Published in final edited form as:

Curr Opin Hematol. 2010 September ; 17(5): 450–456. doi:10.1097/MOH.0b013e32833c0760.

The Role of Thromboprophylaxis in Cancer Patients: Emerging Data

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Abstract

Purpose of Review—Venous thromboembolism (VTE) is a frequent cause of morbidity and mortality in cancer patients. A significant proportion of cancer-associated VTE occurs in the ambulatory setting and is associated with poorer outcomes and reduced survival. Risk for VTE is influenced by patient-, cancer- and treatment-specific factors.

Recent Findings—Recent studies have identified biomarkers associated with increased VTE risk in malignancy including leukocyte and platelet counts, tissue factor, prothrombin split products, D-dimer, P-selectin, Factor VIII and C-reactive protein. Recent and ongoing clinical trials have focused on VTE prophylaxis with low-molecular-weight heparins in high-risk cancer outpatients, particularly those with pancreatic cancer. These studies have yielded encouraging preliminary results but whether thromboprophylaxis provides significant benefit to unselected cancer outpatients remains unclear.

Summary—A risk stratification model incorporating known risk factors and biomarkers can identify those patients at highest risk. This review focuses on emerging data regarding risk assessment and benefit of thromboprophylaxis in patients with cancer.

Keywords

Cancer; Thrombosis; Risk Factors

Introduction

The relationship between malignancy and thromboembolic events has been recognized for more than 140 years. Venous thromboembolism (VTE), which includes deep venous thrombosis (DVT) and pulmonary embolism (PE), is a frequent cause of morbidity and mortality among medical and surgical cancer patients and remains a clinical challenge for providers. Patients harboring a malignancy are at a 4-to 7-fold greater risk of thrombosis when compared to noncancer patient controls [1-2]. Thromboembolism in cancer patients is associated with reduced survival, both in patients actively receiving chemotherapy and in the postoperative setting. Compared to cancer patients without VTE, those with VTE are three times more likely to die within 6 months [3].

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Studies have illustrated that the incidence of VTE in hospitalized cancer cohorts is rising [4-5]. Although thromboprophylaxis recommendations have focused largely on surgical and hospitalized cancer cohorts, studies have shown that a significant percentage of such events occur in the outpatient setting [6]. Recent trials of thromboprophylaxis have therefore focused on cancer outpatients with promising initial results. This narrative review highlights recent literature, particularly studies of predictive biomarkers, risk stratification models and randomized controlled trials (RCTs) which have investigated thromboprophylaxis in the outpatient setting.

Risk Factors, Biomarkers & Predictive Models

A patient's VTE risk depends on patient-, cancer- and treatment-specific factors (Table 1). The interaction of such variables is complex, making assessment of individual risk difficult. The risk of VTE is further influenced by particular anti-neoplastic agents and regimens. Indeed, the risk can vary widely between agents of the same class; in an analysis of patients with metastatic gastric and gastro-esophageal junction cancers, thromboembolism rates were 15.1% in patients receiving cisplatin compared to 7.6% in patients receiving oxaliplatin [7*]. Of particular note is the risk associated with the anti-angiogenic agents bevacizumab, thalidomide and lenalidomide [8-10]. A meta-analysis of 15 RCTs demonstrated that the use of bevacizumab was associated with increased VTE risk (RR = 1.33; 95% CI, 1.13-1.56; $p = 0.001$) [10]. Similar increase in risk has also been reported with supportive care drugs, such as erythropoiesis-stimulating agents. In a meta-analysis, erythropoietin and darbopoetin were associated with a significantly increased risk of VTE (RR = 1.57; 95% CI, 1.31 to 1.87) and mortality (HR = 1.10; 95% CI, 1.01 to 1.20) [11].

Biomarkers

Blood Counts—Prechemotherapy thrombocytosis as defined by a platelet count $>350 \times 10^9/L$ is associated with increased risk of thrombosis [12-13]. In a prospective study of cancer patients receiving chemotherapy, rates of VTE were 4% in patients with elevated platelet counts as compared to 1.3% (adjusted OR 2.8; 95% CI, 1.6 to 5) [12]. The Vienna Cancer and Thrombosis Study (CATS) also found high platelet count to be an independent risk factor for VTE (HR = 3.50; 95% CI, 1.52 to 8.06, $p = 0.0032$) in 665 cancer patients undergoing chemotherapy. Patients with platelet counts in the 95th percentile or above (platelet count of $443 \times 10^9/L$) had a 34.3% cumulative probability of developing VTE in contrast to only 5.9% in the group with counts below the designated threshold [14*].

