Thrombosis and Cancer: A Major Complication of Cancer Care

The close relationship between venous thromboembolism (VTE), malignancy and thrombotic risks/complications of central venous catheters in cancer patients

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The close relationship between cancer and the activation of blood coagulation has been known since 1865, when Professor Armand Trousseau described it in a lecture to the New Sydenham Society on the clinical association between idiopathic VTE and occult malignancy.[1,2] This early observation by Trousseau has since been widely studied and there is an abundance of epidemiologic evidence that supports the close-knit relationship between thrombosis and cancer.

Cancer associated thrombosis affects the lives of patients significantly[3]

Cancer associated thrombosis affects the lives of patients significantly[3] and is associated with an increased risk in venous and arterial thromboembolic events, including deep venous thrombosis and pulmonary embolus. The average annual incidence rate of venous thromboembolism in the general population is approximately 117 per 100,000, whereas the incidence in patients with cancer is approximately 1 in 200.[4]

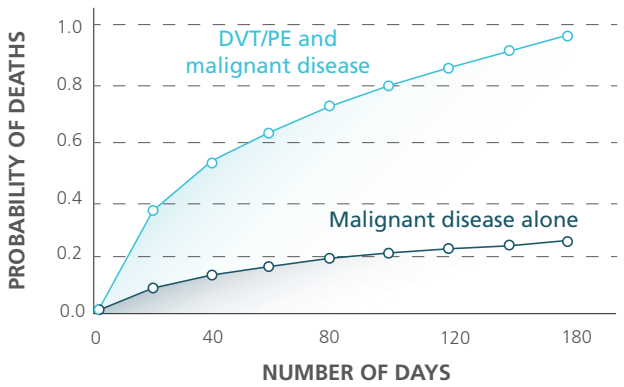
CONSEQUENCES OF CANCER-ASSOCIATED VTE

Association with Mortality

Observational data indicate that patients with cancer and VTE have a poorer prognosis than those with cancer alone. In a population based study, cancer was associated with a 4.1-fold greater risk of thrombosis, whereas the use of chemotherapy increased the risk 6.5-fold.[4]

Cancer related VTE accounts for one-fifth of all DVT and PE[5], and is one of the leading causes of death in cancer patients.[6] In addition, VTE in this patient population is associated with worsened short-term and long-term survival.[3,7] (Figure 1)

Figure 1 Concurrent VTE and Cancer Increases the Risk of Death[8]
Probabilty of death within 183 days of initial hospital admission

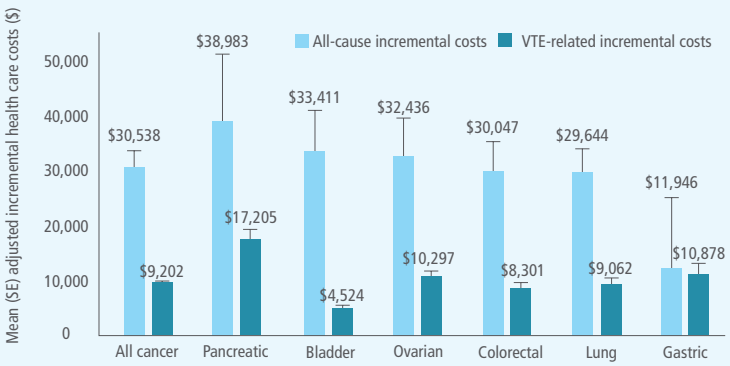


HEALTHCARE COSTS AND RESOURCES ASSOCIATED WITH DVT AND VTE

Given that patients requiring treatment for DVT are often hospitalized initially, the management of DVT also adds considerably to healthcare resource use. Early or late complications of VTE can extend the hospital stay by 7-11 days, adding a mean of $1,784 per day (2002) to hospitalization costs. Costs associated with bleeding complications of DVT have a mean hospital stay of 18 days and significant corresponding hospital costs of $43,181.[9]

In more recent research by Khorana et al. from February, 2013, it was found that cancer patients with VTE had approximately three times as many all-cause hospitalizations, days in hospital and more outpatient claims than cancer patients without VTE. Cancer patients with VTE incurred higher overall all-cause inpatient costs ($21,299 vs. $7,459), outpatient costs ($53,660 vs. $34,232) and total health care costs ($74,959 vs. $41,691) than cancer patients without VTE (all P<.0001).[10]

Costs of VTE[10]
Adjusted incremental health care costs for cancer patients with and without VTE; presented by site of cancer

