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Guidelines for treatment and prevention of venous thromboembolism among patients with cancer

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ABSTRACT

The association between cancer and thrombosis has been recognized for more than 150 years. Not only are patients with cancer at a substantially increased risk of developing venous thromboembolism (VTE), the link between several coagulation factors and tumor growth, invasion, and the development of metastases has been established. Reported rates of VTE in patients with cancer have increased in recent years likely reflecting, in part, improved diagnosis with sophisticated imaging techniques as well as the impact of more aggressive cancer diagnosis, staging, and treatment. Various therapeutic interventions, such as surgery, chemotherapy, hormonal therapy, targeted therapeutic strategies as well as the frequent use of indwelling catheters and other invasive procedures also place cancer patients at increased risk of VTE. The increasing risk of VTE, the multitude of risk factors, and the greater risk of VTE recurrence and death among patients with cancer represent considerable challenges in modern clinical oncology. The American Society of Clinical Oncology (ASCO) originally developed guidelines for VTE in patients with cancer in 2007. ASCO recently updated clinical practice guidelines on the treatment and prevention of VTE in patients with cancer following an extensive systematic review of the literature. Revised 2013 guidelines have now been presented and will be discussed in this review. Although several new studies were identified and considered, many important questions remain regarding the relationship between thrombosis and cancer and the optimal care of patients at risk for VTE.

Introduction

Venous thromboembolism (VTE) is associated with several adverse consequences including increased mortality and recurrent VTE as well as both major and minor bleeding associated with anticoagulation [1-6]. There have been few studies of the impact of VTE on clinical outcomes in cancer patients such as delivery of optimal cancer treatment as well as quality of life and costs [7]. Several clinical practice guidelines that address VTE prophylaxis in cancer patients have been developed. The National Comprehensive Cancer Network (NCCN) representing several NCI-designated comprehensive cancer centers in the United States presented consensus guidelines for the treatment and prevention of VTE in cancer patients that are updated annually [8]. Internationally, several additional organizations have developed guidelines for patients with cancer at risk for VTE including the Italian Association of Medical Oncology, the European Society of Medical Oncology, and the French National Federation of the League of Centers Against Cancer [9-11]. In 2007, the American Society of Clinical Oncology (ASCO) published evidence-based guidelines for the treatment and prevention of VTE in patients with cancer based on a systematic review of the literature [12,13]. ASCO recently presented updated clinical practice guidelines on the treatment and prevention of VTE in patients with cancer following an extensive systematic review of the literature published since the original guidelines [14]. The ASCO Guideline Panel was represented by both content clinical experts in the management of VTE along with methodology experts on the performance of systematic reviews, quality appraisal of the evidence, and evidence summaries. The ASCO Guidelines present updated recommendations on the treatment and prevention of VTE in hospitalized medical and surgical cancer patients as well as ambulatory patients receiving cancer therapy. In addition, recommendations are presented on immediate and extended secondary prophylaxis in patients with established VTE, the potential role of anticoagulation in the treatment of patients with cancer without other recognized indication, and the importance of VTE risk assessment in patients with cancer. Primary questions addressed by the Guidelines included: What is known about risk factors and risk prediction of VTE among patients with cancer? Should hospitalized cancer patients receive anticoagulation for VTE prophylaxis? Should

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Table 1
VTE Treatment and Prophylaxis Recommendations [14]

