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REVIEW ARTICLE

Assessing Risk of Venous Thromboembolism in the Patient With Cancer

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The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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ABSTRACT

Purpose
Patients with cancer are increasingly at risk for venous thromboembolism (VTE). Rates of VTE, however, vary markedly among patients with cancer.

Design
This review focuses on recent data derived from population-based, hospital-based, and outpatient cohort studies of patients with cancer that have identified multiple clinical risk factors as well as candidate laboratory biomarkers predictive of VTE.

Results
Clinical risk factors for cancer-associated VTE include primary tumor site, stage, initial period after diagnosis, presence and number of comorbidities, and treatment modalities including systemic chemotherapy, antiangiogenic therapy, and hospitalization. Candidate predictive biomarkers include elevated platelet or leukocyte counts, tissue factor, soluble P-selectin, and D-dimer. A recently validated risk model, incorporating some of these factors, can help differentiate patients at high or low risk for developing VTE while receiving chemotherapy.

Conclusion
Identifying patients with cancer who are most at risk for VTE is essential to better target thromboprophylaxis, with the eventual goal of reducing the burden as well as the consequences of VTE for patients with cancer.

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INTRODUCTION

The risk of venous thromboembolism (VTE), although considerably elevated in patients with cancer, varies markedly between patients and even within the same patient at different time points during the course of malignancy. A growing body of literature from a variety of sources, including population-based studies,[1] hospital discharge databases,[2,3] cancer registries,[4] retrospective cohorts,[5] and prospective observational studies,[6-9] has led to an increased understanding of the clinical factors affecting risk of VTE. Exploratory studies have also identified candidate biomarkers predictive of VTE in patients with cancer.[7,10,11] This review will discuss the findings and limitations of data, describing known clinical risk factors, candidate laboratory biomarkers, and a recently validated risk model that can help identify patients with cancer most at risk for VTE.

UNDERSTANDING RATES OF VTE

It is difficult to directly compare reported rates of VTE in patients with cancer because the studies vary with regard to patient population, duration of follow-up, period of study, and method of detecting and reporting VTE. This is evident when comparing rates of VTE in large studies of pooled patients with cancer (Table 1). The highest rates of VTE are reported in cohorts consisting of hospitalized neutropenic patients with cancer (6.4%)[13] and patients admitted to an inpatient oncology service (7.8%).[5] Both clinical situations suggest active treatment, which in turn is a well-known risk factor for cancer-associated VTE. In contrast, rates of VTE are lower (0.6% to 3.2%) in study populations from databases with a likely higher proportion of patients who carry a remote diagnosis of cancer.[3,4,12] The frequency of VTE has also increased over time, and rates are therefore higher in more recent studies.[2-4] Further confusion is added by the fact that VTE rates may be significantly underestimated when relying on toxicity data from clinical trials. In a prospective randomized study of patients with advanced colorectal cancer, VTE was initially reported as a toxicity during treatment in only two of 266 patients (0.8%); a subsequent retrospective review of the same population found VTE in an additional 25 patients, for an

Table 1. Reported Incidence of VTE in Large Studies of Pooled Patients With Cancer

First Author	Stage	Type of Study	Years	Population	No. of Patients	Median Follow-Up	Incidence (%)	Risk Factors
Levitan[12]	NA	Retrospective cohort	1984-1990	Hospitalized medicare	1,211,944	NA	0.6	Type of cancer
Sallah[5]	I-IV	Retrospective cohort	1993-2000	Hospitalized with solid tumors	1,041	26 months	7.8	Type of cancer Advanced stage
Stein[3]	NA	Retrospective cohort	1979-1999	Hospitalized	40,787,000	NA	2.0	Type of cancer Year of hospitalization
Agnelli[6]	I-IV	Prospective cohort	1999-2002	Oncologic surgery	2,373	35 days	2.1	Age ≥ 60 years Previous VTE Advanced stage Immobility > 3 days Anesthesia ≥ 2 hours
Khorana[13]	NA	Retrospective cohort	1995-2002	Hospitalized neutropenic	66,106	8 days	5.4	Age ≥ 65 years Comorbidity Type of cancer
Chew[4]	I-IV	Retrospective record linkage cohort	1993-1995	Hospitalized	235,149	2 years	1.6	Race Type of cancer Advanced stage
Blom[14]	I-IV	Retrospective record linkage cohort	1986-2002	Various	66,329	6 months	3.2	Type of cancer Advanced stage Chemotherapy Hormonal therapy
Khorana[2]	NA	Retrospective cohort	1995-2003	Hospitalized	1,015,598	8 days	4.1	Age ≥ 65 years Race Female sex Comorbidity Type of cancer Chemotherapy Year of hospitalization
Khorana[15]	I-IV	Prospective cohort	2002-2005	Ambulatory, receiving chemotherapy	4,066	73 days	2.2	Type of cancer BMI ≥ 35kg/m^2 Platelet count ≥ 350,000/μL Hemoglobin < 10 g/dL and/or erythropoiesis-stimulating agents Leukocyte count > 11,000/μL