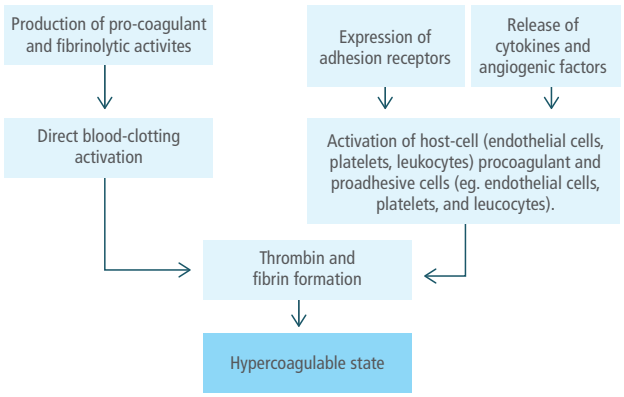


PATHOGENESIS OF CANCER-ASSOCIATED THROMBOSIS

There is increasing evidence to suggest that critical oncologic events may also trigger activation of the coagulation cascade, leading to a pro-thrombotic environment that not only manifests as venous thromboembolic disease, but also promotes the growth and progression of the malignancy.[6]

In patients with cancer, the capability of tumor cells and their pro-coagulant products to interact with platelets, clotting and fibrinolytic proteins contributes to the development of VTE. Other host responses stimulated by tumor cell interactions with endothelial cells and tumor-associated macrophages further promote clotting activation.[6] (Figure 2)

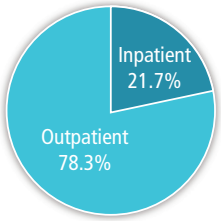
Figure 2. The Pro-thrombotic Properties of Tumor Cells[11]



SHIFT IN CANCER-ASSOCIATED VTE: PREDOMINANCE IN OUTPATIENT SETTINGS

Paradigm changes in cancer therapy have shifted care to primarily outpatient-based regimens. Venous thromboembolism (VTE) is a well-known complication of cancer but contemporary data regarding the burden of VTE in the outpatient versus inpatient cancer settings has been limited. In a recent study of nearly 18,000 cancer patients, University of Rochester Medical Center researchers found that when VTE develops, 78% of the time they occur when a patient is in an outpatient setting while on chemotherapy. Also of note, the cost of care for a patient with VTE was twice as high compared to a patient that did not have that complication.[3]

Clinical Setting of VTE in 17,874 Patients
VTE% by segment



RISK FACTORS

Several factors are known to influence the incidence of VTE in patients with cancer. They include, but are not limited to, patient-related factors such as age, ethnicity, immobilization and obesity; the specific type of cancer, initial period after diagnosis and adenocarcinoma; treatment-related factors such as surgery, Central Venous Catheters (CVCs) and type of chemotherapy.[5,12] This paper will focus on the risks associated with CVCs (including totally implantable ports) and the risks associated with chemotherapy use.

Patient-related Factors
Older age
Race/Ethnicity
Major comorbities
History of VTE
Immobilization
Obesity
Pro-thrombotic mutations

Cancer-related Factors
Site of cancer
Adenocarcinoma
Advanced stage
Initial period after diagnosis

Treatment-related Factors
Major surgery
Hospitalization
Central venous catheters
Chemotherapy
Hormonal therapy
Antiangiogenic agents
Supportive care
- ESAs/Transfustions

BioMarkers
Blood count (leukocyte, platelet)
Tissue factor
D-dimer
Others (sP-selectin, CRP, Factor VIII)

THROMBOTIC COMPLICATIONS OF CVCS IN CANCER PATIENTS

Central Venous Catheters (CVCs) such as tunneled catheters and totally implanted ports play a major role in oncology and the oncology patient, particularly for patients receiving systemic anti-cancer therapy.[13]

Cancer patients usually require repeated venous punctures for treatment monitoring, application of chemotherapy or blood transfusions. Today, these devices provide easy vascular access for delivery of chemotherapy, fluids, medications, blood products and parental nutrition solutions.[14]

Over the last decade, many management changes in oncology have occurred, particularly with respect to new chemotherapy combinations and more complex application schemes.[14] The benefit derived from a CVC may be offset by thrombosis and associated complications, such as infection, pulmonary embolism (PE), CVC dysfunction, or loss of central venous access.[12] Overall, CVCs are a "stress test" of the coagulation system in cancer patients and can precipitate thrombosis due to multiple mechanisms related to the host and/or to the device itself.[13]

Fibrin Sheath Formation and Intraluminal Thrombosis

Soon after the insertion of almost all intravenous lines, a fibrin sheath forms around the catheter. Radiographically, thrombosis can have a typical appearance of an enveloping sleeve surrounding the CVC or be characterized by mural thrombosis (present in approximately 30% of patients with CVCs) adherent to the venous vessel wall.[12] Fibrin sheath is known to impair catheter function, serves as a risk factor for the development of peri-catheter thrombus and can act as a nidus for catheter-related infection.