Prechemotherapy leukocytosis or a white blood cell count exceeding that of $11 \times 10^9/L$ is also associated with increased VTE risk in cancer patients [13]. In a prospective study of 4405 ambulatory outpatients initiating chemotherapy 4.5% of patients with baseline leukocytosis developed VTE compared to only 1.8% without leukocytosis ($p < 0.0001$). Additionally, patients whose leukocytosis persisted beyond the first cycle of chemotherapy had significantly higher VTE rates as compared to patients with normal leukocyte counts or those whose baseline leukocytosis resolved [15*]. This was also confirmed in the previously discussed analysis of gastric cancers (leukocyte count ≥ 11 vs. < 11 , HR = 2.0; 95% CI, 1.26 to 3.17; $p = .003$) [7*].

D-dimer—Several recent studies have examined the role of D-dimer levels prior to chemotherapy or major surgery in predicting risk for VTE. In a prospective, single center study of 124 cancer outpatients, those who developed VTE had higher mean values of D-dimer (2195 ± 1382 vs. 695 ± 1039 ng/ml, $p < 0.001$) [16*]. When D-dimer values were grouped into tertiles, only 2.4% in the first and second tertiles suffered an event compared with 22% in the third tertile (>650 ng/dl, $p = 0.003$) [18]. In a study in colorectal cancer, compression ultrasonography was performed prior to and one week, one month, and one

year after surgery [17*]. In the positive D-dimer group (defined as > 0.3 mg/L), one-year incidence of DVT up to one year after surgery was 20% (95% CI, 12 to 31%) versus 5% (95% CI, 2 to 12%) in the negative D-dimer group (adjusted HR 6.53; 95% CI, 1.58 to 27.0). Similarly, in gynecologic cancers, high D-dimer level (defined as > 5 μ g/mL) on postoperative day 3 was an independent risk factor for postoperative VTE [18*].

Elevated levels of D-dimer in addition to prothrombin split products (as defined by a cutoff set at the 75th percentile of the total study population) were associated with increased risk of VTE (HR = 1.8; 95% CI, 1.0 to 3.2; $p = .048$ and HR = 2.0; 95% CI, 1.2 to 3.6; $p = .015$ respectively). The 6-month cumulative probability of VTE was greatest in patients with both elevated D-dimer and split products (15.2%) versus those with nonelevated levels (5.0%, $p < 0.01$) [19*].

Tissue Factor—Tissue factor (TF), the physiologic initiator of coagulation, is widely expressed by various malignancies and found in the systemic circulation [20]. In a cohort study, cancer patients with VTE (N=53) had significantly higher mean TF microparticle (MP) activity as compared to cancer patients without VTE (N=13) (1.7 ± 3.8 pg/mL vs. 0.6 ± 0.4 pg/mL, $p < 0.05$) [21*]. In a recent case-control study, TF-MPs were detected in patients with advanced malignancy, including two-thirds of patients with pancreatic carcinoma. Elevated levels were associated with VTE in cancer patients (adjusted OR, 3.72; 95% CI, 1.18 to 11.76; $p = 0.01$) [22*]. In a retrospective study of 117 patients with pancreaticobiliary cancers, patients with VTE had significantly elevated mean TF versus those without (3.18 pg/mL vs. 1.40 pg/mL) (adjusted OR for VTE = 1.22, 95% CI 1.02 to 1.47, $p = 0.03$) [23*]. TF thus appears to be a biomarker of potential, although it is unclear whether these results are generalizable to all malignancies or specific to high-TF expressing cancers such as pancreatic cancer.

Others—Elevated levels of C-reactive protein (CRP) (levels above the 75th percentile, ≥ 1.80 mg/dL) were shown to be an independent risk factor for VTE (HR = 1.94; 95% CI, 1.01 to 3.75) [24*]. The cumulative probability of VTE after 6 months in patients with soluble P-selectin levels greater than 75th percentile (> 53.1 ng/mL) was 11.9% (vs. 3.7%, $p = 0.002$; HR = 2.6; 95% CI, 1.4 to 4.9; $p = 0.003$) [25]. Elevated Factor VIII levels have also been reported to increase VTE risk although the association appeared to diminish with increasing age of subjects [26*].