Abbreviations: VTE, venous thromboembolism; NA, not available; BMI, body mass index.

actual VTE rate of 10.2%.[16] Despite these complexities, there is broad agreement in the literature regarding most risk factors for cancer-associated VTE. A comprehensive list of clinical risk factors and candidate biomarkers is provided in Table 2.

CANCER-RELATED RISK FACTORS

Type of Cancer

The primary site of cancer is consistently identified as a risk factor for VTE across a variety of studies. Although specific incidence rates may vary based on the clinical setting, patients with cancers of the pancreas, stomach, uterus, kidney, lung, and primary brain tumors are associated with the highest rates of VTE (Table 3). More recent studies have identified a high risk of VTE in association with hematologic malignancies as well (Appendix Table A1, online only). In a population-based case-control study, patients with hematologic malignancies in fact had the highest risk of VTE (odds ratio [OR] = 28.0; 95% CI, 4.0 to 199.7), followed by lung (OR = 22.2; 95% CI, 3.6 to 136.1) and gastrointestinal cancers (OR = 20.3; 95% CI, 4.9 to 83.0).[1] Rates can vary quite markedly between cancer types. In an analysis of the California Cancer Registry, rates of VTE were 20% and 10.7% among patients with advanced pancreas and stomach cancers, respectively, but only 0.9% and 2.8% in patients with advanced prostate and breast cancers, respectively.[4] VTE rates can also vary by histologic subtype. In patients with non–small-cell lung cancer, rates are higher in patients with adenocarcinoma compared with those with squamous cell carcinoma (hazard ratios [HRs] ranging from 1.9 to 3.1).[20,21]

It should be noted that highly prevalent cancers with lower rates of VTE can contribute significantly to the overall burden of VTE. For instance, in a study of hospitalized patients, more than one third of VTE events occurred in patients with non-Hodgkin's lymphoma and leukemia, even though the highest rates were observed in patients with pancreatic and gastric cancers.[16]

Stage of Cancer

Large cohort studies have identified stage as a major risk factor for VTE.[5,4] In oncologic surgery patients, advanced stage is also associated with increased risk of VTE (OR = 2.7; 95% CI, 1.4 to 5.2).[6] It is possible, however, that in large study populations, advanced stage may be a surrogate for poor performance status. Among ambulatory patients with cancer with good performance status receiving chemotherapy, stage was in fact not a predictor of VTE.[8] Studies in outpatients with ovarian cancer also did not identify an association between stage and VTE.[76,77]

Table 2. Clinical Risk Factors and Candidate Biomarkers for Cancer-Associated VTE

