Understanding Venous Thromboembolism in Patients with Cancer

Idongesit Udoh, DNP, ACNP-BC

ABSTRACT

Venous thromboembolism (VTE) is 1 of the most common complications from cancer and its treatments. It can manifest as a deep vein thrombus or pulmonary embolism in all stages of cancer. Therefore, the purpose of this article is to discuss the ways in which cancer predisposes patients to VTE and the diagnostic and management options available. The article further discusses the importance of anticoagulation as a mainstay of therapy for the prevention and management of VTE and the implications for practice.

Keywords: anticoagulation and cancer, anticoagulation and venous thromboembolism, diagnosis and management of venous thromboembolism, venous thromboembolism and cancer

Venous thromboembolism (VTE) describes a continuum consisting of deep vein thrombosis (DVT) and pulmonary embolism (PE). It is 1 of the most common complications observed in cancer patients throughout various disease stages and across health care settings. The incidence of VTE in patients with cancer is estimated at 1 in 200 patients per year, and approximately 21% of those who had been previously treated will have a recurrence of acute VTE. The rate of recurrence is about 3 times more than what is seen in the general population.[1]

CAUSES OF VTE IN PATIENTS WITH CANCER

The cause of increased incidence of VTE in the cancer population is multifactorial but is largely a result of released procoagulant and factor X—activating cysteine protease from tumor cells as well as compression and invasion of blood vessels by the growing tumor. Cancer treatment such as chemotherapy increases the risk of thrombosis by causing damage to endothelial cells, resulting in the activation of platelets and inflammatory cytokines. Chemotherapy agents such as platinum agents, antimetabolites, hormonal therapy, angiogenesis suppressing agents, and L-aspariginase are more likely to promote thrombosis.[2]

Tumor cells release p-selectin, which mediates platelet adhesion, and also express inflammatory cytokines such as interleukin 6, which activates tissue factor (TF) on the endothelium and monocytes.[3] Elevated levels of TF have been found in patients with cancer, and it is known to contribute to thrombus formation by interacting with the extrinsic coagulation pathway. TF initiates coagulation by binding to and activating factor VIIa to form a complex (TF-VIIa complex), which subsequently activates factor X, leading to thrombin generation. The levels of circulating TF expressed by cancer cells may explain the higher incidence of VTE in certain cancers. For example, pancreatic cancer carries the highest risk of VTE among solid tumors, and some studies have shown higher levels of circulating TF in these patients in comparison with those with other cancers.[4]

In general, hematologic cancers carry the highest VTE risk followed by solid tumors of the pancreas, stomach, lungs, ovaries, uterus, bladder, and brain.[5]

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Some cancers such as that of the prostate and breast carry lower VTE risk. Breast cancer, in particular, is known to have 1 of the lowest risks of VTE, at just 1%. However, the initiation of chemotherapy can increase this risk by up to 6-fold.[6]

The severity of cancer activity also influences the risk of VTE. Patients with metastasis are more likely to have VTE when compared with those with localized disease because the larger tumor burden increases hypercoagulability.[7] The increased incidence of VTE in later cancer stages could also be influenced by treatment toxicity; use of hematopoietic growth factors to counter treatment side effects such as anemia, neutropenia, and thrombocytopenia; and the severity of debilitation resulting in decreased mobility.[8]

Economic Burden of VTE in Patients With Cancer

The morbidity and mortality caused by VTE accounts for a significant portion of the financial burden during hospitalization. Cancer patients undergoing surgery have a higher risk of developing VTE compared with their nonsurgical counterparts, and VTE is the number one cause of death among cancer patients within 30 days postsurgery.[2] Few studies have attempted to shed light on the increased cost of medical care incurred once a patient with cancer develops VTE. One of those studies carried out on patients with lung cancer by Kourlaba et al[9] showed that those who developed VTE had a longer length of hospitalization and incurred 50% more medical cost than those without VTE. The increased cost noted in inpatient settings also translated to outpatient settings; patients with cancer and VTE were noted to have a 20% increase in medical cost compared with those without VTE in outpatient settings.

PREVENTION

The focus of VTE prevention should be both primary (preventing initial occurrence) and secondary (preventing recurrence). Primary prevention will be discussed in this section, whereas secondary prevention will be discussed in the treatment section of this article. The American Society of Clinical Oncology published a comprehensive guideline for the prevention and treatment of VTE in the cancer population in 2007 (Table 1). In this guideline, the American Society of Clinical Oncology recommends that all hospitalized cancer patients and those undergoing major surgery be considered for thromboprophylaxis in the absence of major contraindications to anticoagulation.[10] This recommendation remains the foundation of primary prevention of VTE in the cancer population.

Prevention efforts may be delayed because of concerns for bleeding in the at-risk perioperative

Table 1. Summary of American Society of Clinical Oncology Guidelines for Venous Thromboembolism (VTE) Prevention and Treatment

Patient Groups	Thromboprophylaxis	Recommended Agents and Duration of Treatment
• All hospitalized patients with cancer	Yes	LMWH or UFH for duration of hospitalization
• All outpatients with cancer	No	None
• Outpatients undergoing chemotherapy treatment with thalidomide and lenalidomide with dexamethasone	Yes	LMWH or adjusted dose VKA (international normalized ratio [INR] ~ 1.5) through length of treatment with those medications
• Perioperative patients with cancer	Yes	LMWH or UFH for 7-10 days postoperatively. May continue for up to 4 weeks in very high risk patients after major abdominal or pelvic surgery (those with previous VTE, residual malignant disease, obesity)
• Patients with established VTE	Not applicable (require treatment)	LMWH for 5-10 days initially, can continue for up to 6 months to prevent recurrence. VKA with INR of 2-3 can be used for long-term treatment if LMWH is not available.
• Patients with contraindications to anticoagulation	No	Inferior vena cava filter

LMWH = *low-weight-molecular heparin;* UFH = *unfractionated heparin.*
Data from Lyman et al.[10]