Predictive Models—The first risk assessment model for outpatients receiving chemotherapy using data from a multicenter, prospective study has recently been developed and validated (Table 2) [13]. Five predictive variables help classify risk into three categories: low [score 0], intermediate [score 1 or 2] and high [score ≥ 3]. Observed rates of VTE in the development and validation cohorts were 0.8% and 0.3% in the low-risk category, 1.8% and 2% in the intermediate-risk category and 7.1 and 6.7% in the high-risk category respectively. This model has now been externally validated in 834 cancer patients, with rates of 17.7% in high-risk cohort as compared to 1.5% in low-risk patients, over a 6-month follow-up period [27*]. Furthermore, the analysis suggested that the addition of other biomarkers such as D-dimer and P-selectin could improve risk stratification.

Patients with myeloma are particularly at risk for VTE. A risk assessment algorithm has been proposed by the International Myeloma Working Group (Table 3) [28]. The group recommended that patients with zero to one VTE risk factor receive daily aspirin for prophylaxis whereas those with two or more risk factors receive LMWH or warfarin. All patients receiving thalidomide or lenalidomide in addition to high-dose dexamethasone or doxorubicin should receive LMWH. It should be noted that this algorithm is based on expert

consensus and data extrapolation from small, uncontrolled trials and has not been prospectively validated.

Trials of Thromboprophylaxis in the Outpatient Setting

Thromboprophylaxis remains the standard of care for hospitalized and surgical cancer patients but a significant proportion of events occur in the outpatient setting [6, 29-30]. Four recent large studies have therefore focused on VTE prophylaxis in subgroups of the ambulatory cancer population.

PROTECHT

The Prophylaxis of Thromboembolism during Chemotherapy Trial (PROTECHT) was a multicenter, randomized, placebo-controlled, double-blind study in which prophylaxis was studied in cancer patients thought to be relatively high-risk, including those with locally advanced or metastatic lung, gastrointestinal, pancreatic, breast, ovarian, and head/neck cancers actively receiving chemotherapy [31**] (Figure 1). Patients were randomized to nadroparin or placebo in a 2:1 ratio for the duration of chemotherapy or a maximum of 4 months. The primary outcome was a combined endpoint of symptomatic venous and arterial thromboembolic events. The study did not screen for asymptomatic events. Overall, 2% of the treatment group and 3.9% (15 of 381 patients) of the placebo group developed a thromboembolic event (one-sided 95% CI 0.303%, $p = 0.02$). There was no observed survival benefit. More patients in the treatment arm experienced major bleeding events (0.17% vs. 0% respectively, $p = 0.18$) [31**].

This is the largest study of thromboprophylaxis conducted in the cancer outpatient population to date, and represents a significant step forward for the field. Although the study met its primary endpoint, the overall low event rate has not led to recommendations for prophylaxis or to widespread clinical adoption of these results pending confirmatory studies.

Myeloma

A recent prospective study addressed the efficacy of thromboprophylaxis in 930 newly diagnosed myeloma patients [32*]. Patients were randomized to four treatment arms and in a subsequent sub-study, patients receiving thalidomide-based regimens were randomly assigned to aspirin, LMWH or warfarin. Patients not receiving thalidomide served as controls. Overall incidence of VTE in the aspirin, LMWH, warfarin and control arms was 6%, 5%, 8% and 2% respectively. There was no significant difference between the thromboprophylaxis groups in terms of VTE incidence and bleeding events. Final analyses are pending.

PROSPECT-CONKO-004

Patients with pancreatic cancer are at particularly high risk for VTE [33]. The CONKO-004 study was a prospective, open, randomized multicenter phase III trial (PROSPECT-CONKO-004) evaluated thromboprophylaxis in patients with pancreatic cancer receiving gemcitabine-based chemotherapy. The study was designed after an initial pilot study determined that the addition of enoxaparin to gemcitabine/5-fluorouracil/folinic acid/cisplatin (GFFC) chemotherapy was safe and efficacious in advanced pancreatic cancer [34]

Individuals with confirmed advanced pancreatic cancer and no prior chemotherapy or recent VTE events were eligible for enrollment. The study population was stratified according to Karnofsky performance status (KPS) and renal function; patients with normal renal function and good performance status (KPS > 80%) received GFFC chemotherapy whereas patients with increased plasma creatinine and reduced performance received gemcitabine

monotherapy. Patients were randomized to observation or prophylactic enoxaparin (1 mg/kg daily for 3 months, then 40 mg daily). The primary endpoint was reduction of symptomatic VTE. Time to progression and overall survival were secondary outcomes. VTE occurred in 5.0% (8 of 160) of patients in the enoxaparin arm as compared with 14.5% (22 of 152) in the non-LMWH arm ($p < 0.01$). The frequency of major bleeding events was similar in both groups (6.3 vs. 9.9%, $p = 0.18$). There were no differences in median overall survival or time to progression [35**].