Cancer-related factors
Primary site of cancer[1-5]: brain, pancreas, kidney, stomach, lung, gynecologic, lymphoma, myeloma
Advanced stage of cancer[4-6]
Initial period after diagnosis of cancer[1,17-19]
Histology[20,21]
Treatment-related factors
Major surgery[6]
Hospitalization[2,9,13]
Cancer therapy
Chemotherapy[9,14,16,22]
Hormonal therapy[23]
Anti-angiogenic agents[24-32]: thalidomide, lenalidomide, bevacizumab
Erythropoiesis-stimulating agents[8,33]
Transfusions[34]
Central venous catheters[35-38]
Patient-related factors
Older age[2,6,39]
Female sex[2]
Race[2,21,40]
Higher in African Americans
Lower in Asians/Pacific Islanders
Comorbidities[9,15,21,40-42]: infection, renal disease, pulmonary disease, obesity, arterial thromboembolism
Inherited prothrombotic mutations[1,43,44]: Factor V Leiden, prothrombin gene mutation
Prior history of VTE[6,45-48]
Performance status[6,19,49]
Candidate biomarkers
Blood counts[8,15,39,50-52]
Prechemotherapy platelet count $\geq$ 350,000/μL
Prechemotherapy leukocyte count $>$ 11,000/μL
TF[10,11,53,54]
High grade of TF expression by tumor cells
Elevated systemic TF (antigen or activity)
D-dimer[49,55]
Soluble P-selectin[7]
C-reactive protein[9]

Abbreviations: VTE, venous thromboembolism; TF, tissue factor.

Initial Period After Diagnosis

The risk of VTE is highest in the immediate period after diagnosis of cancer. In a population-based study, the adjusted OR for developing VTE in the first 3 months was 53.5 (95% CI, 8.6 to 334.3), declining to 14.3 (95% CI, 5.8 to 35.2) and 3.6 (95% CI, 2.0 to 6.5) in the 3 month to 1 year and 1 to 3 year intervals, respectively.[1] Indeed, it took 15 years after diagnosis before the risk subsided to levels observed in the general population. Many therapeutic interventions occur in this initial period, which likely contribute to risk. However, even in patients receiving a single treatment modality such as chemotherapy, the risk is highest in the initial period of treatment. For instance, among patients with diffuse large B-cell lymphoma, 82% of VTE events occurred during the first three cycles of chemotherapy.[17] Similarly, in patients with transitional-cell carcinoma and lung cancer undergoing chemotherapy, 77% and 45% of vascular events, respectively, occurred during the first two cycles of therapy.[18,19]

TREATMENT-RELATED RISK FACTORS

Systemic Therapy

Chemotherapy is associated with a two- to six-fold increased risk of VTE compared with the general population.[14,22] Rates of VTE seem to be increasing, particularly in association with chemotherapy. Among hospitalized patients receiving chemotherapy, the rates of VTE increased from 3.9% to 5.7% per admission from 1995 to 2003, an increase of 47%.[2] Specific chemotherapeutic agents may be associated with higher rates of VTE. In a prospective study, platinum-based regimens were significantly associated with VTE ($P = .03$).[9] Even within this class of agents, rates may be higher in patients receiving cisplatin as compared with oxaliplatin.[87] Altering the schedule of chemotherapy, such as by using an intermittent regimen, may reduce the risk of VTE.[16]

Thalidomide has been associated with high rates of VTE, ranging from 12% to 28%, when given in combination with dexamethasone or chemotherapy.[24-26] Regimens containing doxorubicin (OR = 4.3), newly diagnosed disease (OR = 2.5) and presence of chromosome 11 abnormality (OR = 1.8) are predictors of thalidomide-associated VTE.[32] Lenalidomide is also associated with high rates of VTE, ranging from 5% to 75%.[27-29] Bevacizumab-containing regimens were associated with increased risk for arterial events (HR = 2.0; 95% CI, 1.1 to 3.8) but not for VTE (HR = 0.9; 95% CI, 0.7 to 1.2) in an initial individual patient data meta-analysis of randomized clinical trials.[31] However, a larger aggregate data meta-analysis found that patients with cancer receiving bevacizumab had a significantly increased risk of VTE (relative risk, 1.3; 95% CI, 1.1 to 1.6) as well.[88] High rates of both venous and arterial events have been observed in clinical trials of other antiangiogenic agents as well,[30] and this toxicity may therefore be a class effect.

