Association Between Cancer Types, Cancer Treatments, and Venous Thromboembolism in Medical Oncology Patients

Michael B. Streiff, MD, FACP

Dr. Streiff is an Associate Professor of Medicine and Medical Director of Anticoagulation Management Service and Outpatient Clinics at Johns Hopkins Medical Institutions in Baltimore, Maryland.

Address correspondence to:
Michael B. Streiff, MD, FACP
Associate Professor of Medicine
Medical Director, Anticoagulation Management Service and Outpatient Clinics
Johns Hopkins Medical Institutions
1830 East Monument Street, Suite 7300
Baltimore, MD 21205
Phone: 410-614-0727
Fax: 410-614-8601
E-mail: mstreif@jhmi.edu

Keywords
Neoplasms, thrombosis, venous thromboembolism, chemotherapy, anticoagulants

Abstract: Nearly 20% of all venous thromboembolism (VTE) occurs in cancer patients, and as many as 78% of cancer patients who develop a thrombotic event do so as outpatients. The risk of VTE in cancer patients is influenced by the type of cancer, its stage and histology, the presence of thrombophilia, and the many therapeutic interventions they receive (eg, surgery, chemotherapy, radiotherapy, supportive care). The greatest VTE risk appears to occur early after cancer diagnosis and in patients with late- or metastatic-stage malignancy. VTE most often occurs in cancers of the pancreas, ovary, kidney, lung, stomach, and brain, as well as in hematologic malignancies such as lymphoma and myeloma. The clinical consequences of thrombosis in cancer patients are typically more severe and more costly than events in patients without cancer. Patient-, cancer-, and treatment-related factors should be considered when assessing individual patients for their risk of VTE. Primary pharmacologic VTE prophylaxis should be given to all hospitalized medical and surgical oncology patients at risk, and this therapy should be considered for high-risk ambulatory outpatients (eg, myeloma patients receiving highly thrombogenic chemotherapeutic regimens, very-high-risk solid tumor patients with Khorana scores ≥3) who have no contraindications to anticoagulants.

Introduction

The association between venous thromboembolism (VTE) and cancer is well established. Data from large patient registries in the United States and Europe suggest that approximately 20% of all VTE occurs in patients with cancer[1,2] and that a substantial proportion (up to 78%) of these events occur in the outpatient setting.[3,4] Studies of hospitalized cancer patients have noted an incidence of VTE of 0.6% to 7.8%, with higher rates reported among patients receiving chemotherapy and those with tumors of the pancreas, ovary, kidney, lung, stomach, and brain.[5,6]

The incidence of VTE is probably underestimated since, historically, most retrospective reports have focused only on objectively confirmed symptomatic cases.[6] Improvements in computed tomography (CT) scanning have allowed a closer look at the incidence and clinical relevance of unsuspected VTE.[7] A meta-analysis of 12 studies involving

more than 10,000 patients undergoing chest CT assessed the frequency of unsuspected pulmonary embolism (PE) and found a mean incidence of 2.6%.[7] Another retrospective study in 195 cancer patients who experienced PE found that the clinical sequelae of unsuspected PE were similar to those observed in cancer patients with symptomatic events.[8] In this study, the cumulative incidence of VTE recurrence over 1 year was 13.3% in patients with unsuspected PE compared with 16.9% in those with symptomatic PE (*P*=.77). The 1-year mortality rates were also similar, at 52.9% for unsuspected PE and 53.3% for symptomatic PE (*P*=.70).[8]

The risk of VTE in cancer patients and the consequences of a DVT or PE in this population underscore the need for healthcare professionals to carefully assess patient-, cancer-, and treatment-related factors when treating patients in the medical oncology setting. This review article summarizes patient-, cancer-, and treatment-related factors that contribute to VTE in medical patients with cancer and highlights safety and efficacy data from studies of pharmacologic anticoagulants for primary prevention of VTE in medical patients with cancer. A simple risk model developed by Khorana and colleagues[9] for assessing chemotherapy-associated VTE risk levels in outpatients with cancer is also described.

Burden of VTE in Oncology Patients

VTE and its clinical consequences (e.g., recurrent VTE, post-thrombotic syndrome, pulmonary hypertension, treatment-related bleeding complications, risk of VTE-related or anticoagulation-related mortality) are typically more severe and more common among patients with cancer than patients without cancer.[5,6,10] Thrombosis was identified as a leading cause of death among cancer patients as early as 1970.[11] In an analysis of data from 4,466 outpatients receiving chemotherapy reported by Khorana and colleagues in 2007,[12] thrombosis and infection were identified as the second-leading causes of death in this patient population (both 9.2%). A more recent retrospective analysis[13] assessed data from 17,284 commercially insured ambulatory cancer patients on chemotherapy and a matched cohort without cancer. In the cancer cohort, 12.6% of patients developed VTE compared with only 1.4% in the control cohort (*P*<.0001). Compared with the US general population, patients with cancer have an annualized death rate that is 2.7-fold higher (*P*=.08) after arterial thrombosis and 47-fold higher (*P*=.03) after VTE.[12] The poor prognosis associated with VTE was more specifically quantified in a study of Danish cancer patients with VTE (n=668) and a matched cohort of cancer patients without VTE (n=6,668).[14] Only 12% of cancer patients survived beyond 1 year after a VTE event compared with 36% of those who did not experience VTE (*P*<.001). Over a 17-year follow-up, the relative risk (RR) of death for patients with VTE was 2.20 (95% confidence interval [CI] 2.05–2.40) compared with patients without cancer.[14] Another large study, by Chew and colleagues,[15] analyzed data from 235,149 patients diagnosed from 1993–1995 with cancer of the prostate, breast, lung, colon/rectum, uterus, bladder, pancreas, stomach, ovary, or kidney or with melanoma or non-Hodgkin lymphoma. VTE was identified in 3,775 (1.6%) of these patients, and the presence of VTE was independently associated with an increased risk of death within 1 year of cancer diagnosis for all stages and cancer types, with a median overall RR of 3.7 (hazard ratio [HR] range, 1.3–14.4).[15] Cancer patients with VTE may also have their chemotherapy delayed and/or may require long-term treatment with anticoagulants,[16] and they are more likely to suffer from bleeding complications during anticoagulation therapy with unfractionated heparin, low-molecular-weight heparin, or warfarin.[17]

