ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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The Role of the Oncologist in the Management of VTE

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

H&O What is the incidence of venous thromboembolism (VTE) in patients with cancer?

AK VTE in cancer patients is an increasing problem. We have known about the association between VTE and cancer for more than a hundred years. In the past 10 or 15 years, there has been a fairly dramatic increase in incidence. That increase is partly related to the newer drugs that we are using; some of the current chemotherapy regimens are more thrombogenic than older regimens, as are some of the newer classes of drugs, such as antiangiogenic agents. In addition, multidetector computed tomography, in use since the late 1990s, is more sensitive than previous technologies in identifying clots. Oncologists are seeing much more of this complication than we used to. Some estimates suggest that up to 1 in 5 cancer patients will develop VTE at some point during the natural history of their illness. There are subgroups of cancer patients who are at much higher risk than others.

H&O Does VTE influence outcome in cancer patients?

AK There are several clinical consequences to VTE. The association between VTE and mortality is the most important. Pulmonary embolism (PE), a consequence of VTE, can of course be lethal. The presence of an untreated or unprevented PE is believed to be the number one cause of preventable death among hospitalized patients in the United States. My colleagues and I performed an analysis in which we asked oncologists to indicate the causes of death in their patients. Among approximately 4,000 reported deaths, nearly 1 of 10 were related to a thromboembolic event. Cancer, obviously, was the most frequent cause of death in these patients. But the second most common causes, with about equal rates, were thrombosis and infection. VTE is therefore certainly a proximate cause of death in cancer patients.

The second concern with outcomes is the indirect association with mortality. Even if a patient with a VTE does not die from a PE, he or she in general tends to do worse than patients who do not have a VTE. Among patients with the same cancer, matched for state and type of chemotherapy, those who develop a clot are likely to do worse than patients who do not. It may be that having a clot is a surrogate for having a more aggressive cancer, or it may be that the clot itself contributes to mortality, or there may be other associations that we do not quite understand yet. The link between clots and mortality has been proven in several large population studies.

Another set of consequences is related to the presence of the clot itself. A patient with a blood clot must receive a blood thinner. Despite administration of standard therapy, however, cancer patients have very high rates of recurrent VTE. The presence of one blood clot increases the risk of having a second blood clot. Paradoxically, the presence of a clot also increases the risk of bleeding. Cancer patients are more likely to bleed while taking anticoagulants than are patients without cancer.

Finally, there are consequences to the healthcare system. In a study by Elting and colleagues at M.D. Anderson Cancer Center, the cost of treating outpatients with deep vein thrombosis or PE was in the range of $14,000–$18,000 per patient.

H&O Are there factors that are common to both coagulation and angiogenesis?

AK Investigators have been focusing on clinical data showing that cancer patients who develop clots are more

likely to have poor outcomes. They have found that the activation of coagulation is also linked very closely to the activation of angiogenesis. Many known proangiogenic factors are also procoagulant. Many of the natural factors in the body that are antiangiogenic, or that play a role in the regulation of angiogenesis, are also anticoagulant. This association makes sense because physiologically whenever a wound occurs it must first stop bleeding, which is achieved through clotting, and then the body attempts to heal it, which is achieved through angiogenesis. It makes sense that, physiologically, these systems would be very closely interlinked.

An example of this is the molecule called *tissue factor*, which is the physiologic initiator of coagulation. The first step in the coagulation cascade is typically activation of tissue factor. A surprising find of the past 10 years is the role of tissue factor in cancer. Physiologically, it is present only in the lining of blood vessels, which is where it should be. In patients with cancer, however, there is wide expression of tissue factor. Many patients with cancer of the pancreas, colon, liver, or lung, or with malignancies such as leukemias and lymphomas, express tissue factor in malignant tissue. The current belief is that the link between coagulation and angiogenesis exists not because it is advantageous to have a hypercoagulant state—although that might be—but primarily because tissue factor is important for angiogenesis, and it turns out that it causes clots incidentally.

H&O What are the clinical risk factors for VTE in cancer patients?

AK Broadly, there are factors that relate to the patients themselves and also to the type of cancer. Clots are more likely to develop in older patients, sicker patients, and patients with comorbidities, such as lung disease, liver disease, or renal disease. There are some inherited prothrombotic states that might contribute to the risk, but these do not seem to be as important in cancer patients as they are in patients without cancer.