Supportive Therapy

Patients with cancer often receive erythropoiesis-stimulating agents (ESAs) for the treatment of anemia. In a systematic review of randomized controlled trials, 229 of the 3,728 patients treated with darbepoetin or epoetin had thromboembolic events as compared with 118 events in 3,041 untreated controls (relative risk = 1.7; 95% CI, 1.4 to 2.1).[33] Although transfusions are being advocated as an alternative to ESAs for the treatment of anemia, a recent retrospective analysis of hospitalized patients with cancer found RBC transfusions were independently associated with an increased risk of VTE (OR = 1.6; 95% CI, 1.5 to 1.7), arterial events (OR = 1.5; 95% CI, 1.5 to 1.6), and in-hospital mortality.[34] Platelet transfusions were also noted to have a similar association. The evidence supporting an association of myeloid growth factors with VTE is inconclusive.[89]

Surgery

Surgery and the extended postoperative period are historically well-known high-risk settings for VTE. It should be noted, however, that in recent reports, surgery has not been found to be a major risk factor for VTE, relative to other factors.[14,40,41] Rates of VTE in association with major oncologic surgical procedures have also remained relatively stable, in contrast to sharp increases observed in patients receiving chemotherapy.[2] These findings are likely related to higher rates of compliance with thromboprophylaxis in the surgical setting[90]

Table 3. Incidence of VTE in Specific Solid Tumors

First Author	Primary Site of Cancer	Stage	Type of Study	Years of Study	Treatment	No. of Patients	Median Follow-Up	Incidence (%)
Novotny[56]	Bladder	I-III	Retrospective cohort	1993-2005	Surgery	516	19 days	4.7
Levi[57]	Brain	I-IV	Retrospective cohort	1979-1989	Surgery	1,703	4 weeks	1.6
Brandes[58]	Brain	IV	Prospective cohort	1997	Surgery chemotherapy radiation	77	74 weeks	26.0
Auguste[59]	Brain	NA	Retrospective cohort	1997-2000	Surgery	180	5 days	3.3
Semrad[60]	Brain	NA	Retrospective cohort	1993-1999	Surgery chemotherapy radiation	9,489	2 years	7.5
Levine[61]	Breast	II	Prospective randomized	1988	Chemotherapy	205	36 weeks	6.8
Saphner[62]	Breast	I-III	Retrospective cohort	1977-1987	Hormonal therapy chemotherapy	2,673	NA	4.0
Clahsen[63]	Breast	I	Prospective randomized	1986-1991	Surgery chemotherapy	2,624	6 weeks	0.4
McDonald[64]	Breast	I-III	Retrospective cohort	1978-1984	Tamoxifen	1,312	NA	1.9
Pritchard[23]	Breast	II/III	Prospective randomized	1984-1990	Tamoxifen chemotherapy	705	61 months	8.1
Chew[65]	Breast	I-IV	Retrospective cohort	1993-1999	NA	108,255	2 years	1.2
Chen[66]	Cervical	I-III	Prospective cohort	2001-2007	Surgery chemotherapy radiation	295	NA	3.1
Alcalay[40]	Colorectal	I-IV	Retrospective cohort	1993-1999	NA	68,142	2 years	3.1
Mandala[16]	Colorectal	IV	Prospective cohort	2008	FOLFIRI	266	51 months	10.2
Franchi[67]	Endometrial	I-IV	Prospective cohort	1991-2000	Surgery	206	30 days	2.4
Satoh[68]	Endometrial	I-IV	Prospective cohort	2004-2007	Surgery	171	NA	14
Tesselaar[69]	Gastroesophageal	I-IV	Retrospective cohort	1980-2000	Chemotherapy	761	1 years	6.8
Tetzlaff[70]	Gastroesophageal	IV	Retrospective cohort	1997-2003	Chemotherapy	191	8 months	13.6
Connolly[48]	HCC	I-IV	Retrospective cohort	1998-2004	Surgery chemotherapy	194	NA	6.7
Blom[20]	Lung	I-IV	Retrospective cohort	1990-2000	Surgery chemotherapy radiation	537	NA	7.3
Numico[19]	Lung	III/IV	Prospective cohort	2000-2003	Cisplatin and gemcitabine	108	9 months	11.1
Tagalakis[71]	Lung	I-IV	Retrospective cohort	1997-2004	NA	493	NA	13.6
Dentali[72]	Lung	NA	Retrospective cohort	2002-2006	Thoracotomy	693	NA	1.8
Chew[21]	Lung	I-IV	Retrospective cohort	1993-1997	NA	91,933	2 years	3.4
Arbeit[73]	Melanoma	I-III	Prospective cohort	1977-1980	Surgery	44	6 months	13.6
Krown[74]	Melanoma	IV	Prospective cohort	2006	Temozolomide and thalidomide	16	23 weeks	21
Tateo[47]	Ovarian	I-IV	Retrospective cohort	1990-2001	Chemotherapy surgery	253	2.6 years	16.6
Westin[75]	Ovarian	I-IV	Retrospective cohort	1994-2004	Chemotherapy	344	NA	5.5
Rodriguez[41]	Ovarian	I-IV	Retrospective cohort	1993-1999	NA	13,031	24 months	5.2
Satoh[76]	Ovarian	I-IV	Prospective	2004-2007	NA	72	NA	25
Fotopoulou[77]	Ovarian	I-IV	Prospective observational	1995-2002	Various chemotherapies	2,743	NA	2.8
Pinzon[78]	Pancreatic	I-III	Retrospective cohort	1979-1980	NA	130	NA	6.9
Blom[79]	Pancreatic	I-IV	Retrospective cohort	1990-2000	Surgery chemotherapy radiation supportive care	202	NA	8.9
Khorana[53]	Pancreatic	I-IV	Retrospective cohort	1994-2002	Surgery chemotherapy	44	NA	14.6
Mandala[80]	Pancreatic	III/IV	Prospective cohort	2001-2004	Surgery chemotherapy	227	35 months	26
Oh[81]	Pancreatic	III-IV	Retrospective cohort	2003-2005	Chemotherapy radiation supportive care	75	124 days	5.3
Augustin[82]	Prostate	I-III	Prospective cohort	1999-2002	Prostatectomy	1,243	NA	1.3
Secin[45]	Prostate	NA	Prospective cohort	1995-2006	Laparoscopic prostatectomy	5,951	90 days	0.5
Vaishampayan[83]	Renal	IV	Prospective cohort	2005	Fenretinide	19	10 months	5.3
Mitchell[84]	Sarcoma	I-IV	Retrospective cohort	1998-2003	NA	252	NA	5.2
Athale[85]	Sarcoma	I-IV	Retrospective cohort	1990-2005	NA	70	NA	14.3
Weijl[86]	Testicular	NA	Retrospective cohort	1979-1997	Chemotherapies	184	NA	8.4