The risk of recurrent thrombosis is also much greater in patients with cancer than in those without cancer. A study of more than 130,000 patients with and without cancer who experienced an initial VTE found that patients with cancer had a greater than 3-fold risk of rehospitalization for recurrent VTE within 3 months than patients without cancer.[18] These results were confirmed in a later study by Prandoni and colleagues, who compared the risk of recurrent VTE in 181 patients with cancer and 661 patients without cancer after their first episode of symptomatic deep vein thrombosis (DVT).[17] The 1-year cumulative incidence of recurrence was 20.7% in the cancer group and 6.8% in the group without cancer (HR 3.2; 95% CI, 1.9–5.4). Finally, data from the Registro Informatizado de la Enfermedad Trombo Embólica (RIETE) registry[19] from 14,391 patients with and without cancer who had an initial VTE event showed that cancer patients had significantly higher odds of fatal PE (odds ratio [OR] 2.0), recurrent VTE (OR, 2.7), fatal bleeding (OR, 2.9), major bleeding (OR, 2.6), and overall death (OR, 6.2) than patients without cancer (*P*<.001 for all comparisons).

The financial costs of managing VTE-related complications also appear to be much higher for patients with cancer. In a retrospective analysis of 529 cancer patients who developed DVT, the mean duration of DVT-related hospitalizations was 11 days at a cost of $20,065 per episode in year 2002 US dollars.[20] By comparison, the Agency for Healthcare Research and Quality reported the mean overall cost of a thromboembolic episode to be $11,141 for the general medical population in the United States (year 2000 dollars).[20] A retrospective analysis of data from 30,552 patients with lung, pancreatic, stomach, colon/rectum, bladder, or ovarian cancer receiving chemotherapy reported by Lyman and colleagues in 2011 showed that medical costs during the first year after initiating chemotherapy were much higher for patients

with VTE ($110,362) than for those without VTE ($77,984).[21] Another recent retrospective analysis of data from 6,732 ambulatory patients with lung cancer who were receiving chemotherapy showed that total medical costs were approximately 40% higher among those who experienced VTE compared with those without VTE.[22]

Association Between Cancer and VTE Risk

Cancer is associated with an increased risk of VTE, and VTE is associated with an increased risk of death for patients with all stages and types of cancer, although HRs vary depending on the site and stage of cancer, as well as other factors.[15,23-25] Large observational cohort studies have shown that cancer sites associated with the highest rates of VTE include the pancreas, brain, ovary, uterus, kidney, stomach, colon, rectum, and lung.[23-26] The most recent of these studies, by Khorana and colleagues,[24] assessed discharge data from 1,015,598 cancer patients in the University Health System Consortium database to identify frequency and trends of cancer-associated VTE during hospitalizations between 1995 and 2003. Overall, 41,666 cancer patients (4.1%) experienced VTE while in the hospital. In these patients, the cancer sites associated with the highest incidence of VTE were the pancreas (8.1%), ovary (5.6%), kidney (5.6%), lung (5.1%), stomach (4.9%), and brain (4.7%). The incidence of VTE was also high in patients with hematologic malignancies such as leukemia, Hodgkin disease, non-Hodgkin lymphoma, and myeloma, which had VTE rates ranging from 4.2% to 5.0%.[24] Another study assessed VTE data from the National Hospital Discharge Survey of 40,787,000 cancer patients hospitalized from 1979 through 1999.[25] Overall, 2% of these patients had a VTE compared with only 1% of the 662,309,000 hospitalized noncancer patients in the database. While VTE rates were lower in this study than in the study by Khorana and colleagues,[24] the cancer sites associated with the highest relative risks of VTE were generally consistent between the 2 studies (pancreas, brain, stomach, uterus, lung, prostate, and kidney).

The risk of VTE varies over time after a diagnosis of cancer (Figure 1).[27] The risk is highest early after diagnosis, and there is a strong correlation between metastatic-stage cancer and risk of VTE.[15,23,26,28] A case-control study of cancer (n=389) and noncancer (n=2,831) patients with VTE and controls without VTE (n=2,131) found that the risk of VTE was highest during the first 3 months after diagnosis (adjusted OR, 53.5; 95% CI, 8.6–334.3) and diminished after the first year of follow-up (adjusted OR for >3 months to ≤1 year, 14.3; 95% CI, 5.8–35.2; adjusted OR for >1 to ≤3 year, 3.6; 95% CI, 2.0–6.5).[28] Patients with metastatic solid tumors had a much greater risk of VTE than those with localized disease (adjusted OR, 19.8; 95% CI, 2.6–149.1).[28]

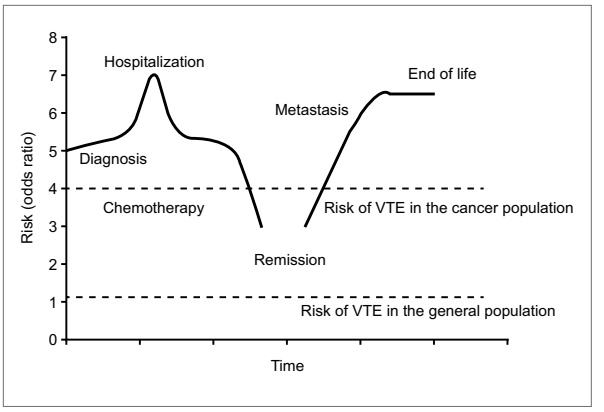

Figure 1. Changes in the risk of VTE over the course of cancer. VTE=venous thromboembolism.

Republished with permission of Informa Healthcare USA, from Who's at risk for thrombosis? Approaches to risk stratifying cancer patients. Rao MV, Francis CW, Khorana AA. In: *Cancer-Associated Thrombosis: New Findings in Translational Science, Prevention, and Treatment*. Khorana AA, Francis CW, eds. 2007.[27] Permission conveyed through Copyright Clearance Center, Inc.

In a retrospective study of patients with cancer of the prostate, breast, lung, colon/rectum, uterus, bladder, pancreas, stomach, ovary, or kidney; melanoma; or non-Hodgkin lymphoma, Chew and colleagues[15] found that VTE incidence was highest during the first few months after diagnosis for patients with more advanced-stage cancer (Figure 2) and that later stages of nearly all cancer types were strongly associated with increased risk of VTE (Table 1).

