed that low molecular weight heparin may be a better treatment option for this group of patients. The antineoplastic effects of anticoagulants are being actively investigated with promising preliminary results. **(*Circulation*. 2003;107:I–17-I-21.)**

Key Words: thrombosis ■ coagulation ■ neoplasm

VTE is a common complication of malignant disease. The association between cancer and thrombosis is well established. However, despite the accumulation of a considerable volume of epidemiologic data since the first observation made by Armand Trousseau in 1865, the pathophysiology remains poorly understood. Patients undergoing surgery for cancer have a higher risk of postoperative deep vein thrombosis (DVT) than those having surgery for nonmalignant diseases.[1] Autopsy series have reported increased rates of pulmonary embolism (PE) in cancer patients compared with patients without cancer.[2] Furthermore, the risk of recurrence after a first episode of VTE is higher in cancer patients than in those without underlying malignancy.[3] Finally, individuals presenting with an unprovoked episode of VTE are more likely to have an underlying cancer than those with an identifiable risk factor for thrombosis.[4,5] In this review, the epidemiology of thrombosis and cancer is discussed in 6 sections: (1) the incidence of VTE in patients with cancer on and off antineoplastic treatment; (2) the tumors most strongly associated with thrombosis; (3) the association between VTE and occult malignancy; (4) management of VTE in patients with cancer; (5) the inverse association between anticoagulation therapy and cancer survival, and (6) the prognosis of cancer patients with venous thrombosis.

Incidence of VTE in Patients With Malignancy and on Cancer Treatment

According to clinical data prospectively collected on the population of Olmsted County, Minnesota, since 1966, the annual incidence of a first episode of DVT or PE in the general population is 117 of 100,000.[6] Cancer alone was associated with a 4.1-fold risk of thrombosis, whereas chemotherapy increased the risk 6.5-fold.[7] Combining these estimates yields an approximate annual incidence of VTE of 1 of 200 in a population of cancer patients.

The most reliable evidence of the incidence of VTE in individuals with a specific malignancy comes from controlled clinical trials of systemic therapy in women with early-stage breast cancer.[8–15] On the basis of the B14 and B20 trials in the National Surgical Adjuvant Breast Project,[8,9] which involved women with estrogen receptor-positive lymph node–negative breast cancer, the 5-year incidences of VTE in women given

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placebo, tamoxifen, and tamoxifen plus chemotherapy were 0.2%, 0.9%, and 4.2%, respectively. In women with node-positive breast cancer on chemotherapy, the rate of thrombosis varies between 1% and 10%, with the highest rates of thrombosis in postmenopausal women.[10–18] In these trials, chemotherapy plus tamoxifen increased the risk for VTE over chemotherapy alone by ≈4-fold. Furthermore, VTE occurred only while patients were on treatment and not during follow-up of adjuvant therapy. Age, hormonal treatment, and chemotherapy play synergistic roles in thrombosis development in patients with cancer.

The extent of cancer also influences the risk of thrombosis. In an earlier case series, the rate of thrombosis in patients receiving chemotherapy for metastatic breast cancer was 17.5%.[19] A much lower risk of 4.5% over 6 months was reported in a more recent randomized trial involving women with metastatic breast cancer.[20] High rates of thrombosis have also been reported in other cancers, especially in patients with advanced disease receiving antitumor treatment. For example, ≈10% of women with advanced ovarian cancer receiving chemotherapy,[21] and up to 28% of patients with malignant gliomas have been reported to develop VTE.[22,23] Patients with hematologic malignancies also have a high risk for thrombotic complications, despite disease-related or chemotherapy-induced thrombocytopenia. Patients with acute lymphoblastic leukemia have a 4% risk of cerebral vascular thrombosis during therapy with L-asparaginase,[24,25] whereas 10% of patients with Hodgkin's or non-Hodgkin's lymphoma develop VTE.[26,27]

Very high rates of VTE have been reported in patients treated with combination therapy including an antiangiogenic agent. For example, when thalidomide is combined with cancer chemotherapy, VTE rates of 28% in patients with multiple myeloma and 43% in patients with renal cell carcinoma have been reported.[28,29] Newer, experimental antiangiogenic agents have also been associated with an unexpectedly high risk of thrombotic complications in early-phase clinical trials.[30,31] The pathophysiology of thrombosis in these settings has not been elucidated, but endothelial dysfunction, alterations in pro- and anticoagulant protein levels, or deregulation of cytokine activity have been proposed as mechanisms.

