

ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

Section Editor: Craig M. Kessler, MD

The NCCN Guidelines on Venous Thromboembolism

Michael B. Streiff, MD
Director, Anticoagulation Management
Service and Outpatient Clinic
Staff Physician, Johns Hopkins Comprehensive
Hemophilia Treatment Center
Assistant Professor of Medicine,
Johns Hopkins University
Baltimore, Md.

H&O What are risk factors for deep vein thrombosis and pulmonary embolism?

MS Deep vein thrombosis (DVT) and pulmonary embolism (PE) are different manifestations of the disease entity known as venous thromboembolism (VTE). Cancer is a potent risk factor for VTE and the associated risk increases with the extent of disease. Thus, patients with localized disease have lower risk than patients with regional disease (eg, lymph nodes), who, in turn, have lower risk than patients with distant metastatic disease. Other VTE risk factors common among cancer patients include chemotherapy and central venous catheters, which are often placed in patients with cancer to facilitate administration of medicines and blood products. Inherited (eg, Factor V Leiden and others) or acquired thrombophilia (eg, antiphospholipid antibody syndrome), major surgery, major trauma, pregnancy, estrogens, and prolonged immobilization (greater than 3 days of bed rest) are other common risk factors for VTE. Finally, I think it is important not to forget the impact of age on the incidence of VTE. Blood clots are uncommon in children and young adults. During adult life there is a gradual increase in the incidence of VTE until age 50, after which there is a steep rise in incidence such that the risk of VTE among patients age 80 and older is approximately 1 per 1,000 population. The reason for this dramatic increase in the incidence of

VTE with older age is not entirely clear but age-related increases in coagulation factor levels and an increased prevalence of cancer, major surgery, and hospitalization has been implicated.

H&O Does the risk of VTE vary between solid-tumor malignancies and hematologic malignancies?

MS It has been well recognized among members of the medical community that solid tumors are associated with an increased risk of VTE since Dr. Armand Trousseau first made this observation in the 1860s. However, I think it is much less widely recognized that patients with hematologic malignancies such as lymphoma and leukemia are also at high risk of VTE. Several recent observational studies have documented this high risk. For instance, Blom and colleagues found that risk of VTE was high not only among patients with malignancies thought traditionally to be at high risk of VTE such as lung cancer (adjusted odds ratio 22.2) and gastrointestinal cancers (odds ratio 20.3) but also among patients with hematologic cancers (adjusted odds ratio 28). Similar findings have been noted by other investigators. Therefore, we need to think about patients with hematologic malignancies as being at high risk for VTE and begin to make sure that these patients, as well as patients with solid tumor malignancies, are receiving appropriate measures to prevent VTE.

H&O What were the circumstances that led to the National Comprehensive Cancer Network issuing its clinical practice guidelines on VTE?

MS The National Comprehensive Cancer Network (NCCN) is an alliance of 20 comprehensive cancer centers across the United States with the goal of developing the highest standards of clinical care for patients with cancer. To achieve this goal, the NCCN has developed clinical practice guidelines to establish standards for the diagno-

sis and treatment of patients with cancer. In light of the common association between cancer and VTE and the significant morbidity and mortality suffered by patients with thrombosis, the NCCN organized a consensus panel of clinical experts from member institutions chaired by Dr. Lawrence Wagman in the Fall of 2005 to develop an evidence-based management guideline for VTE in cancer patients. After a series of meetings and teleconferences, the first version of the NCCN VTE guidelines was finalized and unveiled at the NCCN annual conference in March 2006. A second version of the guidelines including additional topics in VTE is currently being edited. These guidelines represent a consensus and evidence-based approach to what our expert panel felt was the best available approach to the prevention and treatment of VTE. The VTE guidelines are available online at the NCCN's website, <http://www.nccn.org>, under Clinical Practice Guidelines in Oncology, Guidelines for Supportive Care.

H&O Can you discuss what the guidelines recommend for the prevention of VTE?

MS A major part of the guidelines concerns prevention of VTE. All medical or surgical patients with a cancer diagnosis or a suspicion of cancer should be assessed for risk factors for VTE and then receive risk-stratified VTE prophylaxis. In order to prescribe the appropriate form of prophylaxis, physicians should assess their patients for the presence of risk factors for bleeding. In patients at high risk for bleeding, mechanical prophylaxis (eg, sequential compression devices) should be prescribed. Otherwise, pharmacologic (anticoagulant) prophylaxis should be employed as there are more data supporting the effectiveness of pharmacologic VTE prophylaxis and compliance is much less problematic.

H&O Can you discuss the different pharmacologic anticoagulants available?

