Clinical Roundtable Monograph

Clinical Advances in Hematology & Oncology January 2011

The Oncologist's Role in the Management of Venous Thromboembolism

Moderator

Howard A. Liebman, MD
Professor of Medicine and Pathology
Jane Anne Nohl Division of Hematology and
Center for the Study of Blood Diseases
University of Southern California–Keck School of Medicine
Los Angeles, California

Discussants

Alok A. Khorana, MD
Vice-Chief, Division of Hematology/Oncology
Associate Professor of Medicine and Oncology
James P. Wilmot Cancer Center
University of Rochester
Rochester, New York

Craig M. Kessler, MD
Professor of Medicine and Pathology
Georgetown University Medical School
Lombardi Comprehensive Cancer Center
Washington, DC

A CME Activity
Approved for 1.0
AMA PRA
Category 1 Credit(s)™

Release Date: January 2011
Expiration Date: January 31, 2012
Estimated time to complete activity: 1 hour
Project ID: 7496

Abstract

Thromboembolism is the second leading cause of death in cancer patients. Patients with venous thromboembolism (VTE) and malignancy have a significantly higher probability of death. Pulmonary embolism can lead to a fatal outcome, and this condition often goes undiagnosed in cancer patients despite the presence of symptoms. Risk of VTE is increased by a number of clinical factors, which can be patient-derived, cancer-related, and treatment-related. Increasingly, clinicians are seeking predictable biomarkers to identify those patients at the greatest risk. To that end, a newly developed and validated predictive risk model may help identify patients who could benefit from prophylaxis. In addition, serum levels of coagulation cascade factors may predict the survival rate of cancer patients; elevated D-dimer levels are associated with decreased survival time. Anticoagulants, particularly low-molecular-weight heparin, can be useful in preventing the recurrence of clots in cancer patients with VTE. Current and future investigations are aimed at determining if prophylaxis with anticoagulants can improve patient survival. Future management strategies may involve the use of low-molecular-weight heparin or other novel anticoagulants as part of palliative care for high-risk patients. Although treatment with low-molecular-weight heparin can significantly reduce the risks of clots, the impact on cancer survival is unclear.

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Supported through an educational grant from Eisai, Inc.

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Target Audience

This activity has been designed to meet the educational needs of oncologists and other clinicians who treat cancer patients.

Statement of Need/Program Overview

Thromboembolism is the second leading cause of mortality in cancer patients (second only to cancer itself). The rate of venous thromboembolism (VTE) has been steadily rising since the late 1990s. Cancer patients who develop a deep vein thrombosis, especially a pulmonary embolism, have an increased risk of death. Risk of VTE is increased by a number of clinical factors, which can be patient-derived, cancer-related, and treatment-related. Biomarkers include components of the complete blood count. Several recent studies have provided data regarding prevention and management of VTE in cancer patients. Treatment with low-molecular-weight heparin can significantly reduce the risks of clots, but the impact on cancer survival is unclear. Novel anticoagulants are being studied.

Educational Objectives

After completing this activity, the participant should be better able to:

- Describe the importance of new findings and clinical trial data in the natural history of venous thromboembolism (VTE) in cancer patients
- Analyze the importance of initiating prophylaxis treatment in preventing VTE in cancer patients
- Assess the results of current clinical trials evaluating therapy benefits in cancer patients in the treatment of VTE
- Evaluate the importance of duration of therapy with low-molecular-weight heparins
- Integrate into clinical practice the latest knowledge to improve current prognosis statistics for treating VTE in cancer patients
- Identify future research directions for all therapies in VTE in cancer patients

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Clinical Advances in
HEMATOLOGY & ONCOLOGY™
A Peer-Reviewed Journal

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Venous Thromboembolism in Cancer Patients

Alok A. Khorana, MD

Cancer-associated thrombosis is an increasingly common complication of cancer and cancer treatment. Approximately 20% of all cases of venous thromboembolism (VTE) occur in patients with cancer.[1] In addition, patients with cancer have twice the rate of VTE as patients without cancer.[2] VTE, including deep venous thrombosis (DVT) and pulmonary embolism (PE), is associated with decreased short-term and long-term survival. Thromboembolism is the second leading cause of mortality in cancer patients (second only to cancer itself); VTE and arterial events account for 9% of cancer-related deaths.[3]

The rate of VTE has been steadily rising since the late 1990s.[3-5] The increased incidence of DVT and PE is due, in part, to the use of the newer anticancer treatments that are more thrombogenic. High-resolution imaging studies used to stage cancer patients, as well as increased awareness of DVT and PE, have also contributed to the identification of more cases of VTE.

VTE is a significant problem with tremendous consequences. Cancer patients who develop a DVT, especially a PE, have an increased risk of death. Moreover, the development of VTE during chemotherapy is associated with early mortality.[6] Cancer patients with a prior history of VTE are more likely to develop recurrent VTE; the recurrence rate is 21% in the first year after diagnosis.[7,8] In addition, cancer patients with VTE are at an increased risk of bleeding complications. This risk is due, in part, to the anticoagulant therapy necessary to treat VTE. The risk of major bleeding complications is as high as 12% per year following diagnosis and the start of anticoagulation therapy.[8] Also, the presence of VTE impacts chemotherapy delivery, patient quality of life, the cost of hospitalization, and the use of health care resources. Therefore, much emphasis has been placed on clinical factors and predictive biomarkers that identify patients who are at an increased risk for VTE.