The results of this study show that thromboprophylaxis can safely and clinically significantly reduce rates of VTE in this population. One limitation of the study was the use of the GFFC combination, which is not currently considered standard of care. This limitation, however, is addressed by results of the FRAGEM study discussed below.

FRAGEM

In the FRAGEM trial, patients with inoperable pancreatic cancer were randomized to gemcitabine alone or with daily dalteparin for twelve weeks [36]. Primary outcome was reduction in VTE; secondary outcomes were fatal VTE events, sudden death and early death burden (EDB). Interim analysis of data was presented in 2009 with a total of 59 and 64 enrolled patients in the treatment and standard arms, respectively. In the control arm, 25% of patients experienced a VTE event versus 3.5% of the treatment group during the first 100 days status post randomization (RR = 0.14; 95% CI, 0.03 to 0.58; $p = 0.002$). Overall incidence of VTE in patients receiving chemotherapy alone was 31% versus 12% in the treatment arm (RR = 0.38; 95% CI, 0.17 to 0.84; $p = 0.019$). Further, 9% of patients in the chemotherapy alone arm experienced fatal VTE or sudden death as compared to 0% in the thromboprophylaxis arm (RR = 0.08; 95% CI, 0.005 to 1.45; $p = .028$) [37**]. Full data from both the CONKO and FRAGEM studies are awaited. However, these results are consistent with the high known rate of VTE in patients with pancreatic cancer and provide support for considering thromboprophylaxis in this clinical setting.

Meta-Analysis

A meta-analysis of 7 RCTs studies investigating LMWH thromboprophylaxis in cancer outpatients was recently presented. Primary outcomes were all reported VTE and major bleeding events. While ambulatory cancer patients experienced a 46% relative risk reduction in VTE with LMWH, the absolute risk reduction in VTE was small at 2.55% (95% CI 1.06 to 4.05%; $p < 0.001$). Furthermore, thromboprophylaxis was associated with an average absolute risk increase of 0.75% (95% CI 0.17 to 1.33%; $p = 0.011$) in major bleeding [38*].

Conclusion: Future Directions

The results of recent studies emphasize the need for better risk stratification in the outpatient setting, to identify those patients at highest risk thus optimizing risk-benefit ratios. Three large ongoing RCTs will add to the available data (Table 4). SAVE-ONCO is the largest, investigating the efficacy of semuloparin (AVE5026) in preventing VTE (Clinicaltrials.gov number NCT00694382). Eligible patients include those with locally advanced or metastatic solid tumors of the lung, gastrointestinal tract, bladder or ovary receiving chemotherapy. Our group is conducting a prospective study based on the risk model in which cancer outpatients at high risk for VTE (risk score for VTE ≥ 3) will be treated with dalteparin for a total of 12 weeks (Clinicaltrials.gov NCT00876915). In addition, the predictive value of TF is being investigated as a secondary outcome. Finally, a TF-based study, referred to as MicroTEC is investigating enoxaparin in patients with pancreatic, lung and colorectal cancer patients with elevated levels of plasma TF-MPs (Clinicaltrials.gov NCT00908960). The

results of these studies will add to the growing body of literature in this area and, hopefully, allow clinicians to individualize decisions regarding thromboprophylaxis for cancer patients.

Acknowledgments

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

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Figure 1. Recent Trials of Thromboprophylaxis in the Outpatient Setting

Rates of VTE in the various arms of four recent RCTs of prophylaxis are displayed. These included PROTECT (various locally advanced or metastatic solid tumors), GIMEMA (myeloma only) and CONKO-004 and FRAGEM (both pancreatic cancers only). The control arm in PROTECT was placebo and in CONKO and FRAGEM was observation. There was no non-prophylaxis control arm in the GIMEMA study; a non-thalidomide based regimen was used as control with a VTE rate of 2%.