The most important risk factor is the type of cancer. Patients with pancreatic cancer, brain tumors, lung cancer, and lymphoma are much more likely to develop clots than are those with other cancers, such as breast cancer. In addition, treatments such as chemotherapy, antiangiogenic agents, and surgical procedures—as well as hospitalization—substantially increase the risk of VTE.

H&O Are there predictive biomarkers?

AK Until 5 years ago, we did not know of many predictive biomarkers, but this field is emerging. There is now a whole host of candidate biomarkers, and the ones with the most supportive data are also the ones that are easiest to use. Many of these biomarkers are components of the complete blood count. Leukocyte counts and platelet counts are 2 strongly predictive biomarkers. A high leukocyte count is defined as a white blood cell count of more than 11,000/mm^3. A platelet count of 350,000/mm^3 or more increases the risk of a VTE. There is also the suggestion that a hemoglobin level of less than 10 g/dL—anemia—is associated with the risk of VTE, although it is not clear if this association is based on the anemia itself or on the use of erythropoiesis-stimulating agents, which clearly increase risk. There are also good data to support the measurement of D-dimer levels; the higher the level, the higher the risk. However, D-dimers are often elevated in cancer patients, even those without a clot, so the data are not conclusive. Researchers are also examining ways to measure tissue factor in the blood, but this approach is still considered investigational and is not yet ready for clinical use.

Table 1. Predictive Model for VTE Associated With Chemotherapy

Patient Characteristic	Risk Score
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
Prechemotherapy platelet count ≥350 × 10^9/L	1
Hemoglobin level <100 g/L or use of red cell growth factors	1
Prechemotherapy leukocyte count >11 × 10^9/L	1
BMI ≥35 kg/m^2	1

BMI=body mass index; VTE=venous thromboembolism.

Data from Khorana AK et al. *Blood.* 2008;111:4902-4907.

H&O Is there a model that can be used to identify cancer patients at risk of VTE?

AK It is clear that the risks of VTE are multifactorial. My colleagues and I have devised a risk model that incorporates some of the biomarkers as well as some of the clinical risk factors. The patients are assigned a score based on their particular risk factors (Table 1); patients who have a combined score of 3 or more are at very high risk of developing VTE.

This model was studied in a population of approximately 3,000 patients and then verified in an additional 1,000 patients, so it underwent split-sample validation. The data have now been confirmed by other investigators. In a large registry of close to 1,000 patients in Vienna, researchers applied our risk model and found an identical grouping of risk stratification. This model has been validated and is ready to be used, whether in the clinic or at the bedside.

H&O What are the current and future approaches for prevention and management?

AK For prevention of VTE, there are several very large ongoing clinical trials studying use of prophylaxis in high-risk cancer patients identified with the risk model I have described. Other trials are studying prophylaxis in patients with high tissue factor levels. Semuloparin is an ultra-low-molecular-weight heparin currently being studied in a large-scale trial of more than 3,000 patients. Those results should be available early next year.

For treatment of VTE, the best data suggest that patients should receive low-molecular-weight heparins (LMWHs) for an extended period of time. This recommendation is based on a large, randomized study as well as several other smaller randomized studies that all point to the same conclusion: cancer patients who receive LMWH for at least a 6-month period have a much lower risk of VTE than patients who receive warfarin, which is considered by many physicians to be the standard of care.

For the future, there are a number of novel anticoagulants that are just starting to hit the market. Some of these novel agents have been approved in Canada and Europe, but so far none have been approved in the United States. They have not yet been included in large-scale studies in the cancer population, but our hope is that in the near future, we will see these new agents become available and provide additional options for cancer patients.

H&O Should certain patients be referred to specialists in coagulation disorders?

AK Referral is seldom necessary. If a patient has recurrent clots while receiving LMWH, I would refer him or her to a hematologist, to follow factor Xa levels. Patients with severe renal deficiency or other complicated comorbid conditions might best be managed in a specialized setting.

H&O Can treatment of these patients be improved?

AK Despite the evidence showing that extended therapy with LMWH is the best approach, both in terms of safety and efficacy, this strategy has not been adopted as rapidly as we had hoped. Currently, guidelines from the National Comprehensive Cancer Network recommend that extended-duration LMWH therapy be used to treat these patients. It is hoped that oncologists will adopt that paradigm.

Suggested Readings

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