Clinical Risk Factors for VTE in Cancer Patients

There are multiple clinical risk factors for cancer-associated thrombosis.[9] Patient-associated risk factors include age (≥65 years), African American ethnicity, female sex, and comorbid conditions.[4] Obesity, particularly a body mass index (BMI) of 35 kg/m^2 or higher, is strongly associated with the risk of VTE. In addition, pulmonary disease, renal disease, cardiac disease, hospitalization due to an ongoing infection, and surgical procedures all increase the risk that the patient will develop VTE.[10]

There are also cancer-associated risk factors. These include the site of cancer, the stage of cancer, and the time until diagnosis.[10] The primary site of cancer is the most common risk factor for VTE. Cancer in the pancreas, stomach, uterus, and kidney, as well as primary brain tumors, are commonly associated with the highest rates of VTE.[4,10] However, lung cancer and hematologic malignancies, such as lymphomas, myelomas, and leukemias, are also strongly associated with the risk of VTE. In a population-based study, hematologic malignancies were associated with the highest risk of VTE (odds ratio [OR], 28.0; 95% confidence interval [CI], 4.0–199.7), followed by lung cancer (OR, 22.2; 95% CI, 3.6–136.1).[11] The stage of cancer also appears to be important, with an increased risk for VTE in more advanced stages.[5,12] In hospitalized patients, the risk of VTE is greater in patients with metastatic disease than in patients with nonmetastatic disease. In the outpatient setting, however, the stage of cancer does not have as prominent a role in determining a patient's risk of VTE.[13-15] Patients are at the greatest risk for VTE in the first 3–6 months following cancer diagnosis.[11] It is unknown why risk increases during this time period; it may be some inherent property of the tumor or it may be related to the typical interventions that occur during the first 3–6 months of treatment.

Finally, there are treatment-associated risk factors. The most common treatments for cancer are chemotherapy and targeted therapy agents. Patients who receive these treatments have an elevated risk of DVT and PE beyond that associated with the diagnosis of cancer. Patients on chemotherapy have a 2-fold to 6-fold higher risk of VTE compared with the general population.[1,16] In a study of more than 4,000 cancer patients receiving chemotherapy, we found that the occurrence of DVT or PE was strongly associated with the risk of mortality; cancer patients who underwent chemotherapy were at a 47-fold

increased risk for mortality from VTE compared with the general population.[3] In fact, nearly 1 out of 10 deaths in cancer patients on chemotherapy could be related to a thrombotic event.[3]

The choice of chemotherapy agent can affect the patient's risk for VTE. In a study by Starling and colleagues,[17] patients with advanced gastroesophageal cancer received 4 different types of similar chemotherapeutic regimens (epirubicin, cisplatin, and fluorouracil; epirubicin, cisplatin, and capecitabine; epirubicin, fluorouracil, and oxaliplatin; and epirubicin, oxaliplatin, and capecitabine). Patients treated with cisplatin-based chemotherapy regimens had more thromboembolic events (15.1%) compared with patients receiving oxaliplatin-based regimens (7.6%). Thus, even when the site and stage of cancer is controlled, the chemotherapy agent can significantly affect the patient's risk factors for VTE.

Recently approved antiangiogenic agents include thalidomide and lenalidomide, which are commonly used for the treatment of myeloma and other malignancies. The use of thalidomide or lenalidomide is strongly associated with the risk of DVT, but only when combined with either steroids, such as dexamethasone, or other chemotherapeutic agents, such as doxorubicin.[18-20] Another antiangiogenic agent associated with VTE is bevacizumab. Initial reports, particularly from phase II randomized clinical trials, suggest that patients receiving bevacizumab have a higher risk of both venous and arterial clots.[21,22] Subsequently, Scappaticci and associates[23] performed a post-hoc analysis of pooled data from 5 randomized controlled trials. The study found that there was an increased risk of arterial thromboembolic events (hazard ratio [HR], 2.0; 95% CI, 1.05–3.75; *P*=.031), but not an increased risk of VTE events (HR, 0.89; 95% CI, 0.66–1.20; *P*=.44) for bevacizumab plus chemotherapy versus chemotherapy alone. A subsequent larger pooled meta-analysis published by Nalluri and colleagues[24] suggested there was, in fact, a significantly increased risk of VTE (relative risk of 1.33; 95% CI, 1.13–1.56; *P*<.001). However, the authors did not adjust for the time that the patients were on bevacizumab; after adjustment, no increased risk was seen. These conflicting data make it difficult to ascertain if there is a definitive increased risk of venous events associated with the use of bevacizumab, although there is certainly a clear increased risk for arterial events.

