ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

Section Editor: Craig M. Kessler, MD

The Incidence of Venous Thromboembolism in Cancer Patients: A Real-World Analysis

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H&O Are cancer patients at greater risk of developing a venous thromboembolism (VTE)?

GL The association between cancer and VTE has been known for more than a century, but only recently has the magnitude of the risk of VTE in cancer patients begun to be recognized. The risk of developing a blood clot in the deep venous system of the legs is about two-fold to four-fold higher in cancer patients than in the general population. Deep venous thrombi can dislodge, usually from a peripheral vein, and embolize to the lung. Not infrequently, a pulmonary embolism is fatal. Treatment of a blood clot while it is still in the legs or in the more peripheral veins can reduce this risk of pulmonary embolism.

H&O How is VTE in cancer patients managed?

GL VTE in patients with or without cancer is treated with anticoagulants, which are associated with an increased risk of bleeding. Cancer patients may already have an increased risk of bleeding, due to low platelet counts or factors associated with the tumor, recent surgery, or chemotherapy. Therefore, treatment of cancer patients with anticoagulants involves a careful balance between benefit and risk. Current guidelines recommend that, whenever possible, patients with cancer who develop a VTE should be treated with a low-molecular-weight heparin for several weeks at least. The American Society of Clinical Oncology (ASCO) VTE Guidelines recommend that treatment be continued up to 4–6 months after the initial event, to prevent a recurrence. Following a VTE, patients with active cancer should be considered for continued anticoagulation therapy for secondary prophylaxis, even after cancer treatment has ended.

H&O Which patients should receive prophylaxis, and how is it administered?

GL Hospitalized patients are at increased risk for VTE and its complications due to bed rest, surgery, or other interventions. Current guidelines encourage VTE prophylaxis of hospitalized patients with cancer, usually a low-molecular-weight heparin. It has also become routine to begin prophylaxis with an anticoagulant, either before or immediately after surgery, to prevent VTE complications.

A more challenging issue in the cancer population is how to manage outpatients, such as ambulatory patients receiving chemotherapy. In general, the risk that these patients will develop a VTE is not as high as in the inpatient or the surgical setting. There is no recommendation that ambulatory cancer patients should receive routine prophylactic anticoagulation, with the exception of selected patients with multiple myeloma. What has become apparent, however, is that among ambulatory cancer patients, there is a higher risk subgroup that, because of their treatment, type of cancer, or other medical conditions, are at even greater risk than the average cancer patient in the outpatient setting.

Table 1. Predictive Model for Chemotherapy-Associated VTE

Patient Characteristic	Risk Score
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
Prechemotherapy platelet count ≥350,000/mm^3	1
Hemoglobin <10 g/dL or use of red cell growth factors	1
Prechemotherapy leukocyte count >11,000/mm^3	1
Body mass index ≥35 kg/m^2	1

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

When reassessing the risk of patients in the outpatient setting, we consider the type of cancer, the patient's overall status, and the type of treatment. Cancers that carry a higher risk of VTE include gastrointestinal cancers—particularly pancreatic and gastric cancers—lung cancer, ovarian cancer, and lymphomas. There is ongoing investigation as to whether the risk associated with some of these newer biologic therapies, particularly antiangiogenesis agents, might place patients with cancer at greater risk for VTE. There has been concern in recent years about the risk of VTE associated with some of the new antiangiogenesis therapies for cancer. For example, thalidomide and lenalidomide (Revlimid, Celgene), when combined with high-dose dexamethasone or chemotherapy, seem to be associated with a greater risk of VTE. Most guidelines recommend consideration of prophylactic anticoagulation in multiple myeloma patients receiving thalidomide or lenalidomide in this setting.

We recently developed and validated a risk model to help identify those patients with a higher risk of VTE (Table 1). We are conducting a National Institutes of Health (NIH)-funded trial in which we are studying whether ambulatory cancer patients at higher risk of VTE according to this risk model should be prophylaxed with a low-molecular-weight heparin, based on the balance between the benefit of preventing blood clots and what is probably a small increased risk of bleeding from anticoagulation in that setting.

The primary concern associated with deep vein thrombosis is that blood clots will embolize to the lung, the brain, or another critical location that will prove life-threatening. In addition, cancer patients who develop a VTE are at greater risk for recurrence whether or not they receive any prophylactic anticoagulation. An important study published in the *New England Journal of Medicine* by Agnes Lee found that cancer patients who were randomized to a low-molecular-weight heparin for their VTE had a 50% reduction in the risk of recurrence, compared to the traditional warfarin.

H&O Are there any theories regarding the association between VTE and cancer?