Thrombotic complications are also frequent with indwelling catheters. The incidence is not well established, but earlier studies have reported rates of symptomatic catheter thrombosis as high as 14% of patients or 1 event per 1000 device days.[32] However, recent prospective studies suggest the risk of catheter thrombosis is lower, at 4% of patients.[33,34] Although the pathogenesis of catheter thrombosis is also not well characterized, it may involve endothelial damage and local activation of blood coagulation. Infusion of chemotherapeutic agents or local radiation of the chest or shoulder area can add to the injury of the involved vessel and increase the risk of thrombosis in patients receiving active cancer treatment.

Some patients with cancer may also have hereditary thrombophilia that can predispose to thrombotic complications, but only a few small studies have addressed this issue. The 2 most common genetic causes of thrombophilia identified to date, factor V Leiden and the prothrombin gene mutation, have not been specifically associated with thrombosis in patients with cancer based on case–control studies.[35,36]

Tumors Most Strongly Associated With Thrombosis

Autopsy studies and retrospective reviews suggest that cancers of the pancreas, lung, and stomach, and adenocarcinomas of unknown primary, are most strongly associated with thrombosis,[37,38] leading to the view that mucin-producing cancers are the most often associated with VTE. More recent studies that have adjusted for the prevalence of these tumor types do support this hypothesis. In a large population-based study that used the discharge diagnoses of >7000 Medicare patients (>65 years of age) admitted to hospital with a diagnosis of both malignancy and VTE, Levitan et al found the highest rates of VTE in cases of ovarian cancer (1.2%), brain tumors (1.2%), and cancer of the pancreas (1.1%).[39] Still, these are not the tumors observed most frequently in individuals who present with VTE. In contemporary clinical trials evaluating antithrombotic agents, in which ≈20% of subjects have some form of cancer, the most common cancers involve the prostate, colon, lung, and brain in men, and the breast, lung, and ovary in women.[40] These findings are consistent with the report by Levitan et al, in which lung cancer accounted for 21% of cases, colon cancer for 18%, and prostate cancer for 17%.[39]

In summary, although patients with mucin-producing adenocarcinomas seem more likely to develop thrombosis, the most frequent types of cancers found in patients with thrombosis are those most prevalent in the population.

The Association Between VTE and Occult Cancer

An association between thrombosis and occult cancer has long been recognized. Thrombotic events can manifest as classical DVT or PE, but they can also develop in less common sites, such as the veins of the arms or neck, the vena cavae, or the visceral, portal, or cerebral circulation.[41]

A diagnosis of cancer is more likely to arise in patients without identified risk factors for thrombosis who present with apparently spontaneous DVT than in those in whom secondary DVT occurs postoperatively or in another high-risk situation, or patients with signs and symptoms of DVT in whom thrombosis is subsequently excluded. On the basis of a pooled analysis of 4 cohort studies, the odds ratio for newly diagnosed malignancy in patients with VTE compared with those who had VTE excluded was 3.2.[4] Similarly, there is a higher incidence of subsequent cancer in patients with idiopathic thrombosis than in those with a definite but transient risk factor at the time of VTE (Table 1).[5,42–46] The variation in reported incidence likely reflects the different definitions for idiopathic and secondary cases, and variation in the intensity of cancer surveillance in each study. In a pooled analysis of these studies, the odds ratio for subsequent cancer in patients presenting with idiopathic VTE compared with secondary VTE was 4.8.[44] On the basis of results from cohort studies and clinical trials, ≈10% of persons presenting with idiopathic VTE are subsequently diagnosed with cancer over

Incidence of Cancer After Diagnosis of VTE

Study	Rate of Cancer	
	Idiopathic (%)	Secondary (%)
Aderka 1986[43]	9/35 (25.7)	2/48 (4.2)
Prandoni 1992[42]	11/145 (7.6)	2/105 (1.9)
Ahmed 1996[46]	3/113 (2.7)	0/83 (0.0)
Monreal 1997[44]	4/96 (4.2)	4/563 (0.7)
Hettiarachchi 1998[5]	10/137 (7.3)	3/189 (1.6)
Rajan 1998[45]	13/152 (8.6)	8/112 (7.1)

5 to 10 years, and the diagnosis is established within the first year of presentation of DVT in >75% of cases.[5,42–47]

This likelihood of identifying occult cancer after an episode of idiopathic VTE is supported by 2 population registry studies. Using data from national hospital and cancer registries, Baron et al found that the standardized incidence ratio (SIR, the observed number of cases divided by the expected number of cases in the age-matched normal population) was 4.4 for cancer at 1 year after diagnosis of VTE.[48] Using a similar database linkage strategy, Sørensen et al found a lower SIR of 1.3 for cancer in patients with DVT or PE over 15 years of follow-up.[49] In both studies, the SIR was highest within the first 6 months, dropping almost to baseline levels 12 months after presentation with VTE. The strongest associations were seen with cancers of the pancreas, ovary, liver, and brain. In the study by Sørensen et al, 40% of patients diagnosed with cancer within 1 year after VTE had distant metastases by the time of cancer diagnosis.