Abbreviations: VTE, venous thromboembolism; NA, not available; FOLFIRI, fluorouracil, irinotecan, leucovorin; HCC, hepatocellular carcinoma.

and should not be interpreted to mean that oncologic surgical interventions are no longer associated with VTE. In a recent study of cancer surgical patients, risk factors for postoperative VTE included age more than 60 years (OR = 2.6; 95% CI, 1.2 to 5.7), previous VTE (OR = 6.0; 95% CI, 2.1 to 16.8), advanced cancer (OR = 2.7; 95% CI, 1.4 to 5.2), anesthesia lasting more than 2 hours (OR = 4.5; 95% CI, 1.1 to 19), and bed rest longer than 3 days (OR = 4.4; 95% CI, 2.5 to 7.8).[6] Of note, 40% of VTE events occurred more than 21 days after surgery.

Hospitalization

Hospitalization substantially increases the risk of VTE in patients with cancer (OR = 2.3; 95% CI, 1.6 to 3.4).[9] The risk of VTE in a recent US study was 4.1% per hospitalization, but the risk varies widely and can be as high as 12% to 18% in specific subgroups.[2,13] In an analysis of more than 1 million hospitalized US patients between 1995 and 2003, the rate of VTE increased by 28%, secondary to a near-doubling of pulmonary embolism rates from 0.8% to 1.5% ($P < .0001$).[2]

Central Venous Catheters

Indwelling vascular access devices such as central venous catheters (CVCs) are widely used in patients with cancer for infusing chemotherapy. The incidence of symptomatic catheter-related deep venous thrombosis (DVT) in adult patients ranges from 0.3% to 28%, whereas the rate of catheter-related DVT assessed by venography is