Predictive Biomarkers

Recent studies have focused on identifying biomarkers that may be predictive of cancer-associated VTE. One set of biomarkers that are relatively easy to evaluate are components of the complete blood count. A platelet count greater than or equal to 350,000/mm^3, a leukocyte count greater than 11,000/mm^3, or a hemoglobin level lower than 10 g/dL have all been linked to the risk of cancer-associated thrombosis.[25]

Several other biomarkers are currently under investigation. The most prominent area of focus is tissue factor, a physiologic initiator of coagulation. In addition to its procoagulant activity, tissue factor is also proangiogenic. Tissue factor is strongly expressed across a wide variety of both solid tumors and hematologic malignancies. The overexpression of tissue factor likely plays a role in cancer-associated thrombosis. In fact, elevated levels of tissue factor antigen and increased tissue factor activity are associated with the development of VTE in patients with pancreatic cancer.[26] In addition, cancer patients with VTE had significantly higher levels of tissue factor activity in the blood than cancer patients without VTE, and the presence of tissue-factor–bearing microparticles may be predictive of cancer patients developing VTE.[27,28] These preliminary studies suggest that tissue factor should be investigated as a possible candidate biomarker for VTE. Unfortunately, there are no current standardized assays available, so the use of tissue factor as a predictive biomarker is some time away from clinical adaptation.

Other proteins that have been proposed as biomarkers of VTE include C-reactive protein, soluble P-selectin, and D-dimers. Assays to measure C-reactive protein and D-dimers are widely available across different hospitals and health systems. The majority of the information regarding these biomarkers is preliminary and requires further validation in large, prospective studies before they can be recommended for use in patients with VTE.

Models to Identify Patients at Risk

The risk of VTE in the cancer-patient population is multifactorial. Since 1 or 2 simple risk factors alone cannot account for or identify truly high-risk cancer patients, we have recently developed a risk score that allows clinicians to predict the risk of VTE in cancer patients starting a new chemotherapy regimen.[29] We conducted a prospective observational study of 2,700 ambulatory cancer patients receiving systemic chemotherapy. A risk score was calculated based on the factors found to be associated with the risk of VTE. These factors included the site of cancer, low hemoglobin levels (>10 g/dL), high platelet count (≥350,000/mm^3), high leukocyte count (>11,000/mm^3), and obesity (BMI >35 kg/m^2). Patients were then categorized by the risk score into 3 different categories: low risk (score of 0), intermediate risk (score of 1 or 2), and high risk (score of ≥3 or higher). In the development cohort, the observed rates of VTE were less than 1% in the low-risk patients, 2% or less in the intermediate-risk patients, and 7% in the high-risk patients. The score was then vali-

dated in an independent cohort of 1,300 patients from the same observational study. These data have now been validated by a second group, which is part of the Vienna Cancer Thrombosis Study.[30] In this validation study, low-risk patients had a VTE probability rate of 1.5%, intermediate-risk patients had a VTE probability rate of 3.8%, and high-risk patients had a VTE probability rate of 17.7%. Results from these studies indicate that this risk model is clinically relevant for identifying cancer patients at high risk for VTE. Studies are currently under way to study prophylaxis in the high-risk subgroup of cancer patients identified by this model. Although the benefit of prophylaxis in this population remains to be confirmed, clinicians can use the risk score to determine a patient's relative risk for VTE or as a springboard to discuss the risk for VTE in patients initiating chemotherapy.

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Clinical Consequences to Venous Thromboembolism

Howard A. Liebman, MD

VTE is associated with significant clinical consequences. The majority of VTE events occur in ambulatory cancer patients receiving treatment. These events cause treatment delays that have an impact on the overall outcome for cancer treatment and affect the patient's quality of life. In addition, the development of VTE in a patient with cancer is a poor prognostic sign, placing the patient at an increased risk of mortality.

Pulmonary Embolism

VTE is associated with significant morbidity, including lower extremity thrombosis and PE. The development of PE, in particular, can lead to a fatal outcome. In a recent phase IIb study of patients with advanced or metastatic pancreatic cancer, the rate of PE was reduced by prophylaxis therapy with low-molecular-weight heparin.[1] This study suggests that patients at high risk for VTE are dying of clots. Unfortunately, physicians can overlook the signs and symptoms of PE in cancer patients. Advances in routine computed tomography angiography for cancer staging have increased the detection of "unexpected" PE. Interestingly, a retrospective case-control analysis with age- and stage-matched patients found that many of the patients who were thought to have asymptomatic PE in fact were symptomatic for their clots.[2] In fact, 44% of the patients had signs and symptoms commonly associated with PE, such as chest pain, shortness of breath, tachycardia, and/or limb pain or swelling. When fatigue was also taken into account, the percentage of patients with signs and symptoms of PE rose to 75%. The patients with unsuspected PE were significantly more likely to experience fatigue and shortness of breath compared with the age- and stage-matched control patients. In addition, patients with unsuspected PEs also had several risk factors for PE, including a prior history of VTE and major surgery within the past 2 months. It is important to note that cancer patients who undergo surgery are 3 times more likely to develop a fatal PE compared with noncancer patients who undergo a similar surgery.[3] Even though these PEs were not initially detected by the patients' health care providers, they are clinically relevant and can lead to increased morbidity and reduced quality of life. Therefore, patients with cancer and risk factors for VTE should be carefully evaluated.

