Management of Cancer-Associated Venous Thromboembolism in the Emergency Department

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Patients with cancer are at increased risk of venous thromboembolism, and emergency physicians can play a significant role in addressing one of the leading causes of morbidity and mortality in this patient population. However, there are no comprehensive guidelines addressing the approach to cancer-associated venous thromboembolism in the emergency department. Here, we review the guidelines put forth by various national and international cancer societies and highlight how emergency physicians can help institute appropriate treatment and prevent the recurrence of venous thromboembolism in cancer patients. We also address areas of controversy and highlight topics that require further research. [Ann Emerg Med. 2017;69:768-776.]

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INTRODUCTION

Venous thromboembolism has long been recognized as a leading cause of mortality in cancer patients.[1,2] One recent retrospective study showed that the incidence of venous thromboembolisms in cancer patients ranges from 8% to 19% in the 12 months after initiation of chemotherapy, depending on the tumor type.[3] Furthermore, cancer patients with venous thromboembolism have a 3-fold increase in hospitalizations and a significant increase in both inpatient and outpatient health care costs.[4] The emergency physician is well placed to recognize, treat, and prevent future venous thromboembolisms in cancer patients. In the last 10 to 15 years, there has been a surge in research on the topic of thromboembolic disease in cancer patients. However, there are still fundamental gaps in our knowledge, particularly with respect to the approach that should be taken by the emergency physician. In this article, we will review the various guidelines that have been put forth on the treatment and prevention of venous thromboembolisms. Although the diagnosis of venous thromboembolisms is outside the scope of this review, we will address the topics of the use of direct oral anticoagulants, the relative and absolute contraindications to anticoagulation, the approach to recurrent venous thromboembolisms in patients already receiving anticoagulation, and the evaluation for occult malignancy in unprovoked venous thromboembolism.

MATERIALS AND METHODS

To our knowledge, there is no primary literature addressing the approach to cancer-associated venous thromboembolism in the emergency department (ED). Instead, to develop this set of recommendations, we reviewed the major guidelines put forth by various national and international societies, including the American Society of Clinical Oncology,[5,6] the National Comprehensive Cancer Network,[7] the European Society for Medical Oncology,[8] and the International Society on Thrombosis and Haemostasis,[9] who have put forth regularly updated guidelines. We also included recommendations from the Canadian consensus,[10,11] and the Anticoagulation Forum[12] because they included a thorough assessment of the most recent primary literature. We examined the latest guidelines from the American College of Chest Physicians[13] but did not formally include them in this analysis because they were not specific to venous thromboembolism in cancer patients. We analyzed these various guidelines and adopted those recommendations most pertinent to the emergency physician. In addition, we also conducted primary literature searches on PubMed to address specific questions that warranted further examination, such as the use of direct oral anticoagulants and absolute versus relative contraindications to anticoagulation.

The incidence of deep venous thrombosis and pulmonary embolism in cancer patients varies widely, depending on cancer type, cancer aggressiveness, and chemotherapy, among other factors.[14] A large meta-analysis conducted in 2012 showed that the overall risk of venous thromboembolism in cancer patients ranges from 13 per 1,000 patient-years in low-risk patients to 200 per 1,000 patient-years in high-risk ones, such as those with primary