Patients with cancer are a heterogeneous population[29] and, beyond stage and type of cancer, other possible risk factors need to be considered when assessing VTE risk in individual patients (Table 2).[24,30] Hospitalized patients, patients undergoing surgery, and patients receiving chemotherapy are at particularly high risk for VTE.[5] Several prothrombotic mechanisms are believed to be involved with the occurrence of cancer therapy–induced VTE, including direct vascular endothelial toxicity, platelet activation, monocyte/macrophage expression of tissue factor, alterations in coagulation and fibrinolytic proteins, tumor cell cytokine secretion, endothelial cell apoptosis, and increases in tissue factor expression/activity (Figure 3).[16]

Cancer Treatment as an Additional Risk Factor For VTE

Chemotherapy is an independent risk factor for development of VTE, and chemotherapy-associated thrombosis risk adds to the risk conferred by the underlying cancer. Cancer treatments such as chemotherapy, adjuvant chemotherapy, hormonal therapy, antiangiogenic and immunomodulatory agents, and erythropoiesis-stimulating agents, as well as combinations of these pharmacologic treatments, are all known to have prothrombotic effects in patients with cancer.[16,30] A

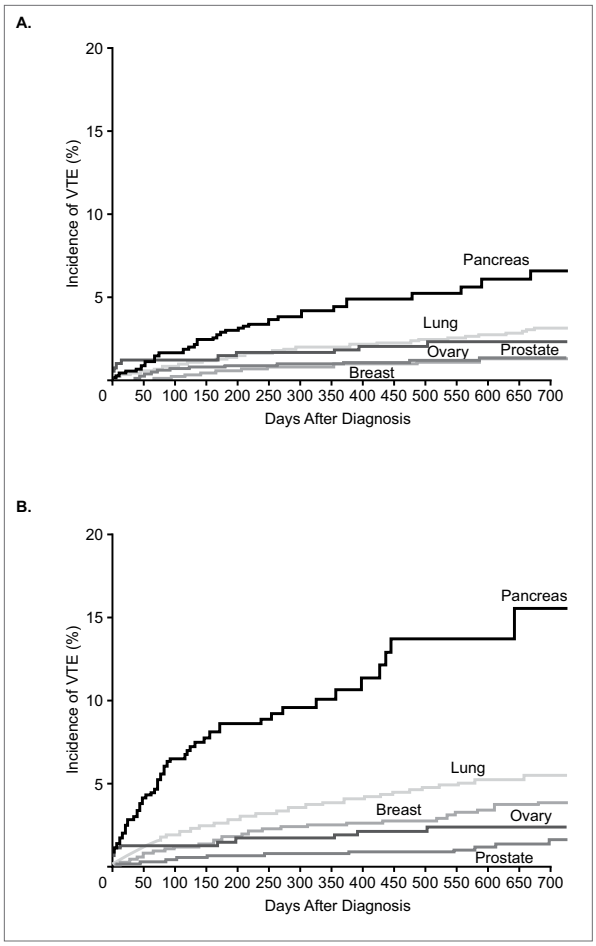

Figure 2. Kaplan-Meier plot of the incidence of venous thromboembolism within 2 years of diagnosis of 5 different types of cancer with regional stage (A) or metastatic stage (B) disease at the time of diagnosis.

Table 1. Effect of Cancer Stage on the Development of Venous Thromboembolism Within 1 Year of Diagnosis

	Hazard Ratio (95% CI)*	
Cancer Site	**Regional**	**Metastatic**
Prostate	1.3 (1.0–1.7)†	1.1 (0.7–1.6)
Breast	1.9 (1.5–2.5)§	5.2 (3.6–73)§
Lung	1.9 (1.4–2.6)§	3.5 (2.7–4.5)§
Colon/rectum	2.7 (2.1–3.4)§	4.3 (3.3–5.6)§
Melanoma	3.7 (1.1–12.8)†	21.5 (10.1–46.0)§
Lymphoma	2.0 (1.3–3.1)‡	1.4 (0.9–2.1)
Uterus	1.7 (1.0–2.9)	6.1 (3.7–9.8)§
Bladder	3.8 (2.2–6.7)§	9.6 (5.6–17.8)§
Pancreas	1.1 (0.6–2.1)	3.3 (1.8–6.2)§
Stomach	1.3 (0.8–2.2)	2.8 (1.7–4.5)§
Ovary	2.5 (0.9–7.1)	3.8 (1.7–8.8)‡
Kidney	3.1 (1.8–5.1)§	3.8 (2.3–6.2)§

CI=confidence interval.
*Localized disease used as reference stage; †P<.05; ‡P<.01; §P<.001.

population-based case-controlled study[31] investigated VTE risk factors in 625 patients who had a VTE compared with 625 individuals in an age- and sex-matched control group without VTE. Results showed that the risk of VTE was increased 4.1-fold (95% CI, 1.93–8.52) in patients with cancer and 6.5-fold (95% CI, 2.1–20.2) in cancer patients receiving chemotherapy. The overall annual incidence of VTE in patients receiving chemotherapy for various types of malignancies is estimated at 8% to 11%,[32,33] and VTE accounts for approximately 9% of deaths in chemotherapy-treated cancer patients.[12] Patients receiving chemotherapy have a 2-fold to 3-fold increase in risk of VTE compared with cancer patients not receiving chemotherapy.[26,32]

Whether any chemotherapeutic agent is more prothrombotic than others is unclear.[6] However, cisplatin, doxorubicin, L-asparaginase, 5-fluorouracil, and cyclophosphamide have all been shown to increase thrombosis risk, with reported thrombosis rates of up to 18% when the agent is used in single or combination chemotherapeutic regimens or as adjuvant therapy in various types of malignancies.[16,34-37]

Hormonal agents, particularly tamoxifen and anastrozole (Arimidex, AstraZeneca), have been studied extensively in the treatment of breast cancer.[38] Women with early-stage breast cancer treated with tamoxifen had a 1.5-fold to 7.1-fold increased risk of VTE compared with those who received placebo or observation only. In a large study of 9,366 patients with early-stage breast cancer[39] treated for a median of 33 months, the observed incidence of VTE was 2.1% in the anastrozole group, 3.5% in the tamoxifen group, and 4.0% in the group that received both agents (P=.0006 for anastrozole vs tamoxifen). Studies in women with late-stage breast cancer revealed VTE rates up to 8.0% among those treated with tamoxifen and up to 6.7% among those treated with anastrozole.[38]