Association With Mortality

Several large registry studies demonstrate that cancer patients who develop VTE have a worse clinical outcome and a greater mortality at follow-up. In a large Medicare database review study by Levitan and colleagues,[4] patients with DVT/PE and malignancy had a significantly higher probability of death than patients with malignancy only, DVT/PE only, or nonmalignant disease. Patients with VTE and cancer had a 3-fold higher risk of recurrent VTE and death than patients with VTE and without cancer. Similar results were obtained using a large database of Danish patients with cancer and VTE.[5] In that study, patients were matched to control subjects by type of cancer, age, sex, and year of diagnosis. The cancer patients with VTE had a poor prognosis; the 1-year survival rate of cancer patients with VTE was 12%, compared with a survival rate of 36% in the matched control patients. In a retrospective study conducted by Alcalay and coworkers,[6] the development of VTE in all stages of colon cancer resulted in a shorter survival time compared with patients at the same stage of disease without VTE. These results were further confirmed in a study of patients with unexpected PE.[7] Once again, patients with VTE had a shorter survival time compared with matched control patients without VTE.

Coagulation and Angiogenesis

Peripheral blood concentrations of factors involved in the coagulation cascade may predict survival in cancer patients. Numerous studies demonstrate that cancer patients with increased markers of thrombin generation, such as elevated D-dimer (fibrin-degradation product) levels, have significantly worse outcomes compared with patients with the same malignancy but lower levels of hemostatic activation. Pretreatment plasma levels of D-dimer predicted survival independent of stage, tumor size, performance status, or histology in patients with lung cancer.[8,9] In a univariate analysis of survival, a prolonged

value of prothrombin time and higher values of fibrinogen and D-dimer were associated with a poor prognosis.[8] In addition, a multivariate analysis of D-dimer levels found that patients with low D-dimer levels (<150 ng/mL) had a longer survival time than patients with elevated D-dimer levels (≥150 ng/mL; HR for high D-dimer group, 4.7; 95% CI, 1.8–11.7).[9] Similar results were observed in patients with metastatic breast cancer; almost 89% of the metastatic breast cancer patients had elevated D-dimer levels.[10] These results indicate that D-dimer levels are associated with poor outcomes in cancer patients.

The question then becomes why do patients with increased thrombin generation have worse outcome or worse survival? It is believed that activation of the coagulation and fibrinolytic cascades at the tumor site is associated with the tumor's growth and metastasis. In fact, a number of studies show a strong correlation between the initiator of coagulation-tissue factor and angiogenesis. Increased tissue factor expression is associated with aggressive forms of cancer and results in increased secretion of proangiogenic factors, such as vascular endothelial growth factor (VEGF), interleukin 8, and interleukin 6 (IL-6), by various tumor cells.[10-14] In a study by Dirix and associates,[10] patients with breast cancer had increased levels of D-dimer, fibrinogen, IL-6, and VEGF. The elevated levels of D-dimer were associated with poor clinical outcomes. In addition, there was a strong correlation between expression of the D-dimer level as a marker of thrombin generation, and tumor load, number of metastatic sites, progression kinetics, and concentrations of IL-6 and VEGF. This study confirms a strong association between thrombin generation, angiogenic factors, and poor clinical outcomes. Thus, high levels of tissue factor activate the coagulation cascade and the secretion of proangiogenic factors, contributing to cancer-associated VTE.

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Prevention and Management of Venous Thromboembolism

Craig M. Kessler, MD

Malignancy is associated with complications, many of which are caused by medications, chemotherapy, or radiation therapy. The incidence of hypercoagulable events, in the context of carcinoma, has become an increasingly recognized issue for patients. In fact, the incidence of thrombotic complications in cancer patients is quite high and is associated with significant morbidity.[1,2]

Thrombotic complications have some role in the mortality events in cancer patients. This information comes indirectly from the analysis by Levitan and colleagues of Medicare records in hospitalized older adults with VTE alone or VTE and cancer.[3] This study is retrospective and needs prospective validation, but a strength is that it includes many thousands of patients. The study found that within 183 days of initial hospitalization, there was a 0.29 probability of death for patients with VTE alone compared with 0.94 probability of death for patients with cancer and VTE (P=.001).

The question becomes: Is the cancer driving the mortality of these patients by increasing the risk of VTE, and does that VTE directly lead to death? Alternatively, does the presence of the VTE complication affect the actual biology of the malignancy, due to the thrombin that is generated in a thrombotic complication?

According to the available epidemiologic data, patients with cancer have a much higher incidence of VTE, but it does not appear that the presence of VTE per se causes death. It is more likely that the aggressiveness of the tumor is being fueled by the presence of the clot. Numerous small clinical trials suggest that patients with unaggressive malignancies who have evidence of thrombotic complications have a much greater rate of eventual metastatic disease and shorter survival time.[4,5] Perhaps what we need to do now is to accept this relationship between malignancy and thrombotic complications and begin to focus on how to prevent and treat the thrombotic complications when they arise.