In an autopsy study of patients with CVCs, all 55 patients examined developed this sleeve and, in phlebographic studies, 45 of 57 (78%) patients had a fibrin sheath.[13] A venographic study by DeCicco et al. showed that 83 of 95 (87%) patients had these sheaths. Finally, all 16 patients who were analyzed at the removal of their CVCs after 3–34 months (median 12.5 months) of use had these sheaths.[13]

Additionally, a common and underreported event is the development of clotting within the lumen of the catheter (intraluminal thrombosis). This usually is uncovered when the catheter fails to allow blood to be withdrawn or fails to allow infusion through a port. The frequency of this event varies from .6 to .81 events per 1,000 catheter days and are lysed in most situations with fibrinolytic agents such as urokinase, streptokinaise and tissue plasminogen activator (TPA).[13]

CVC-RELATED BLOOD VESSEL THROMBOSIS (DVT)

The major thrombotic complication of CVCs is DVT. Rates of DVT among patients with a CVC in place have ranged from 11.7% to 66%; these are higher than the rates reported for mechanical or septic complications of CVCs.[14] In those that are symptomatic, symptoms include arm/neck/head swelling or pain, headache, numbness of the extremity, phlegmasia, venous distention and jaw pain.

In a large prospective study, 19 of 444 patients (4.3%) had symptomatic catheter-related thrombosis (CRT) in 19 of 500 catheters (0.3 per 1,000 catheter-days).[15] Significant baseline risk factors for CRT included more than one insertion attempt (OR = 5.5; 95% CI, 1.2 to 24.6; P = .03); ovarian cancer (OR = 4.8; 95% CI, 1.5 to 15.1; P = .01); and previous CVC insertion (OR = 3.8; 95% CI, 1.4 to 10.4; P = .01). In a recent meta-analysis of 11 studies comparing the risk of thrombosis related to peripherally inserted central catheters (PICCs) with that related to CVCs, PICCs were associated with an increased risk of deep vein thrombosis (OR 2.55, 1.54-4.23, p<0.0001) but not pulmonary embolism (no events).[16] The authors concluded that PICCs are associated with a higher risk of deep vein thrombosis than CVCs, especially in patients who are critically ill or with malignancy.

Incidence of venous catheter-related thrombosis in cancer patients[14]

Reference	No. of patients (n)	Method of diagnosis	Catheter-related thrombosis (%)
Bern et al	42	Phlebography	37.5
De Cicco et al.	127	Phlebography	66.0
Balestieri	57	Phlebography	56.0
Monreal et al.	29	Phlebography	62.0
Newman et al.	690	Clinical diagnosis	63.5
Drakos et al.	480	Phlebography	57.2
Lokich and Becker	53	Clinical diagnosis	41.5
Koksoy et al.	44	Clinical diagnosis	40.0
Cortelezzi et al.	416	Clinical diagnosis	12.0

Pulmonary Embolism (PE)

Most thrombotic events associated with CVCs remain subclinical, or complications such as PE are the first presenting symptom.[12] DVT of the upper extremity has long been considered of trivial importance for embolization due to its location and modest size. Symptomatic pulmonary emboli have been reported in approximately 6% of all patients with upper extremity DVT.[13]

In a study of 86 consecutive patients with CVC-related DVT, 15% of the patients were considered to have Pulmonary Embolism (PE).[9]

Infection

CVC-related thrombosis and CVC-related infection have been reported to be associated by many authors.[12,15,17,18,19] The pathogenesis of catheter-related infection seems to depend on the development of thrombosis of the catheter. Results from a postmortem study in 72 patients with a CVC at death revealed that in all patients with catheter related sepsis, they also had CVC mural thrombosis.[19]

CVC-related infection increased the risk of thrombosis 24%[12]

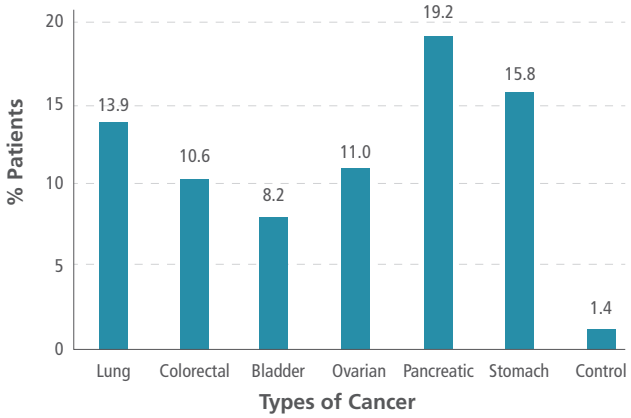
In addition, CVC-related infection may also increase the risk of subsequent clinically manifest thrombosis. In one study CVC-related infection increased the risk of thrombosis (24%) markedly in comparison with those without infection (3%).[12]

TOTALLY IMPLANTABLE VENOUS PORT SYSTEMS

Port systems are permanently implantable venous access devices and are an important component in the management of oncology patients.[20] Although totally implantable port systems are generally associated with a lower long-term risk of infection as compared to Hickman-type central venous catheters,[16] complications during placement and long-term use are still a matter of concern. These complications, including infection, catheter fracture, thrombosis and extravasation may necessitate device replacement, resulting in additional patient stress and treatment delays.