MS For VTE prevention, we recommend the use of either unfractionated or low molecular weight heparin (LMWH) or fondaparinux. The LMWHs available in the United States include dalteparin, enoxaparin, and tinzaparin, each of which is administered subcutaneously once daily. In high-risk patients such as those with cancer, unfractionated heparin is generally administered three times daily at a dose of 5,000 units. Fondaparinux, a pentasaccharide, is administered at a dose of 2.5 mg subcutaneously once daily. These agents should be administered according to the needs of individual patients and the institutions' own guidelines. Cost and ease of administration, as well as presence of kidney disease, should factor into decisions on what agent to use. Additionally, risks for each drug

should be considered, as some are more reversible than others and some have a higher risk of an uncommon side effect of heparin-based anticoagulants, heparin-induced thrombocytopenia (highest with unfractionated heparin, rare with LMWH, never reported with fondaparinux). In a bleeding situation, unfractionated heparin is the most reversible, with the shortest half-life. LMWH has a longer half-life than unfractionated heparin, but it is partially reversible with protamine. At the other end of the spectrum, fondaparinux is not reversible by protamine and has a 17-hour half-life.

These same drugs can be used for acute treatment of VTE. In the guidelines, we discuss the efficacy of the three drug classes based on data from studies. It is important to note that with unfractionated heparin, the laboratory therapeutic range should be correlated with heparin levels and weight-based doses should be used, rather than a fixed therapeutic range. Both LMWH and fondaparinux can be used without therapeutic monitoring. For long-term therapy, several studies over the last 10 years, including the largest and best-designed study, conducted by Dr. Agnes Lee and colleagues, showed that dalteparin is more effective for chronic therapy of VTE in cancer patients than vitamin K antagonists such as warfarin. In the CLOT trial reported by Dr. Lee, all patients received dalteparin for acute therapy and then were randomized for 6 months to either dalteparin or warfarin adjusted to the usual therapeutic range. There were approximately half as many episodes of recurrent VTE in the dalteparin-treated patients (9%) as there were in the warfarin group (17%), with no significant difference in bleeding events. As a result, the NCCN guidelines recommend the use of LMWH, in particular, dalteparin, for the chronic treatment of VTE in patients with advanced cancer. Because cancer patients remain at high risk for recurrent VTE as long as they have active cancer, antithrombotic therapy should continue until the cancer is eliminated or for a duration appropriate for the thrombotic event, whichever is longer. As medication cost remains an important issue for patients and physicians, it is essential to take this factor into consideration when making treatment plans for individual patients.

H&O What is the role of imaging in the diagnosis and risk stratification of VTE?

MS For DVT diagnosis, venous duplex imaging is the standard. Venograms are rarely performed today because they are more invasive, although they may be useful in some situations. Although use of D-dimer testing in conjunction with use of a clinical prediction model such as the Wells model is beginning to be applied to the diagnosis of VTE in noncancer patients, this approach remains

controversial in cancer patients and so diagnosis of VTE in cancer patients remains largely based upon diagnostic imaging. For PE diagnosis, the primary imaging modalities recommended by the NCCN guidelines are computed tomography (CT) angiography or ventilation perfusion scanning. If the index of diagnostic suspicion is high but CT angiography is negative, a duplex study of the lower extremities can be useful to rule out the presence of VTE. When managing patients with PE, it is important to assess patients' risk for adverse outcomes as not all patients with PE are at the same risk of complications. Dr. Samuel Goldhaber and others have used imaging studies such as echocardiography or CT angiography and cardiac biomarkers such as troponin and brain natriuretic peptide to assess PE risk status in patients with PE. Clinical prediction rules, such as the Geneva PE rule, can also be used to risk stratify PE patients. These tools are useful to identify patients who may need more aggressive therapy, such as thrombolytic therapy, or patients who are at low risk and may be managed as outpatients after an initial hospital stay. Because not all PE patients are alike, the NCCN guidelines recommend that PE risk stratification be incorporated in the management of cancer patients with PE.

H&O Can you describe the relevance of central venous catheters and vena caval filters to VTE?

MS Central venous catheters are a common cause of upper extremity DVT in cancer patients. Anticoagulation is the mainstay for treatment of catheter-associated DVT and should be continued for as long as the catheter is in place and up to 1–3 months after catheter removal. Central venous catheters need not be removed solely because a DVT has developed unless the catheter is no longer needed or symptoms of venous stasis fail to resolve with anticoagulation. Use of thrombolytic agents may be considered for patients with particularly symptomatic

limbs. Superficial venous thrombophlebitis can be managed with nonsteroidal anti-inflammatory medications or anticoagulation depending on the location and severity of symptoms. It is particularly important to consider the entity of Trousseau syndrome in cancer patients with recurrent episodes of migratory thrombophlebitis, as this entity responds only to heparin anticoagulation.

Although anticoagulation is the therapy of choice for the vast majority of cancer patients with VTE, vena caval filters are a useful alternative for patients who have an acute episode of VTE and anticoagulation is contraindicated. As vena caval filters do not treat the underlying thrombotic process, it is important to employ anticoagulation as soon as the contraindication is no longer present. Advice on the treatment of catheter-associated DVT, superficial venous thrombophlebitis, and indications for the use of vena caval filters in the treatment of VTE in cancer patients are also included in the NCCN guidelines.

Suggested Reading

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