Warfarin Versus Low-Molecular-Weight Heparin

Several seminal trials have changed the standard of care for cancer patients. The study that has received the most scrutiny is the CLOT (Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer) study that was conducted by Lee and colleagues.[6] In this prospective, double-blind, randomized study, patients with cancer presenting with their first VTE complication were treated for 7 days with the low-molecular-weight heparin dalteparin. The patients were then randomized to receive either the oral anticoagulant warfarin (target international normalized ratio of 2.5) or dalteparin. After 6 months, there was a 50% reduction in the occurrence of repeat thrombotic complications in the patients who received the low-molecular-weight heparin. These results indicate the superiority of low-molecular-weight heparin in preventing recurrent VTE in the cancer patient. This study provided the US Food and Drug Administration with the justification to approve dalteparin as an anticoagulant for patients with cancer and VTE.

In an ad hoc analysis of the data, there were no mortality differences when all patients were considered; the mortality rate was approximately 40% in both the low-molecular-weight heparin group and the warfarin group. On the other hand, patients with low-grade, low-stage malignancies who received the low-molecular-weight heparin had a statistically significant increase in survival compared with those patients who received warfarin. This result suggests that once the tumor becomes too widely spread, too active, or too resistant to chemotherapy, the biology cannot be reversed. Conversely, if the tumor is low-grade, low-stage, early in its evolution as an aggressive malignancy, and responding very well to chemotherapy, then intervention with a medication that might alter tumor cell biology may be beneficial.

Prospective data as to whether altering the clot recurrence or decreasing the clot generation will improve survival are limited. In a double-blind study of patients with metastasized or locally-advanced solid tumors without VTE, a 6-week course of the low-molecular-weight heparin nadroparin increased median survival by 1.4 months (median survival was 8 months in treated patients vs 6.6 months in placebo patients).[7] In a subgroup of patients with a life expectancy of 6 months or more at enrollment,

the median survival increased by 6 months (15.4 months for the patients on low-molecular-weight heparin vs 9.4 months for the placebo).

There is no question that the recurrence of a VTE in a cancer patient can be prevented with a low-molecular-weight heparin. In the past, studies of warfarin versus placebo in cancer patients showed, at least in lung cancer, that there is some survival advantage to any kind of anticoagulation.[8] This finding alone should increase the likelihood that an oncologist would prescribe low-molecular-weight heparin or any anticoagulation agent to a cancer patient who has had a clot or to a cancer patient who has not had a clot but is at high risk for clotting because of the underlying malignancy.

Novel Anticoagulants

Although data on the use of oral specific anti-10A and anti-2A anticoagulant drugs in the cancer population are limited, it appears that novel anticoagulants can be used safely in this population. The number of cancer patients who have been included in all categories of VTE is too small to allow any conclusions regarding the efficacy of these treatment options.

Several questions surround the use of the novel anticoagulants. First, we do not know if they will be useful in cancer patients. A key issue with the novel anticoagulants is that they are being compared with warfarin or placebo rather than with low-molecular-weight heparin. The study by Lee and colleagues suggests that low-molecular-weight heparin is better than oral anticoagulants for the prevention of VTE in cancer patients.[6] Without a low-molecular-weight heparin control arm, it remains unclear whether the novel anticoagulants are better than what we currently have available for the prevention of secondary VTE complications in the cancer patient. Therefore, the benefit and efficacy of these agents remain to be seen. In addition, the safety of a new drug is always a concern. In particular, it is unknown whether safety will be sacrificed for VTE efficacy, or if patients will bleed more than they do with warfarin or a low-molecular-weight heparin.

An attractive feature of the novel anticoagulants is that monitoring of laboratory parameters is not required in most of the patient populations that have been studied thus far. It remains to be determined if this monitoring can be avoided in cancer patients. In addition, many of the novel anticoagulants have fewer drug interactions than are seen with warfarin. However, pharmacokinetics of the cancer patient can be affected by concomitant use of certain types of medications, particularly some of the antifungal drugs that are used frequently in this patient population. The metabolism of warfarin can be affected by cotreatment with drugs such as antifungal agents or antibiotics. In addition, warfarin is often influenced by dietary intake of foods that contain vitamin K. In the case of a cancer patient with lapses in eating because of nausea or vomiting, a widely fluctuating international normalized ratio would result. The new anticoagulants are not vitamin K–dependent in their mechanism. Therefore, the dietary intake of cancer patients is not likely to affect the antithrombotic effects.

Future Treatment Approaches

Researchers are studying whether the development of DVT or PE can be prevented in patients with a malignancy that has been associated with a high incidence of VTE. It is currently not known whether avoidance of an initial VTE will eventually alter the survival of patients who are receiving low-molecular-weight heparin.