27% to 66%.[38] Rates seem to be lower in more recent studies. In a recent prospective study of more than 400 patients with cancer with CVCs, 4.3% developed symptomatic CVC-related DVT.[35] Risk factors associated with CVC-related DVT include more than one insertion attempt (OR = 5.5; 95% CI, 1.2 to 24.6), previous CVC insertion (OR = 3.8; 95% CI, 1.4 to 10.4), left-sided placement (OR = 3.5; 95% CI, 1.6 to 7.5), catheter tip position in the superior vena cava as compared with right atrium (OR = 2.7; 95% CI, 1.1 to 6.6), and arm ports as compared with chest ports (OR = 8.1; 95% CI, 3.5 to 19.1).[35,36] The particular antineoplastic agent infused through the port may additionally influence the risk of catheter-associated DVT.[37]

Radiation

Radiation therapy does not seem to be associated with a risk for VTE, although this has only been evaluated in a small number of studies.[14,91]

PATIENT-RELATED RISK FACTORS

Comorbid Conditions

The presence and number of comorbidities influence the risk of VTE. Among hospitalized patients, comorbidities most strongly associated with VTE include infection (OR = 1.8), arterial thromboembolism (OR = 1.5), renal disease (OR = 1.5), pulmonary disease (OR = 1.4), and anemia (OR = 1.4).[2] Anemia (OR = 2.4) and obesity (OR = 2.5) are associated with the risk of VTE in ambulatory patients with cancer as well.[9,15] In patients with ovarian cancer, HRs for the development of VTE increase from 2.1 in patients with one comorbidity to 3.9 in patients with three comorbidities.[41] This increase in risk with increasing number of comorbid conditions has been documented for patients with lung, breast, and colorectal cancer as well.[21,40,65]

Prior Thromboses

A past history of thrombotic events is a risk factor for developing VTE. In a study of patients with cancer undergoing surgery, those with previous VTE had a significantly higher risk of developing new thrombosis (OR = 6.0; 95% CI, 2.1 to 16.8).[6] Prior VTE has also been demonstrated to be a risk factor for VTE in patients with ovarian and prostate cancers and myeloma.[45-47] Local thromboses may predispose to systemic events as well. In a retrospective study of patients with hepatocellular carcinoma, there was a 2.6-fold increase in VTE in patients with concurrent portal vein thrombosis compared with those without.[48] Finally, arterial thrombotic events are associated with venous events (OR = 1.5; 95% CI, 1.4 to 1.5).[2]

Prothrombotic Mutations

A population-based case-control study estimated that patients with cancer and factor V Leiden had an increased risk of VTE compared with patients with cancer without the mutation (OR = 2.2; 95% CI, 0.3 to 17.8).[1] Other studies have shown similar increased risk with presence of factor V Leiden mutation (OR, 0.6 to 1.7).[43,44,92] Similarly, patients with cancer with prothrombin gene mutation also have an increased risk of VTE (OR, 1.2 to 6.7).[43,44] In a recent meta-analysis, the estimated attributable risk of CVC-related thrombosis was 13.1% for factor V Leiden and 4.5% for prothrombin gene mutation.[93] A family history of VTE, which may be a surrogate for inherited thrombophilia, has also been associated with VTE.[9]

Age, Sex, and Race

In hospitalized patients with cancer, older age (≥ 65 years) is associated with a slightly elevated risk of VTE (OR = 1.1; 95% CI, 1.0 to 1.1).[2] Similarly, in the surgical setting, VTE occurred more frequently in patients older than 60 years of age (OR = 2.6; 95% CI, 1.2 to 5.7).[6] However, in the ambulatory setting, age was not a significant risk factor when the study population overwhelmingly comprised patients with a good performance status.[8]

Many studies have shown no significant sex difference in VTE rates.[4,5,8,21,40] However, a study of hospitalized patients reported an overall increased risk of VTE in women (OR = 1.1; 95% CI, 1.1 to 1.2).[2] Some studies have demonstrated an association between race and risk of VTE in cancer. Rates of VTE seem to be higher in African American patients (OR = 1.2; 95% CI, 1.2 to 1.2) and lower in Asians/Pacific Islanders (OR = 0.7; 95% CI, 0.7 to 0.8).[2] Some of these differences may be related to the type of cancer. In an analysis of the California Cancer Registry, African Americans with uterine cancer were more likely to develop VTE, but those with lung cancer and lymphoma were less likely to develop VTE.[4]