GL The role played by the clotting system in the development and progression of cancer constitutes an active area of basic and translational research. Tissue factor and various cytokines appear to play a role in the increased risk of VTE. Several studies have examined whether the administration of anticoagulants to cancer patients—even those without a history of VTE—might have a direct or indirect impact on the cancer itself and constitute a form of treatment for cancer or prevent the spread of disease. Although some of these studies have shown positive results, there is no consensus about the overall value of administering anticoagulants, in the absence of documented VTE, as a form of cancer treatment. Additional studies are ongoing.

H&O What was the impetus for your recent study on the incidence of VTE in cancer patients?

GL There have now been at least 8 randomized trials of VTE prevention in outpatients receiving cancer chemotherapy. Most of the studies have shown some reduction in the risk of VTE, although often this decrease has been too small to be statistically significant. Meta-analyses have shown that there is a significant reduction in the relative risk of VTE with the low-molecular-weight heparins given prophylactically to cancer outpatients. However, the risk of VTE, even in the control groups (the patients who did not receive prophylactic therapy) has been quite low in these studies, with an average of approximately 5%. This finding raises the question of whether the patients in these trials were truly representative of cancer patients, or whether the true rate of VTE in cancer patients might be greater. We know that patients in randomized controlled trials are often highly selected, with patients often excluded if they have serious medical problems or abnormal laboratory values. Therefore, we wanted to examine the risk of VTE in unselected ambulatory cancer patients initiating chemotherapy in a setting closer to the real world.

Our study was presented at the 2011 meeting of the European Society of Medical Oncology. We obtained data from a large, US-based integrated health care information system on patients treated between early 2005 through the

end of 2008. The incidence of VTE was assessed after 3–4 months and after 1 year. We chose cancers that were very similar to those seen in the SAVE-ONCO (Evaluation of AVE5026 in the Prevention of Venous Thromboembolism in Cancer Patients Undergoing Chemotherapy) trial of a new anticoagulant, semuloparin (namely, lung cancer, gastric and pancreatic cancer, colon cancer, colorectal cancer, bladder cancer, and ovarian cancer). Results of the SAVE-ONCO trial were reported at the 2011 ASCO meeting and updated at the 2011 annual meeting of the American Society of Hematology. Although this trial demonstrated a significant reduction of VTE in the outpatient setting, the rate of VTE observed in the study population was low.

H&O What were your findings?

GL We observed considerably higher rates in the real-world sample of patients in the large database of patients treated across the United States. These patients had a risk of VTE that ranged from 5% to more than 11% at 3–4 months, and increased to 15% and up to more than 20% at 1 year after the start of treatment. The risks were greatest, as one might expect, in certain cancers, such as pancreatic cancer and gastric cancer. In patients with lung cancer, the rates ranged from approximately 10–15% at 1 year. If these data are confirmed, it would suggest that patients selected for the randomized controlled trials may not be representative of the risk in real-world cancer patients, where the actual rates of VTE may be two- to three-fold greater.

It should be noted that our study findings are based on retrospective data, whereas the gold standard for demonstrating the benefit of treatment or prophylaxis remains prospective, randomized trials. Nevertheless, our study raises the possibility that in the real-world setting—in community practice, where most cancer patients are treated—the risk of VTE complications is considerably greater than what the clinical trials have suggested. This finding is critically important to decision-making. With rates of 3%, 4%, or 5%, it is difficult for oncologists to consider giving all patients anticoagulation for the small number that might benefit. However, if those rates are 10%, 15%, or 20%, then prophylactic anticoagulation becomes a more reasonable option to discuss with patients. Nevertheless, these data must be confirmed with other population data. These data should then be subjected to a randomized controlled trial in a real-world setting, to see if this higher rate of observed VTE can be significantly reduced with prophylactic anticoagulation. For now, the increase in observed rates in the general population, as compared to what has been seen in most of the randomized trials, suggests that we have been underestimating the risk of these complications and the potential benefit of prevention.

H&O When are new guidelines expected?

GL Guidelines from the European Society for Medical Oncology and the National Comprehensive Cancer Network have recently been updated, and we are currently in the process of updating the VTE guidelines for ASCO, reviewing all the new data from the past few years. VTE prophylaxis in cancer patients is a rapidly evolving field, with emerging new agents that will have to be carefully evaluated for benefit and safety in the cancer setting. In the coming years, we hope to have more effective, safer, and even easier-to-administer treatments. And, we also hope to determine which patients require VTE prophylaxis and when prophylaxis should be administered, in an effort to prevent these life-threatening complications.

Suggested Readings

Agnelli G. 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* (2011 ASCO Annual Meeting Proceedings). 2011;29:504s. Abstract #LBA9014.

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Lyman GH. Thromboprophylaxis with low-molecular-weight heparin in medical patients with cancer. *Cancer.* 2009;115:5637-5650.

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