Limited information is available regarding patient survival. In the PROTECHT (Prophylaxis of Thromboembolism During Chemotherapy) study,[9] patients with all types of solid tumors were randomized to receive either no treatment or the low-molecular-weight heparin nadroparin. There was no difference in the survival of these patients, nor was there any marked decrease in the incidence of VTE. It is important to note that the incidence of VTE was extremely low in both groups, which may reflect an inaccurate interpretation of the data. The statistical significance for use of the low-molecular-weight heparin approached .05, but it was calculated using a 1-tailed T-test instead of a 2-tailed T-test. It is questionable whether it provides an accurate statistical perspective of what was happening in the study. Perhaps most useful from this study is the breakdown of the patient populations that received the low-molecular-weight heparin. The patients with lung cancer or gastrointestinal cancer who received the low-molecular-weight heparin had a decrease in the incidence of their first DVT or PE. Importantly, these are the malignancies associated with a higher incidence of DVT and PE complications. Several smaller studies suggest a similar finding with pancreatic cancer. For example, in the FRAGEM (A Phase II Randomized Study of Chemo-Anticoagulation [Gemcitabine-Dalteparin] Versus Chemotherapy Alone [Gemcitabine] for Locally Advanced and Metastatic Pancreatic Adenocarcinoma) study, the incidence of VTE complications in patients with pancreatic cancer and gastrointestinal cancer was decreased when patients received low-molecular-weight heparin.[10] In fact, there was some hint that survival may also be improved, although more information is required for complete interpretation.

Conclusion

Future treatment approaches must be expanded in the VTE realm. If long-term survival of the cancer patient can be improved with the use of an anticoagulation medication alone, as indicated by the Levitan[3] and Klerk[7] trials, then survival may be affected almost as much as it is by chemotherapy agents. For example, a 20% increase in survival time (an increase of 2 to 3 months) is almost as good as the increase seen with much more expensive chemotherapy agents, which have produced 1 or 2 months of increased survival.

In addition, palliative care may play a bigger role in the future. A recent study by Temel and coworkers[11] demonstrated that cancer patients who were placed into early palliative care integrated with standard care had a better quality of life with a longer median survival time than those patients who received standard care only. In the realm of palliative care, the addition of low-molecular-weight heparin, novel anticoagulants (once they become available), or even oral anticoagulation may be beneficial.

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Recommendations for the Oncologist

Alok A. Khorana, MD, Howard A. Liebman, MD, and Craig M. Kessler, MD

There are a number of recommendations that oncologists and health care providers should keep in mind when treating cancer patients. There should be an increased awareness of the high risk of thrombosis in cancer patients, as well as of the high incidence of symptoms in cancer patients that could be linked to "unexpected" PE.[1] Patients who have these unexpected PEs are more likely to complain of fatigue, shortness of breath, and cough. Therefore, oncologists should be sensitive to the fact that patients' symptoms may not be related to the cancer treatment, but to PE.

It is very important for oncologists to understand the risk of VTE, and to communicate that risk to patients. In a recent survey of cancer patients receiving chemotherapy, the majority of patients were unaware that they were at high risk for VTE.[2] They were also unaware of the warning signs and symptoms of clots, such as leg swelling, sudden chest pain, and shortness of breath. These results indicate that oncologists need to improve communication with their patients regarding the risk of DVT or PE, particularly with patients about to start chemotherapy. Although most oncologists discuss side effects such as the risk of infection, hair loss, fatigue, or anemia that may occur in chemotherapy, the risk of VTE is often neglected. Clinicians should be careful to mention the risk of VTE during the initial discussion about the side effects of treatment.

Changes in treatment recommendations are also important to keep in mind. Optimization of VTE treatment in the cancer population is important for effective patient care. Clinical trial data indicate that the best treatment for blood clots in patients with cancer is not warfarin, which is the old standard, but extended duration (up to 6 months) of low-molecular-weight heparin.[3] This recommendation is supported by guidelines from the American Society of Clinical Oncology[4] and the National Comprehensive Cancer Network.[5] Moreover, the standard of care for cancer patients with VTE should be changed accordingly. Unfortunately, for logistical reasons or because of concerns about patient perception, those guidelines are not being followed as well as they should be. It is important to note that except for the prevention of clots, or the prevention of recurrent clots, there are currently no data to support the use of anticoagulants to improve the survival of cancer patients. As of yet, no studies have definitively shown that use of an anticoagulant has a strong impact on cancer outcome.

In addition, oncologists should be aware that there are settings in which prophylaxis has successfully reduced the rate of clots. In particular, patients who are hospitalized due to an acute medical illness (eg, infection, pneumonia, or febrile neutropenia) or complications of treatment would benefit from prophylaxis unless contraindicated. Typically, contraindications include either active bleeding or a platelet count less than 50,000/mm^3. Other than those risk factors, most patients should be candidates for prophylaxis. This approach is not oncology-dependent, although oncologists can be advocates of prophylaxis. It is a health system issue, and all health systems must have a VTE protocol in place for appropriate prophylaxis of indicated patients. In fact, many leading organizations describe this tactic as the number one safe practice that can be done for patients in the hospital. This approach is particularly important for cancer patients, who are often at a high risk of developing clots when in the hospital. In particular, compliance with prophylaxis should be a priority for hospitalized patients with cancer, surgical patients with cancer, and selected cancer outpatients.

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Question and Answer Forum

Is there anything that patients can do to minimize their chances of developing VTE?