Antiangiogenic/immunomodulatory agents such as thalidomide and its derivative lenalidomide (Revlimid, Celgene) are used as adjuvant treatments in patients with various hematologic malignancies, particularly multiple myeloma and myelodysplastic syndromes.[40,41] In a meta-analysis of published studies involving 3,322 multiple myeloma patients,[40] those who received thalidomide were found to have a statistically significant 2.6-fold increase in risk of VTE compared with those who did not receive thalidomide (P<.01; 95% CI, 1.8–3.6). The risk of VTE conferred by thalidomide was found to be additive when

Table 2. Risk Factors for Cancer-Associated Thrombosis[24,30]

Patient-Specific Factors
Older age
Ethnicity (higher in African Americans; lower in Asian-Pacific Islanders)
Comorbid conditions (neutropenia, infection, obesity, renal disease, pulmonary disease)
Female sex
Immobilization
Heritable prothrombotic mutations (Factor V Leiden, prothrombin gene mutation)
Prior history of thromboembolism
Cancer-Specific Factors
Primary tumor site (pancreatic, ovarian, kidney, lung, gastric, brain, and hematologic)
Histologic subtype (adenocarcinoma > squamous cell carcinoma)
Locally advanced tumors/presence of distant metastases
Time from diagnosis
Treatment-Specific Risk Factors
Recent major surgery
Current hospitalization
Central venous catheters
Chemotherapy
Antiangiogenic therapy (thalidomide, lenalidomide, bevacizumab [?])
Hormonal therapy (tamoxifen)
Erythropoiesis-stimulating agents
Transfusions

this agent was used in combination chemotherapy or with dexamethasone. Multiple myeloma patients treated with lenalidomide in combination with high-dose dexamethasone experienced VTE rates that were 3–4 times higher than rates in patients receiving high-dose dexamethasone without lenalidomide.[42,43] However, data from post hoc analyses of these studies suggest that concomitant use of erythropoiesis-stimulating agents may have contributed to the risk attributed to lenalidomide.[44]

Bevacizumab (Avastin; Genentech, A Member of the Roche Group), another antiangiogenic agent that is well studied in various malignancies, has also been associated with an increased risk of VTE (P<.001).[45] A meta-analysis of data from 15 randomized controlled studies involving 4,292 cancer patients treated with bevacizumab and 3,664 cancer patients not treated with bevacizumab found the RR of VTE was 1.33 (95% CI, 1.13–1.56; P<.001) with bevacizumab; risk was significant with both high-dose (P<.04) and low-dose (P=.007) regimens. Studies in this meta-analysis included patients with renal, lung, colorectal, pancreatic, and breast cancer, as well as mesothelioma. In contrast, another recent meta-analysis of 6,055 patients from 10 randomized, controlled studies did not note a significant risk of VTE associated with bevacizumab therapy (OR, 1.14; 95% CI, 0.96–1.35; P=.13).[46]

Supportive treatments such as erythropoiesis-stimulating agents, blood or platelet transfusions, and high doses of corticosteroids (eg, ≥80 mg dexamethasone per cycle of chemotherapy) are also known to increase thrombosis risk in patients with cancer. In a meta-analysis of 38 phase III studies including more than 8,100 cancer patients,[47] the RR of VTE was increased by 57% in patients receiving epoetin alfa or darbepoetin alfa compared with a control group that did not receive an erythropoiesis-stimulating agent (RR, 1.57; 95% CI, 1.31–1.87). Similarly, in a retrospective analysis of discharge data from approximately 504,000 cancer patients,[48] the observed incidence of VTE was 7.2% in those who received red blood cell (RBC) transfusion and/or platelet transfusion compared with 3.7% in hospitalized cancer patients who did not receive transfusions (P<.001). In this population, RBC transfusion was independently associated with a 60% increase in risk of VTE (OR, 1.60; 95% CI, 1.53–1.67), and platelet transfusion was associated with a 20% increase in risk (OR, 1.20; 95%, CI, 1.11–1.29). A retrospective review of 179 germ-cell cancer patients on chemotherapy also found that use of high-dose dexamethasone (≥80 mg per cycle) was an independent risk factor for thromboembolic complications (OR, 3.5; 95% CI, 1.2–10.3).[49]

Guideline Recommendations and Evidence Supporting Pharmacologic VTE Prophylaxis in Medical Oncology Patients

Frequent coexistence of multiple VTE risk factors in cancer patients and clinical trial data supporting use of pharmacologic thromboprophylaxis in the cancer setting have led to current guidelines recommending that primary pharmacologic VTE prophylaxis be considered for all hospitalized patients with active cancer, those undergoing major cancer surgery, and in select high-risk outpatients including those receiving thalidomide or lenalidomide with chemotherapy or dexamethasone.[5,50-53] Providers should consider the risks and benefits of pharmacologic VTE prophylaxis in patients with high-risk solid tumors receiving chemotherapy.[51-53]

A search of the PubMed database was conducted in January 2012 using the Medical Subject Heading Terms *venous thromboembolism* and *neoplasms* to identify English-language articles summarizing data from comparative studies of pharmacologic prophylaxis for