Performance Status and Mobility

Immobility, which leads to venous stasis, has long been recognized as a risk factor for VTE. In patients with cancer, performance status is a widely used clinical assessment tool used to assess mobility. In a prospective study, 31% of patients with lung cancer with poor performance status on chemotherapy had VTE, compared with 15% with better performance status.[19] In a large study of cancer outpatients, there was a nonsignificant trend toward higher rates of VTE in patients with poor performance status, but more than 90% of patients had an excellent performance status.[8] Poor performance status has also been associated with higher rates of recurrent VTE in patients with cancer.[49] In surgical patients with cancer, those on bed rest for a period longer than 3 days had significantly higher rates of VTE (OR = 4.4; 95% CI, 2.5 to 7.8).[6]

CANDIDATE BIOMARKERS

Promising initial and exploratory studies have identified laboratory biomarkers—ranging from tests as simple as components of the complete blood count to a variety of novel assays—that may be predictive of VTE in cancer (Table 2).

Platelet and Leukocyte Counts

In an initial analysis of data from a prospective observational study of patients initiating chemotherapy, elevated prechemotherapy platelet counts were strongly associated with VTE.[8] VTE occurred in nearly 4% over 2.5 months for patients with a prechemotherapy platelet count ≥ 350,000/μL, significantly higher than the rate of 1.25% for patients with prechemotherapy platelet count of less than 200,000/μL (P for trend = .0003). Additionally, patients who developed VTE had significantly elevated mean platelet counts before each cycle of chemotherapy when compared with patients who did not develop VTE (P = .001). In an expanded analysis of this registry, a prechemotherapy leukocyte count more than 11,000/μL was also found to be significantly and independently associated with an increased risk of

subsequent VTE.[15] In multivariate analysis, both elevated baseline platelet (OR = 1.8; 95% CI, 1.1 to 3.2) and leukocyte (OR = 2.2; 95% CI, 1.2 to 4.0) counts were independently associated with VTE. Additional reports seem to confirm these findings.[39,50-52,87]

Tissue Factor

Tissue factor (TF) is the physiologic initiator of coagulation. TF is commonly expressed in a variety of malignancies, and researchers are increasingly focused on its role in the pathophysiology of cancer-associated thrombosis.[11,94] TF can be evaluated in a variety of ways, including by studying the degree of TF expression in tumor cells by immunohistochemistry,[53,95] measuring systemic TF antigen levels,[10,96] or TF activity.[10,11] In a small, retrospective study, patients with pancreatic cancer with high TF expression in resected tumor specimens had a subsequent VTE rate of 26.3% compared with 4.5% in patients with low TF expression ($P = .04$).[53] Similar data have been reported in ovarian cancer as well.[70] In another small pilot study of patients with pancreatic cancer, elevated levels of systemic TF, measured either in terms of antigen or activity levels, were predictive of VTE.[10] Of note, in patients with ovarian cancer, preoperative TF levels were associated with worsened mortality.[96] Several ongoing studies are studying the utility of TF as a biomarker for cancer-associated VTE. It remains to be seen whether this approach can be generalized to all patients with cancer or will only be useful in specific cancer types. Investigators are also yet to agree on the most optimal assay for measuring TF.

D-Dimer

Markers of hemostatic activation, particularly D-dimer, have been observed to be elevated in patients with cancer.[55] In a prospective analysis, patients with colorectal cancer had significantly higher levels of TAT and F1 + 2 than controls with benign colorectal disease.[97] Elevated postoperative levels of these hemostatic markers also predicted for development of postoperative DVT. Elevated D-dimer levels have also been shown to be predictive of recurrent VTE in patients with cancer.[49] Conversely, a negative D-dimer test in the setting of low likelihood of VTE can be used to effectively rule out a diagnosis of DVT, although this combination rarely occurs in patients with cancer.[98,99]