Alok A. Khorana, MD In cancer outpatients, the risk of VTE is driven by cancer and treatments, rather than patient lifestyle factors. Although regular exercise and a healthy BMI are beneficial, once a patient has cancer, it is hard to control for those risk factors. It is very important that patients be counseled regarding the signs and symptoms of DVT or PE. Many clots are found incidentally despite the presence of symptoms, such as fatigue and shortness of breath, that are often attributed to the underlying cancer. Therefore, if patients experience a new onset of chest pain, shortness of breath, a pleuritic type of chest pain, blood streaks in the sputum, or lower extremity swelling, they should know to call their oncologist or primary care doctor immediately.

Which biomarkers are most useful for clinicians today?

Alok A. Khorana, MD Elevated platelet and leukocyte counts and low hemoglobin levels are highly predictive of the risk for cancer-associated VTE. In fact, these are easy laboratory tests that every cancer patient receives, particularly at the start of chemotherapy. Assays for C-reactive protein and D-dimer levels are also readily available and easily accessible. Tissue factor and P-selectin are promising biomarkers for VTE. However, it should be noted that these latter biomarkers are preliminary and require further validation in larger studies.

Howard A. Liebman, MD There are several studies in lung cancer, breast cancer, and other tumors that show that patients with elevated D-dimer levels have significantly worse outcomes.

Is there risk associated with anticoagulant treatment?

Alok A. Khorana, MD Cancer patients with VTE are at an increased risk for bleeding complications compared with patients without cancer. Anticoagulation treatment increases the risk of bleeding to as high as 12% in patients with cancer and VTE compared with 5% in patients with VTE and no cancer. Most bleeding incidences occur during the first month of anticoagulation.

Howard A. Liebman, MD The use of anticoagulants, particularly low-molecular-weight heparin, may improve the survival of patients with cancer, but it may also increase the risk of bleeding complications. At this time, prophylaxis cannot be recommended to improve survival of cancer patients who do not have a history of VTE.

Craig M. Kessler, MD In the CLOT study, there does not seem to be much difference in the bleeding incidence of patients who receive anticoagulation with chemotherapy versus patients who do not receive anticoagulation with chemotherapy. Bleeding, although potentially problematic, can be minimized by careful selection of patients who will receive anticoagulation. Close observation of patients is also necessary.

Why are some oncologists resistant to use anticoagulation in their cancer patients?

Craig M. Kessler, MD Surveys have indicated that the oncologist is much less likely to use anticoagulation for rethrombosis purposes in the cancer patient than, say, a cancer surgeon is. This difference may be because managing a cancer patient receiving active chemotherapy is very difficult when anticoagulation is used at the same time. Many chemotherapies induce thrombocytopenia and bone marrow suppression; therefore, it is much more difficult to monitor and manage the patient on anticoagulation. However, the CLOT study demonstrated that low-molecular-weight heparin could be dosed in such a way that when the patient's platelet count decreased, the dose of the low-molecular-weight heparin was also decreased. If the platelet level dropped too low, then the low-molecular-weight heparin was discontinued until the patient's platelet count recovered. In certain malignancies, titrating the low-molecular-weight heparin will be more difficult. For example, in hematologic malignancies, the thrombocytopenias are typically more intense and more prolonged following chemotherapy regimens. In contrast, solid tumor malignancies may be associated with thrombocytopenia that is less intense or shorter. In the future, patients with myelosuppression induced by chemotherapy may benefit from thrombopoietin drugs that can stimulate the growth of platelets, allowing the continuation of an anticoagulation regimen concurrent with chemotherapy.

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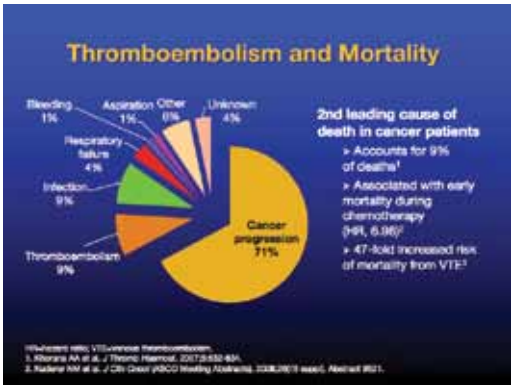