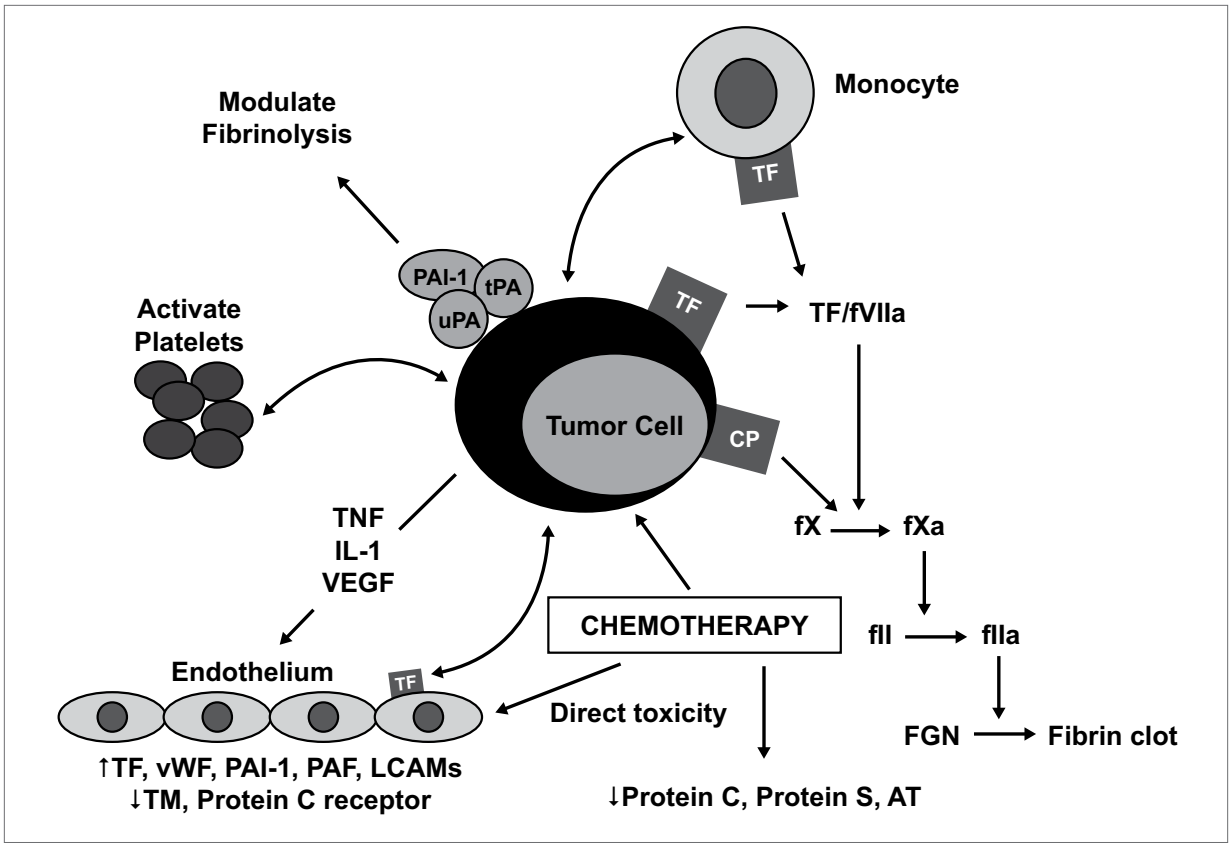

Figure 3. Pathophysiology of chemotherapy-associated thrombosis.

AT=antithrombin; CP=cancer procoagulant; FGN=fibrinogen; IL-1=interleukin-1; LCAMs=leukocyte adhesion molecules; PAF=platelet activating factor; PAI-1=plasminogen activator inhibitor-1; TF=tissue factor; TM=thrombomodulin; TNF=tumor necrosis factor; t-PA=tissue plasminogen activator; u-PA=urinary plasminogen activator; VEGF=vascular endothelial growth factor; vWF=von Willebrand factor. Reprinted with kind permission from Springer Science+Business Media: *Cancer Treatment and Research*. Chemotherapy-associated thrombosis. Volume 148, 2009, 181-206, Ashrani AA, Rajkumar SV.[16]

thrombosis not related to use of central venous catheters in medical patients with cancer. Of the 15 studies identified,[54-68] 3 focused specifically on acutely ill inpatient populations that included a relatively small number of patients with cancer.[55,56,62] Two of the 3 studies reported significant reductions (P=.042 and P<.05) in VTE risk associated with enoxaparin treatment in hospitalized cancer patients,[55,62] while the third, a single-center study, found no significant treatment effect associated with nadroparin, although this study included only 10 patients in each treatment group.[56] Six studies focused on cancer patients with multiple myeloma[57-60] or solid tumors[57,63,64] without specifying whether the study populations were inpatients or outpatients. In 5 of these studies, warfarin,[57,60] low-dose aspirin,[58] enoxaparin,[63] and dalteparin[64] were all shown to significantly reduce VTE risk compared with placebo or no prophylaxis without increasing risk of clinically significant or major bleeding. The sixth study, reported by Palumbo and colleagues[59] showed low-dose aspirin, warfarin, and enoxaparin to have similar efficacy for reducing risk of VTE in multiple myeloma patients on thalidomide. In this study, major bleeding occurred in 1.4% of patients in the aspirin group; no major bleeding events were reported in the warfarin and enoxaparin groups.[59]

The use of anticoagulants for thrombosis prophylaxis in ambulatory cancer patients is an active area of research, and results from several studies suggest a potential benefit associated with prophylaxis for outpatients receiving chemotherapy. Six reports focusing specifically on ambulatory patients receiving chemotherapy for various solid-tumor malignancies were identified.[54,61,65,66,68,69] In 5 of these studies, prophylaxis with warfarin,[54] the low-molecular-weight heparins nadroparin and certoparin,[61,65,66] or the ultra-low-molecular-weight heparin semuloparin[69] significantly reduced the incidence of VTE. Clinical development of semuloparin was suspended by the manufacturer in July 2012. The report from the 1 phase II placebo-controlled dose-finding study[68] of the factor Xa inhibitor apixaban (Eliquis, Bristol-Myers Squibb/Pfizer) in patients with metastatic cancer who were receiving chemotherapy did not include between-group statistical

Table 3. Khorana Score: A Predictive Model for Chemotherapy-Associated Venous Thromboembolism

Patient Characteristic	Risk Score
Risk associated with site of cancer Very high risk (stomach, pancreas) High risk (lung, lymphoma, gynecologic, bladder, testicular)	 2 1
Prechemotherapy platelet count ≥350 × 109/L	1
Hemoglobin level <100 g/L or use of RBC growth factors	1
Prechemotherapy leukocyte count >11 × 109/L	1
BMI ≥35 kg/m^2	1

BMI=body mass index; RBC=red blood cell.

analysis. In addition, a randomized open-label study of dalteparin (Fragmin, Eisai) versus no anticoagulation treatment for primary prevention of VTE in ambulatory cancer patients receiving chemotherapy is ongoing.[70]