brain cancer.[15] Primary brain cancer carries the highest venous thromboembolism risk, whereas cancers with brain metastases carry a lower risk that is equivalent to that of cancers that have metastasized to other organs. A retrospective cohort study released in 2013 showed that venous thromboembolisms occurred in 12.6% of cancer patients during the 12-month period after the initiation of chemotherapy versus an incidence of 1.4% in matched controls without cancer.[3] Furthermore, studies have shown that venous thromboembolism recurs frequently within the first 6 to 12 months, with a particularly increased risk of recurrence in patients with malignant neoplasm.[16] In addition to cancer's being an inherently hypercoagulable state, chemotherapy has been shown to amplify the procoagulant effect of cancer cells.[17] Surgery, with associated postoperative limited mobility, as well as the use of central venous catheters, also increases the risk of developing deep venous thromboses.[18] The diagnosis of deep venous thrombosis and pulmonary embolism is outside the scope of this review; however, traditional algorithms may not be applicable because cancer patients are known to have on average a 3-fold increase in D-dimer level.[19] A recent meta-analysis of studies that addressed the diagnostic accuracy of the Wells score for excluding deep venous thrombosis found that only 9% of cancer patients had both a low Wells score and a negative D-dimer test result.[20] However, deep venous thromboses were still present in 2.2% of these patients, leading the authors to suggest that the Wells criteria and D-dimer testing are inappropriate in cancer patients and alternative screening parameters should be explored.

Guidelines for the treatment of venous thromboembolism in the noncancer population favor the use of low-molecular-weight heparin or unfractionated heparin for the first 5 to 10 days, followed by oral anticoagulants (ie, warfarin, direct factor Xa and thrombin inhibitors) for the following 3 months.[13] Because of the increased risk of recurrence in cancer patients, as outlined above, most guidelines agree that the treatment of these venous thromboembolisms should be continued for at least 6 months (Table 1). In terms of selecting an anticoagulant, a number of randomized clinical trials and meta-analyses conducted in the past 15 years have shown that low-molecular-weight heparin is superior to vitamin K antagonists (ie, warfarin) and likely superior to unfractionated heparin for both the immediate and long-term treatment of cancer-associated venous thromboembolisms.[21-26] It has also been suggested that vitamin K antagonists be avoided in the setting of cancer because drug interactions, malnutrition, and liver dysfunction can cause wide fluctuations in international normalized ratio (INR) level, resulting in both a higher rate of venous thromboembolism recurrence and higher risk of major bleeding events.[24] The typical treatment strategy is a full therapeutic dose of low-molecular-weight heparin for the first month, which is then decreased to 75% for the following 5 months (Table 2). The decision to continue anticoagulation after 6 months should be determined by the oncology team and is based on the various risk factors specific to the patient, including active malignancy, ongoing chemotherapy, and limitations with ambulation. None of the guidelines differentiate between deep venous thromboses and pulmonary embolisms, and both should be treated with the same dosages and the same time frame. No guidelines actively advocate thrombolysis during acute treatment; however, the National Comprehensive Cancer Network and European Society for Medical Oncology suggest that catheter-directed thrombolysis or thrombectomy may be considered in the case of large clots at risk of causing post-thrombotic syndrome or chronic thromboembolic pulmonary hypertension.[7,8] For patients with venous thromboembolism who are hemodynamically unstable or show signs of right-sided ventricular strain, the emergency physician should revert to traditional treatment algorithms and institute thrombolysis as indicated.

Given the prevalence of venous thromboembolisms in cancer patients and the high volume of imaging that is performed in the ED, it is unsurprising to find incidental pulmonary embolisms or deep venous thromboses in this patient population. The guidelines address a similar issue with incidental findings on imaging for cancer staging (Table 1). A number of retrospective studies in different cancer types have shown similar rates of recurrent venous thromboembolism and mortality in patients with incidental findings of venous thromboembolism compared with patients with symptomatic venous thromboembolism.[27-29] Therefore, it is important for the emergency physician to both treat incidental venous thromboembolisms and ensure that these patients have appropriate follow-up. There has been recent debate about the necessity to treat subsegmental pulmonary embolisms in the wider population, particularly because they are being more frequently diagnosed owing to the increased sensitivity of multidetector computed tomography pulmonary angiography.[30,31] The guidelines reviewed here do not address this issue, but the latest guidelines from the American College of Chest Physicians suggest that patients who have active malignancy or are receiving chemotherapy are considered high risk and would be appropriate for anticoagulation.[13] The approach to incidental findings of visceral vein thrombosis (eg, involving the portal or mesenteric veins) is also poorly defined, and guidelines that