C-Reactive Protein

C-reactive protein is a downstream marker of the inflammatory process and is considered a predictor of cardiovascular events and mortality. In a prospective single-institution observational study of 507 patients with cancer, an elevated C-reactive protein (> 400 mg/dL) was associated in multivariate analysis with the development of VTE.[9]

Soluble P-Selectin

Interactions between P-selectin and circulating carcinoma mucins have been proposed as a possible explanation for Trousseau's syndrome.[100] In a prospective observational study of 687 patients with cancer with newly diagnosed or recurrent cancer, elevated plasma soluble P-selectin levels (> 53.1 ng/mL, representing the 75th percentile) were found to be predictive of VTE (HR = 2.6; 95% CI, 1.4 to 4.9; $P = .003$).[7]

A RISK MODEL FOR CHEMOTHERAPY-ASSOCIATED VTE

The majority of patients with cancer are currently treated primarily in the outpatient setting. Multiple clinical trials of thromboprophylaxis have been conducted in ambulatory patients with cancer selected by individual risk factors, such as metastatic breast and lung cancer or presence of intravenous catheters.[101-105] However, results have been conflicting, with a majority of studies not showing a benefit for prophylaxis owing to low event rates (typically < 5%). To reduce the public health burden of VTE, it is important to identify patients with cancer at highest risk for VTE for whom prophylaxis may be beneficial. Conversely, a majority of patients with cancer do not develop VTE, and it is equally important to exclude such low-risk patients from studies of prophylaxis. A short-term symptomatic VTE rate of approximately 5% to 7% would be similar to or greater than that reported in hospitalized or postoperative patients for whom VTE prophylaxis has been shown to be highly effective.[106-108]

A validated risk model for identifying patients at high risk for VTE has recently been published (Table 4).[15] Risk factors for VTE were studied in a randomly selected development cohort of 2,701 ambulatory patients with cancer initiating chemotherapy. The risk model was then validated in an independent cohort of 1,365 patients from the same study. Five predictive variables present before initiation of chemotherapy were identified in a stage-adjusted multivariate model in the development cohort: primary site (type) of cancer, platelet count ≥ 350,000/μL, hemoglobin less than 10 g/dL and/or use of ESAs, leukocyte count more than 11,000/μL, and body mass index ≥ 35 kg/m^2. Rates of 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 to 2), and 7.1% and 6.7% in the high-risk category (score ≥ 3) over a median period of 2.5 months (C statistic = 0.7 for both cohorts). At the cutoff point for high risk (score ≥ 3), the model had a negative predictive value of 98.5%. Thus the model is successful in identifying a low-risk population for whom prophylaxis is unlikely to be beneficial, as well as a high-risk population for whom prophylaxis studies are necessary. One limitation of this study is that patient accrual was completed before widespread use of bevacizumab. Further, the value of the C statistic suggests that incorporating additional variables such as biomarkers may increase the robustness of this model. However, the high rate of symptomatic VTE observed in the high-risk subgroup of patients is similar to that seen in hospitalized or surgical patients for whom prophylaxis is both safe and effective.[106-108] A recent analysis reveals that this risk model is also highly predictive of mortality in

Table 4. Predictive Model for Chemotherapy-Associated VTE[15]

Patient Characteristic	Risk Score
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
Prechemotherapy platelet count ≥ 350,000/μL	1
Hemoglobin < 10g/dL or use of RBC growth factors	1
Prechemotherapy leukocyte count > 11,000/μL	1
Body mass index ≥ 35 kg/m^2	1

NOTE: High risk defined as risk score ≥ 3.
Abbreviation: VTE, venous thromboembolism.

patients with cancer.[109] The National Heart, Lung, and Blood Institute has recently funded a study of thromboprophylaxis in patients deemed high-risk based on this model (www.clinicaltrials.gov No. NCT00876915).

In conclusion, important strides have been made in the past decade regarding our understanding of risk factors for cancer-associated thrombosis. Yet, many gaps remain in our knowledge and understanding of this devastating illness. Ongoing and future studies that further explore the role of model- and biomarker-based approaches will hopefully allow for targeting prophylaxis based on individual risk in the patient with cancer. In turn, this could lead to a reduction of the public health burden of VTE and its attendant consequences for patients with cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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