Despite well-established consensus guidelines, the appropriate use of guideline-recommended VTE prophylaxis is particularly low in medical patients with cancer—only an estimated 37% of patients with active malignancy receive prophylaxis.[71] Reasons for the underuse of prophylaxis in medical cancer patients are unclear but may be related to unawareness of the risk in medical patients, difficulty in identifying patients who are at high risk, concerns regarding bleeding risk in cancer patients, or perceptions that pharmacologic prophylaxis is unnecessary or may not benefit medical patients with cancer.[72] Khorana and colleagues[9] developed a simple risk assessment model to aid clinicians in identifying high-risk cancer outpatients on chemotherapy who might be appropriate candidates for thromboprophylaxis (Table 3). The model assigns scores for the site of cancer (stomach or pancreas, 2 points [very high risk]; lung, lymphoma, gynecologic, bladder, or testicular cancer, 1 point [high risk]), prechemotherapy platelet count ≥350 × 10^9/L (1 point); hemoglobin level <100 g/L or use of red blood cell growth factors (1 point); prechemotherapy leukocyte count >11 × 10^9/L (1 point); and body mass index ≥35 kg/m^2 (1 point). A cumulative score of 1–2 connotes an intermediate risk of VTE, and a score of 3 or higher connotes a high risk. In the cohort of patients used to validate the model, the incidence of VTE over a 2.5-month follow-up period was 2% for *intermediate-risk* patients and 7% for *high-risk* patients, suggesting that patients in the latter category may benefit from thromboprophylaxis.[9] The Khorana VTE risk score has been subsequently validated by multiple independent investigative groups including Ay and colleagues.[73,74] Other biomarkers of thrombosis risk that may prove useful in identifying cancer patients at increased risk for VTE include D-dimer and prothrombin fragment 1+2,[75] P selectin,[76] tumor-derived tissue factor microparticles,[77] and endogenous thrombin generation.[78] Except for D-dimer, each of these other biomarkers have the distinct disadvantage of requiring specialized laboratory equipment and expertise that may not be available in many clinical settings. Khorana and colleagues from the University of Rochester and Duke University are currently testing the value of risk-guided VTE prophylaxis in high-risk ambulatory oncology patients receiving chemotherapy.[70] The results of this study should help to clarify the risks and benefits of pharmacologic VTE prophylaxis in ambulatory oncology patients receiving chemotherapy. Until these results are available, VTE prophylaxis for ambulatory cancer patients receiving chemotherapy should be discussed with patients on a case-by-case basis, weighing the risks and benefits of this treatment.[5,51-53] Risk assessment models such as the Khorana score should provide useful data for these discussions, and prophylaxis could be considered in high-risk patients (Khorana score ≥3).

Conclusions

The burden of thrombosis is high in patients with cancer, with up to 78% of VTE events occurring in the ambulatory setting. Chemotherapeutic and supportive therapies independently increase this risk further. Thrombosis risk also varies according to the site and stage of cancer. Thus, it is important to take into consideration all relevant patient-, cancer-, and treatment-related factors when assessing VTE risk for an individual patient. Appropriate use of pharmacologic VTE prophylaxis should be considered for all high-risk cancer patients, including those undergoing major cancer surgery, those who are hospitalized, and those who are outpatients receiving highly thrombogenic cancer therapies. In the future, risk-assessment models such as the Khorana score may help identify ambulatory cancer patients who may benefit from outpatient VTE prophylaxis. Broad implementation of VTE prophylaxis among ambulatory medical oncology patients awaits data from randomized trials testing the utility of the Khorana score in guiding prophylaxis decisions.

Acknowledgments

Writing and editorial support was provided by Michael Morren, RPh, of Peloton Advantage, LLC, and was funded by sanofi-aventis U.S. The opinions expressed in the current article are those of the author. The author received no honoraria or other form of financial support related to the development of this manuscript.