Rates of VTE by Cancer Type[9]

All cancer types were associated with a significant higer rate of VTE (p<0.0001 for all comparisons vs. controls



In a study of 3,498 venous port implantations, a total of 199 complications occurred with the most frequently encountered complications being infection (n=85) and thrombosis (n=63) as demonstrated by color Duplex ultrasonography. In recent port studies with sufficient patient population (n>200) thromboembolic complications ranged between 1.4 and 9.2 percent.[20]

In a 2010 study that looked at the occurrence of catheter related thrombosis and infections in patients with central venous catheters and totally implantable chest ports, they found catheter related thrombosis in 9.3% of the port patient population and catheter related infection in 11.6% of the port patient population. Of note, time to infection was 32.5 days in the CVC group compared to 88 days in the totally implanted port group.[21]

Early CVC Removal and Catheter Dysfunction

The CVC dysfunction because of clot formation may occur due to obstruction within the CVC lumina, or occlusion due to enveloping sheath obstructing the CVC luminal tip. In a large study based on the Strategic HealthCare Programs National Database, catheter complications that occurred in 45,333 CVCs used in an outpatient setting in a 17 month period between 1999 and 2000 were evaluated. In 1,871 catheters, dysfunction occurred and in 511 cases (27%) dysfunction occurred as a consequence of clot formation. In this study different types of central catheters were shown to carry a different complication rate but thrombosis was the most commonly reported cause of catheter dysfunction for peripherally and centrally inserted CVC with implantable ports.[12]

CHEMOTHERAPY

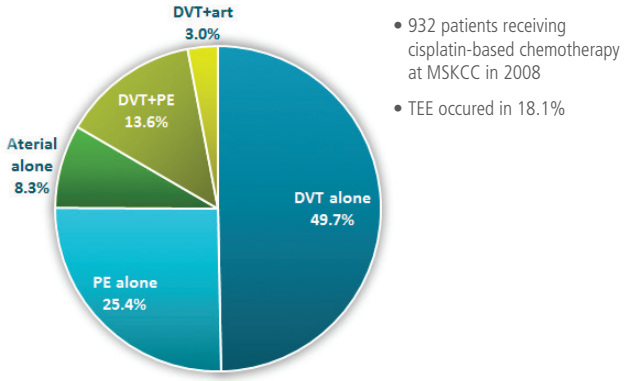
A large cohort study has shown that although cancer alone is associated with a 4.1-fold increase in the risk of thrombosis, the addition of chemotherapy enhances that risk to 6.5-fold.[4,9] Cytotoxic agents can alter coagulation protease levels and may directly injure the endothelium. Hormonal agents, such as tamoxifen, likely promote thrombogenesis by reducing plasma levels of natural anticoagulants. Surgery and catheterization cause direct trauma to vessels and initiate clotting via Tissue Factor exposure or contact pathway activation.[6]

Chemotherapy and Risk for VTE[22]

Chemotherapy Regimen	VTE Rate (%)
Thalidomide + gemcitabine + fluorouracil	43
Thalidomide + doxorubicin	20–40
Bevacizumab + ESA	30
Thalidomide + Dexamethasone	10–20
Cisplatin + gemcitabine	17.6
CMFVP	7–18
Fluorouracil + leucovorin	15–17
Lenalidomide + Dexamethasone	9–15
Asparaginase	4–14
Bevacizumab	11
Epirubicin + cyclophosphamide	10
Cisplatin + bleomycin	8.4
Tamoxifen	0–8

In a large retrospective study of all patients treated with cisplatin-based chemotherapy for any type of malignancy at Memorial Sloan-Kettering Cancer Center in 2008: among 932 patients, 169 (18.1%) experienced TEE (venous and arterial thromboembolic event) during treatment or within 4 weeks of the last dose. TEEs included deep vein thrombosis (DVT) alone in 49.7%, pulmonary embolus (PE) alone in 25.4%, DVT plus PE in 13.6%, arterial TEE alone in 8.3% and DVT plus arterial in 3%.[4]

MSKCC Retrospective Analysis



CONCLUSIONS

Cancer-associated VTE is a major complication that affects cancer patients throughout the course of their illness. A major risk factor for VTE in cancer is the presence of central venous catheters. Catheters are essential for the delivery of effective systemic therapy but can be complicated by the presence of fibrin sheaths or DVT, potentially resulting in PE. Systemic anticoagulation to prevent catheter-associated VTE has not been shown to be effective. Novel technology approaches to minimize the risk of catheter-associated thrombotic complications are urgently needed.

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