Table 1

Patient-, Cancer-, and Treatment-Specific Risk factors for Cancer-associated Thrombosis

<u>Patient-Specific Risk Factors</u>
Advanced age
Ethnicity (higher in African Americans; lower in Asian-Pacific Islanders in some cancers)
Comorbid conditions (neutropenia, infection, anemia, pulmonary disease, renal disease)
Immobilization
Obesity
Heritable prothrombotic mutations (Factor V Leiden, prothrombin 20210A)
Prior history of thromboembolism
<u>Cancer-Specific Risk Factors</u>
Primary tumor site (pancreatic, ovarian, kidney, lung, gastric, and brain)
Hematologic malignancies (myeloma, non-Hodgkin's lymphoma, Hodgkin's disease)
Histologic subtype
Locally advanced tumors/presence of distant metastases
Time from diagnosis (highest risk within three months of initial diagnosis)
<u>Treatment-Specific Risk Factors</u>
Recent major surgery
Current hospitalization
Central venous catheters
Chemotherapy, particularly combination therapy
Anti-angiogenic therapy (thalidomide, lenalidomide, bevacizumab)
Hormonal therapy (tamoxifen)
Erythropoiesis-stimulating agents
Transfusions

Table 2

Predictive Model for Chemotherapy-associated VTE

Patient Characteristics	Risk Score
Site of cancer	2
Very high risk (stomach, pancreas)	1
High risk (lung, lymphoma, gynecologic, bladder, testicular)	
Prechemotherapy platelet count 350000/mm ³ or more	1
Prechemotherapy leukocyte count more than 11000/mm ³	1
Hemoglobin level less than 10g/dl or use of red cell growth factors	1
Body mass index 35kg/m ² or more	1

Reproduced with permission from Khorana AA, Kuderer NM, Culakova E, et al. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood*. 2008 May 15;111(10): 4902-7.

Table 3**International Myeloma Working Group Thromboprophylaxis Recommendations**

<p><u>Individual risk factors</u>: obesity (BMI $\geq$ 30), prior VTE, central venous catheter</p> <p><u>Comorbid risk factors</u>: cardiac disease, chronic renal disease, diabetes, acute infection, immobilization</p> <p><u>Surgery risk factors</u>: trauma, general surgery or any anesthesia</p> <p><u>Medications</u>: erythropoietin</p> <p><u>Myeloma-related risk factors</u>: diagnosis, hyperviscosity</p> <p><u>Myeloma therapy risk factors</u>: multiagent chemotherapy, doxorubicin, high-dose steroids</p> <ul style="list-style-type: none"> • Patients with $\leq$ 1 VTE risk factor: Aspirin (81-325 mg daily) • Patients with $\geq$ 2 VTE risk factors: LMWH (enoxaparin 40 mg/d) or full-dose warfarin, although less existing supporting data for the latter • Patients receiving thalidomide/lenalidomide concurrently with high-dose dexamethasone or doxorubicin should receive LMWH thromboprophylaxis • Anticoagulant treatment can continue for 4 to 6 months or longer if additional risk factors are present
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Adapted with permission from Palumbo A, Rajkumar SV, Dimopoulos MA, et al. Prevention of thalidomide- and lenalidomide associated thrombosis in myeloma. *Leukemia*. 2008 Feb;22(2): 414-23.

Table 4

Ongoing Studies of Thromboprophylaxis in Cancer

Study	Intervention	Inclusion Criteria	Number of Patients (N)	Trial Endpoints
Evaluation of AVE5026 in the Prevention of Venous Thromboembolism in Cancer Patients Undergoing Chemotherapy (SAVE-ONCO)	Semuloparin (AVE5026) up to 4 months	<ul style="list-style-type: none"> Lung, GI, ovary, or Bladder cancer Locally advanced or metastatic 	3200	DVT, PE, VTE-related death
A Prospective Randomized Multicenter Study of Dalteparin Prophylaxis in High-Risk Ambulatory Cancer Patients (PHACS)	Dalteparin for 12 weeks	<ul style="list-style-type: none"> Risk score ≥ 3 	404	Asymptomatic and symptomatic VTE
Enoxaparin Thromboprophylaxis in Cancer Patients With Elevated Tissue Factor Bearing Microparticles (MicroTEC)	Enoxaparin for 6 months	<ul style="list-style-type: none"> Lung, colon, pancreatic cancer Metastatic or unresectable Elevated TF MPs 	227	VTE