References

1. Heit JA, O'Fallon WM, Petterson TM, et al. Relative impact of risk factors for deep vein thrombosis and pulmonary embolism: a population-based study. *Arch Intern Med*. 2002;162:1245-1248.
2. Imberti D, Agnelli G, Ageno W, et al. Clinical characteristics and management of cancer-associated acute venous thromboembolism: findings from the MASTER Registry. *Haematologica*. 2008;93:273-278.
3. Spencer FA, Lessard D, Emery C, Reed G, Goldberg RJ. Venous thromboembolism in the outpatient setting. *Arch Intern Med*. 2007;167:1471-1475.
4. Khorana AA, Dalal M, Tangirala K, Miao R. Higher incidence of venous thromboembolism in the outpatient versus the inpatient setting among U.S. cancer patients. *Blood* (ASH Annual Meeting Abstracts). 2011;118: Abstract 674.
5. Lyman GH, Khorana AA, Falanga A, et al. American Society of Clinical Oncology guideline: recommendations for venous thromboembolism prophylaxis and treatment in patients with cancer. *J Clin Oncol*. 2007;25:5490-5505.
6. Falanga A. The incidence and risk of venous thromboembolism associated with cancer and nonsurgical cancer treatment. *Cancer Invest*. 2009;27:105-115.
7. Dentali F, Ageno W, Becattini C, et al. Prevalence and clinical history of incidental, asymptomatic pulmonary embolism: a meta-analysis. *Thromb Res*. 2010;125:518-522.
8. den Exter PL, Hooijer J, Dekkers OM, Huisman MV. Risk of recurrent venous thromboembolism and mortality in patients with cancer incidentally diagnosed with pulmonary embolism: a comparison with symptomatic patients. *J Clin Oncol*. 2011;29:2405-2409.
9. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood*. 2008;111:4902-4907.
10. Khorana AA, Dalal M, Lin J, Connolly G. Venous thromboembolism (VTE) in the cancer outpatient setting: contemporary rates and predictors in the U.S. *J Thromb Haemost*. 2011;9(suppl 2): Abstract 53.
11. Ambrus JL, Ambrus CM, Mink IB, Pickren JW. Causes of death in cancer patients. *J Med*. 1975;6:61-64.
12. Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. *J Thromb Haemost*. 2007;5:632-634.
13. Khorana AA, Dalal M, Lin J, Connolly GC. Incidence and predictors of venous thromboembolism (VTE) among ambulatory high-risk cancer patients undergoing chemotherapy in the United States. *Cancer.* 2013;119:648-655.
14. Sorensen HT, Mellemkjaer L, Olsen JH, Baron JA. Prognosis of cancers associated with venous thromboembolism. *N Engl J Med*. 2000;343:1846-1850.
15. Chew HK, Wun T, Harvey D, Zhou H, White RH. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. *Arch Intern Med*. 2006;166:458-464.
16. Ashrani AA, Rajkumar SV. Chemotherapy-associated thrombosis. *Cancer Treat Res*. 2009;148:181-206.
17. Prandoni P, Lensing AW, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. *Blood*. 2002;100:3484-3488.
18. Levitan N, Dowlati A, Remick SC, et al. Rates of initial and recurrent thromboembolic disease among patients with malignancy versus those without malignancy. Risk analysis using Medicare claims data. *Medicine*. 1999;78:285-291.
19. Monreal M, Falga C, Valdes M, et al. Fatal pulmonary embolism and fatal bleeding in cancer patients with venous thromboembolism: findings from the RIETE registry. *J Thromb Haemost*. 2006;4:1950-1956.
20. Elting LS, Escalante CP, Cooksley C, et al. Outcomes and cost of deep venous thrombosis among patients with cancer. *Arch Intern Med*. 2004;164:1653-1661.
21. Lyman GH, Wang Y, Wang H, Cohen AT. Venous thromboembolism (VTE) in cancer patients receiving chemotherapy: a real-world analysis of VTE risk and the impact of VTE on healthcare expenditure. Presented at the Biennial Multidisciplinary Congress of the European CanCer Organisation and European Society for Medical Oncology; September 23-27, 2011; Stockholm, Sweden: Abstract 3002.
22. Connolly GC, Dalal MR, Lin J, Khorana AA. Incidence and predictors of venous thromboembolism (VTE) among ambulatory patients with lung cancer. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2011;29: Abstract 7066.
23. Khorana AA, Francis CW, Culakova E, Fisher RI, Kuderer NM, Lyman GH. Thromboembolism in hospitalized neutropenic cancer patients. *J Clin Oncol*. 2006;24:484-490.
24. Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH. Frequency, risk factors, and trends for venous thromboembolism among hospitalized cancer patients. *Cancer*. 2007;110:2339-2346.
25. Stein PD, Beemath A, Meyers FA, Skaf E, Sanchez J, Olson RE. Incidence of venous thromboembolism in patients hospitalized with cancer. *Am J Med*. 2006;119:60-68.
26. Blom JW, Vanderschoot JP, Oostindier MJ, Osanto S, van der Meer FJ, Rosendaal FR. Incidence of venous thrombosis in a large cohort of 66,329 cancer patients: results of a record linkage study. *J Thromb Haemost*. 2006;4:529-535.
27. Rao MV, Francis CW, Khorana AA. Who's at risk for thrombosis? Approaches to risk stratifying cancer patients. In: Khorana AA, Francis CW, eds. *Cancer-Associated Thrombosis: New Findings in Translational Science, Prevention, and Treatment*. New York, NY: Informa Healthcare USA, Inc; 2007:169-192.
28. Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. *JAMA*. 2005;293:715-722.
29. Khorana AA, Rao MV. Approaches to risk-stratifying cancer patients for venous thromboembolism. *Thromb Res*. 2007;120(suppl 2):S41-S50.
30. Menapace LA, Khorana AA. The role of thromboprophylaxis in cancer patients: emerging data. *Curr Opin Hematol*. 2010;17:450-456.
31. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ III. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. *Arch Intern Med*. 2000;160:809-815.
32. Shah MA, Capanu M, Soff G, Asmis T, Kelsen DP. Risk factors for developing a new venous thromboembolism in ambulatory patients with non-hematologic malignancies and impact on survival for gastroesophageal malignancies. *J Thromb Haemost*. 2010;8:1702-1709.
33. Otten HM, Mathijssen J, ten Cate H, et al. Symptomatic venous thromboembolism in cancer patients treated with chemotherapy: an underestimated phenomenon. *Arch Intern Med*. 2004;164:190-194.
34. Starling N, Rao S, Cunningham D, et al. Thromboembolism in patients with advanced gastroesophageal cancer treated with anthracycline, platinum, and fluoropyrimidine combination chemotherapy: a report from the UK National Cancer Research Institute Upper Gastrointestinal Clinical Studies Group. *J Clin Oncol*. 2009;27:3786-3793.
35. Pritchard KI, Paterson AH, Paul NA, Zee B, Fine S, Pater J. Increased thromboembolic complications with concurrent tamoxifen and chemotherapy in a randomized trial of adjuvant therapy for women with breast cancer. National Cancer Institute of Canada Clinical Trials Group Breast Cancer Site Group. *J Clin Oncol*. 1996;14:2731-2737.
36. Levine MN. Adjuvant therapy and thrombosis: how to avoid the problem? *Breast*. 2007;16(suppl 2):169-174.
37. Moore RA, Adel N, Riedel E, et al. High incidence of thromboembolic events in patients treated with cisplatin-based chemotherapy: a large retrospective analysis. *J Clin Oncol*. 2011;29:3466-3473.
38. Deitcher SR, Gomes MP. The risk of venous thromboembolic disease associated with adjuvant hormone therapy for breast carcinoma: a systematic review. *Cancer*. 2004;101:439-449.
39. Baum M, Budzar AU, Cuzick J, et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. *Lancet*. 2002;359:2131-2139.
40. El Accaoui RN, Shamseddeen WA, Taher AT. Thalidomide and thrombosis. A meta-analysis. *Thromb Haemost*. 2007;97:1031-1036.
41. Yang X, Brandenburg NA, Freeman J, et al. Venous thromboembolism in myelodysplastic syndrome patients receiving lenalidomide: results from postmarketing surveillance and data mining techniques. *Clin Drug Investig*. 2009;29:161-171.
42. Dimopoulos M, Spencer A, Attal M, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med*. 2007;357:2123-2132.
43. Weber DM, Chen C, Niesvizky R, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med*. 2007;357:2133-2142.
44. Knight R, DeLap RJ, Zeldis JB. Lenalidomide and venous thrombosis in multiple myeloma. *N Engl J Med*. 2006;354:2079-2080.
45. Nalluri SR, Chu D, Keresztes R, Zhu X, Wu S. Risk of venous thromboembolism with the angiogenesis inhibitor bevacizumab in cancer patients: a meta-analysis. *JAMA*. 2008;300:2277-2285.
46. Hurwitz HI, Saltz LB, Van CE, et al. Venous thromboembolic events with chemotherapy plus bevacizumab: a pooled analysis of patients in randomized phase II and III studies. *J Clin Oncol*. 2011;29:1757-1764.
47. Bennett CL, Silver SM, Djulbegovic B, et al. Venous thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia. *JAMA*. 2008;299:914-924.
48. Khorana AA, Francis CW, Blumberg N, Culakova E, Refaai MA, Lyman GH. Blood transfusions, thrombosis, and mortality in hospitalized patients with cancer. *Arch Intern Med*. 2008;168:2377-2381.