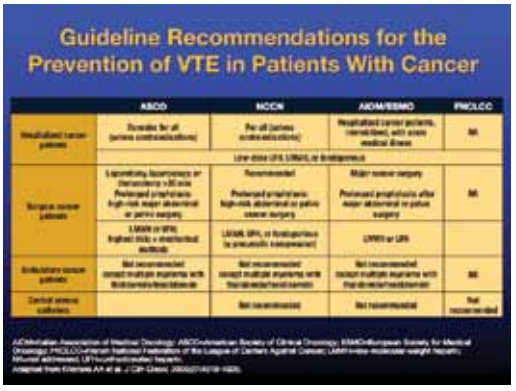

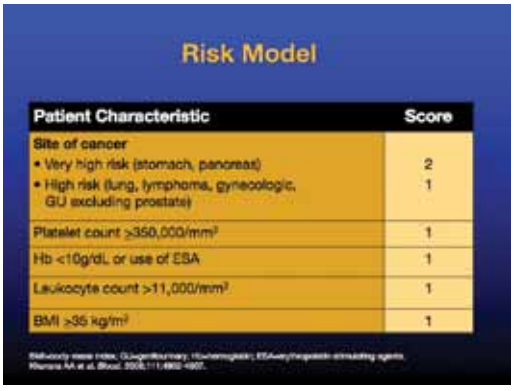

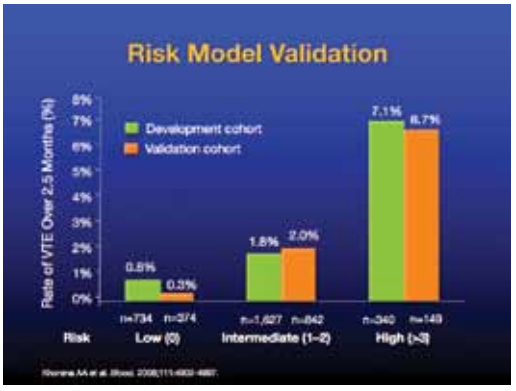

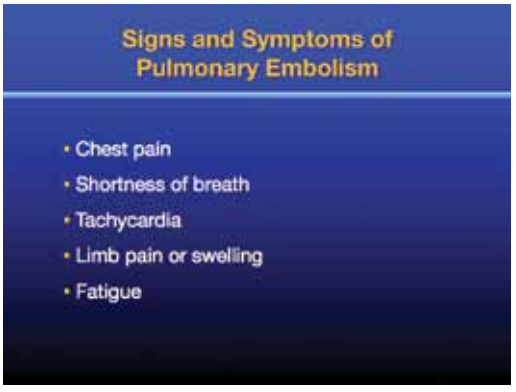

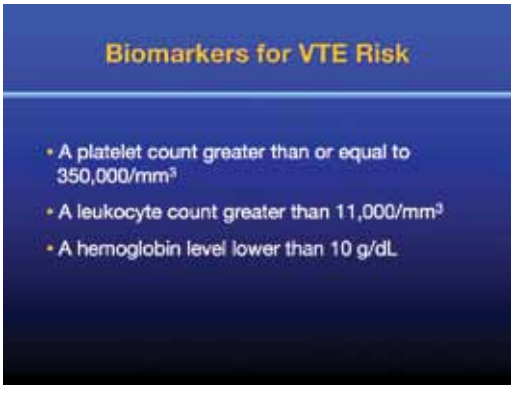

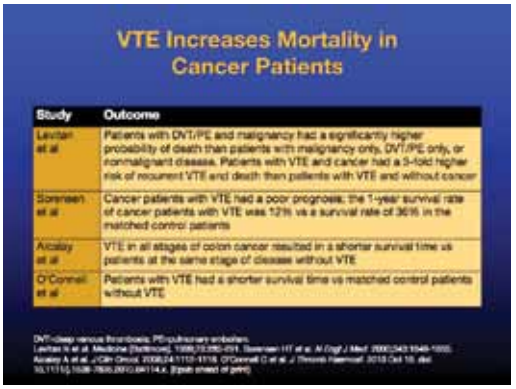

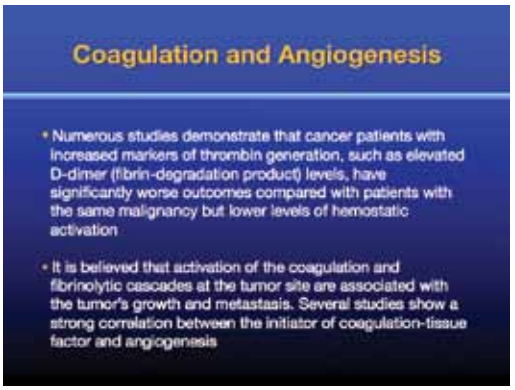

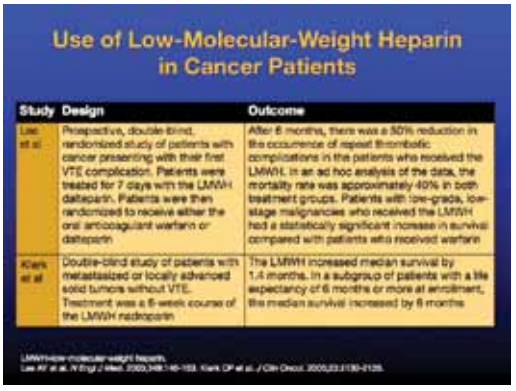

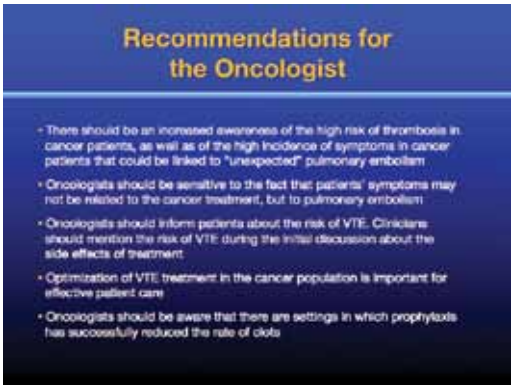

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