Given the association between idiopathic VTE and occult cancer, it has been suggested that patients with unprovoked thrombosis routinely undergo investigation for underlying malignancy. However, there is little evidence to date that routine cancer screening would be worthwhile or cost-effective in this situation. The preliminary results of a small randomized trial evaluating extensive screening versus no screening in patients presenting with idiopathic VTE were reported recently.[50] The battery of tests used for extensive screening included ultrasound and computed tomography of the abdomen and pelvis, stool guaiac examination, gastroscopy, colonoscopy, sputum cytology, mammography, manual pelvic or prostate examination, and measurement of tumor markers (eg, prostate-specific antigen and carcinoembryonic antigen). Thirteen of 99 patients allocated to the extensive screening group compared with 0 of 102 patients in the control group were initially found to have cancer by these means. During the 2-year follow-up period, a diagnosis of cancer was established in 10 patients in the control group and 1 in the screened group. There was no significant difference in cancer-related mortality between the 2 groups (3.9% versus 2.0%, respectively), although this finding may be a reflection of the small number of study subjects. Still, these results give rise to the preliminary conclusion that earlier diagnosis of cancer does not translate into improved prognosis and survival. In patients with idiopathic VTE, supplementation of a comprehensive medical history and a physical examination with basic blood work, and a chest x-ray in smokers, can be expected to detect ≈90% of occult cancers.[51]

In summary, acute VTE can be the first manifestation of an occult malignancy, and patients presenting with idiopathic VTE are more likely to have underlying cancer than those in whom a secondary cause of thrombosis is apparent. Extensive screening for cancer in patients with idiopathic VTE is not routinely warranted. However, further large-scale studies of the role of such screening in idiopathic VTE are necessary.

Treating VTE in Patients With Cancer

Long-term anticoagulation using vitamin K antagonists is associated with high rates of recurrent VTE and bleeding in patients with cancer. This therapy is also difficult to supervise in this group of patients, as it requires frequent blood testing to maintain dosage levels within the therapeutic range. Investigators with the recent CLOT trial reported a significant reduction in recurrent VTE in patients randomized to a low-molecular-weight heparin (LMWH) compared with patients who received the heparin plus a vitamin K antagonist.[52] This benefit was achieved without any increase in bleeding. The results from the trial may change the way this special subset of patients is treated.

Anticoagulation Therapy and Cancer Progression

The potential for anticoagulant therapy to retard tumor progression and improve survival was first examined in a large clinical trial in 1984.[53] Since then, supportive but inconclusive evidence for an antineoplastic effect of heparins and other antithrombotic agents has come from animal tumor models and retrospective analyses of clinical trials.[54,55] The first study designed to specifically examine the influence of LMWH on overall survival in cancer patients with advanced solid tumors was reported recently.[56] In this randomized, placebo-controlled study, Kakkar et al found no difference in survival at 1, 2, and 3 years between 185 patients treated with dalteparin and 181 patients who received placebo. However, in a subgroup analysis of good prognosis patients, there was a statistically significant improvement in survival in favor of LMWH. These results are encouraging, and further trials evaluating the antineoplastic effect of LMWH are warranted.

Prognosis of Patients With Cancer and VTE

Patients with cancer who develop VTE have reduced life expectancy. On the basis of long-term follow-up data on patients with thrombosis, those with cancer have a 4- to 8-fold higher risk of dying after an acute thrombotic event than patients without cancer.[57,58] Furthermore, patients with cancer and thrombosis have a lower survival rate than those with cancer without thrombosis. In a large population-based study, Sørensen and colleagues examined the survival of patients with cancer and VTE compared with those without VTE matched for type of cancer, sex, age, and the year of diagnosis.[59] The 1-year survival rate for patients with thrombosis was 12% compared with 36% in control patients ($P<0.001$). The mortality ratio associated with VTE was 2.2 for the 1-year follow-up period. This high mortality probably reflects deaths due to both thromboembolism and a more aggressive course of malignancies associated with VTE.

Conclusion

Patients with cancer have multiple risk factors for thromboembolic disease. Further epidemiological research will provide more reliable estimates of the thrombotic risk associated with different types of tumors, stages of disease, and antitumor treatments. It is anticipated that a better understanding of the interactions between tumor growth and blood coagulation, together with the results of the CLOT trial, will help to improve the prophylactic and treatment strategies for VTE in these complex patients.

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