49. Weijl NI, Rutten MF, Zwinderman AH, et al. Thromboembolic events during chemotherapy for germ cell cancer: a cohort study and review of the literature. *J Clin Oncol*. 2000;18:2169-2178.
50. Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2 suppl):e227S-e277S.
51. Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed. American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2 suppl):e195S-e226S.
52. Streiff MB, Bockenstedt PL, Cataland SR, et al. Venous thromboembolic disease. *J Natl Compr Canc Netw*. 2011;9:714-777.
53. Mandala M, Falanga A, Roila F. Management of venous thromboembolism (VTE) in cancer patients: ESMO Clinical Practice Guidelines. *Ann Oncol*. 2011;22(suppl 6):vi85-vi92.
54. Levine M, Hirsh J, Gent M, et al. Double-blind randomised trial of a very-low-dose warfarin for prevention of thromboembolism in stage IV breast cancer. *Lancet*. 1994;343:886-889.
55. Hull RD, Schellong SM, Tapson VF, et al. Extended-duration venous thromboembolism prophylaxis in acutely ill medical patients with recently reduced mobility: a randomized trial. *Ann Intern Med*. 2010;153:8-18.
56. Weber C, Merminod T, Herrmann FR, Zulian GB. Prophylactic anti-coagulation in cancer palliative care: a prospective randomised study. *Support Care Cancer*. 2008;16:847-852.
57. Ikhlaque N, Seshadri V, Kathula S, Baumann MA. Efficacy of prophylactic warfarin for prevention of thalidomide-related deep venous thrombosis. *Am J Hematol*. 2006;81:420-422.
58. Baz R, Li L, Kottke-Marchant K, et al. The role of aspirin in the prevention of thrombotic complications of thalidomide and anthracycline-based chemotherapy for multiple myeloma. *Mayo Clin Proc*. 2005;80:1568-1574.
59. Palumbo A, Cavo M, Bringhen S, et al. Aspirin, warfarin, or enoxaparin thromboprophylaxis in patients with multiple myeloma treated with thalidomide: a phase III, open-label, randomized trial. *J Clin Oncol*. 2011;29:986-993.
60. Cini M, Zamagni E, Valdre L, et al. Thalidomide-dexamethasone as up-front therapy for patients with newly diagnosed multiple myeloma: thrombophilic alterations, thrombotic complications, and thromboprophylaxis with low-dose warfarin. *Eur J Haematol*. 2010;84:484-492.
61. Agnelli G, Gussoni G, Bianchini C, et al. Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: a randomised, placebo-controlled, double-blind study. *Lancet Oncol*. 2009;10:943-949.
62. Alikhan R, Cohen AT, Combe S, et al. Prevention of venous thromboembolism in medical patients with enoxaparin: a subgroup analysis of the MEDENOX study. *Blood Coagul Fibrinolysis*. 2003;14:341-346.
63. Riess H, Pelzer U, Deutschinoff G, et al. A prospective, randomized trial of chemotherapy with or without the low molecular weight heparin (LMWH) enoxaparin in patients (pts) with advanced pancreatic cancer (APC): results of the CONKO 004 trial. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2009;27: Abstract LBA4506.
64. Maraveyas A, Waters J, Roy R, et al. Gemcitabine with or without prophylactic weight-adjusted dalteparin in patients with advanced or metastatic pancreatic cancer (APC): a multicentre, randomised phase IIB trial (the UK FRAGEM study). *Eur J Cancer.* 2009(suppl 7):362.
65. Haas SK, Kakkar AK, Kemkes-Matthes B, et al. Prevention of venous thromboembolism with low-molecular-weight heparin in patients with metastatic breast or lung cancer—results of the TOPIC studies. *J Thromb Haemost*. 2005;3(suppl 1):OR059.
66. Verso M, Gussoni G, Agnelli G. Prevention of venous thromboembolism in patients with advanced lung cancer receiving chemotherapy: a combined analysis of the PROTECHT and TOPIC-2 studies. *J Thromb Haemost*. 2010;8:1649-1651.
67. Agnelli G, George DJ, Fisher W, et al. The ultra-low molecular weight heparin (ULMWH) semuloparin for prevention of venous thromboembolism (VTE) in patients with cancer receiving chemotherapy: SAVE ONCO study. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2011;29: Abstract LBA9014.
68. Levine MN, Deitchman D, Julian J, et al. A randomized phase II trial of a new anticoagulant, apixaban, in metastatic cancer. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2009;27: Abstract e20514.
69. Agnelli G, George DJ, Kakkar AK, et al. Semuloparin for thromboprophylaxis in patients receiving chemotherapy for cancer. *N Engl J Med*. 2012;366:601-609.
70. ClinicalTrials.gov. A study of dalteparin prophylaxis in high-risk ambulatory cancer patients (PHACS). http://clinicaltrials.gov/ct2/show/NCT00876915. Identifier: NCT00876915.
71. Cohen AT, Tapson VF, Bergmann JF, et al. Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study. *Lancet*. 2008;371:387-394.
72. Kakkar AK. Current use of venous thromboembolism prophylaxis in cancer patients. *Clin Adv Hematol Oncol*. 2009;7:231-233.
73. Ay C, Dunkler D, Marosi C, et al. Prediction of venous thromboembolism in cancer patients. *Blood*. 2010;116:5377-5382.
74. Khorana AA. Cancer and coagulation. *Am J Hematol*. 2012;87(suppl 1):S82-S87.
75. Ay C, Vormittag R, Dunkler D, et al. D-dimer and prothrombin fragment 1 + 2 predict venous thromboembolism in patients with cancer: results from the Vienna Cancer and Thrombosis Study. *J Clin Oncol*. 2009;27:4124-4129.
76. Ay C, Simanek R, Vormittag R, et al. High plasma levels of soluble P-selectin are predictive of venous thromboembolism in cancer patients: results from the Vienna Cancer and Thrombosis Study (CATS). *Blood*. 2008;112:2703-2708.
77. Zwicker JI, Liebman HA, Neuberg D, et al. Tumor-derived tissue factor-bearing microparticles are associated with venous thromboembolic events in malignancy. *Clin Cancer Res*. 2009;15:6830-6840.
78. Ay C, Dunkler D, Simanek R, et al. Prediction of venous thromboembolism in patients with cancer by measuring thrombin generation: results from the Vienna Cancer and Thrombosis Study. *J Clin Oncol*. 2011;29:2099-2103.