2013 Recommendations
Inpatient
1.1 Hospitalized patients who have active malignancy with acute medical illness or reduced mobility should receive pharmacologic thromboprophylaxis in the absence of bleeding or other contraindications.
1.2 Hospitalized patients who have active malignancy without additional risk factors may be considered for pharmacologic thromboprophylaxis in the absence of bleeding or other contraindications.
1.3 Data are inadequate to support routine thromboprophylaxis in patients admitted for minor procedures or brief infusional chemotherapy, or in patients undergoing stem cell/ bone marrow transplantation.
Outpatient
2.1 Routine pharmacologic thromboprophylaxis is not recommended in cancer outpatients.
2.2 Based on limited RCT data, clinicians may consider LMWH prophylaxis on a case-by-case basis in highly selected outpatients with solid tumors receiving chemotherapy. Consideration of such therapy should be accompanied by a discussion with the patient about the uncertainty concerning benefits and harms, as well as dose and duration of prophylaxis in this setting.
2.3 Patients with multiple myeloma receiving thalidomide- or lenalidomide-based regimens with chemotherapy and/or dexamethasone should receive pharmacologic thromboprophylaxis with either aspirin or LMWH for low-risk patients and LMWH for high-risk patients.
Perioperative
3.1 All patients with malignant disease undergoing major surgical intervention should be considered for pharmacologic thromboprophylaxis with either UFH or LMWH unless contraindicated because of active bleeding or a high-risk of bleeding with the procedure.
3.2 Prophylaxis should be commenced preoperatively.
3.3 Mechanical methods may be added to pharmacologic thromboprophylaxis, but should not be used as monotherapy for VTE prevention unless pharmacologic methods are contraindicated because of active bleeding or high bleeding risk.
3.4 A combined regimen of pharmacologic and mechanical prophylaxis may improve efficacy, especially in the highest-risk patients.
3.5 Pharmacologic thromboprophylaxis should be continued for at least 7-10 days in all patients. Extended prophylaxis with LMWH for up to 4 weeks postoperatively should be considered for patients undergoing major abdominal or pelvic surgery for cancer who have high-risk features such as restricted mobility, obesity, history of VTE, or with additional risk factors.
Treatment and Secondary Prophylaxis
4.1 LMWH is preferred over UFH for the initial 5 to 10 days of anticoagulation for the cancer patient with newly diagnosed VTE who does not have severe renal impairment (defined as creatinine clearance < 30 mL/min).
4.2 For long term anticoagulation, LMWH for at least 6 months is preferred due to improved efficacy over Vitamin K antagonists. Vitamin K antagonists are an acceptable alternative for long-term therapy if LMWH is not available.
4.3 Anticoagulation with LMWH or Vitamin K antagonist beyond the initial 6 months may be considered for select patients with active cancer, such as those with metastatic disease or those receiving chemotherapy.
4.4 The insertion of a vena cava filter is only indicated for patients with contraindications to anticoagulant therapy. It may be considered as an adjunct to anticoagulation in patients with progression of thrombosis (recurrent VTE or extension of existing thrombus) despite maximal therapy with LMWH.
4.5 For patients with central nervous system malignancies, anticoagulation is recommended for established VTE as described for other patients with cancer. Careful monitoring is necessary to limit the risk of hemorrhagic complications.
4.6 Use of novel oral anticoagulants for either prevention or treatment of VTE in cancer patients is not recommended at this time.
4.7 Incidental PE and DVT should be treated in the same manner as symptomatic VTE. Treatment of splanchnic or visceral vein thrombi diagnosed incidentally should be considered on a case-by-case basis, considering potential benefits and risks of anticoagulation.
Anticoagulation and Survival
5.1 Anticoagulants are not recommended to improve survival in patients with cancer without VTE.
5.2 Patients with cancer should be encouraged to participate in clinical trials designed to evaluate anticoagulant therapy as an adjunct to standard anticancer therapies.
Risk Assessment
6.1 Cancer patients should be assessed for VTE risk at the time of chemotherapy initiation and periodically thereafter.
6.1a In the outpatient setting, risk assessment can be conducted based on a validated risk assessment tool
6.2b Solitary risk factors, including biomarkers or cancer site, do not reliably identify cancer patients at high-risk of VTE.
6.2 Oncologists should educate patients regarding VTE, particularly in settings that increase risk such as major surgery, hospitalization, and while receiving systemic anti-neoplastic therapy. Patient education should at least include a discussion of the warning signs and symptoms of VTE, including leg swelling or pain, sudden-onset chest pain, and shortness of breath.

ambulatory patients with cancer receive anticoagulation for VTE prophylaxis during systemic chemotherapy? Should patients with cancer undergoing surgery receive perioperative VTE prophylaxis? What is the best method for treatment of cancer patients with established VTE to prevent recurrence? Should patients with cancer receive anticoagulation in the absence of established VTE to improve survival? The final recommendations of the Guideline Panel are summarized in Table 1.

Risk of Venous Thromboembolism in Cancer Patients

The risk of VTE is substantially increased in patients with cancer. most notably in hospitalized patients, the elderly and those with major medical comorbidities including obesity, pulmonary disease, and renal failure [3,15-17]. The rates of VTE reported in hospitalized cancer patients have increased substantially in recent years [17]. The primary site of cancer is particularly important with highest rates of VTE observed in patients with brain, pancreas, stomach, kidney, ovary, and lung cancers, and hematologic malignancies including lymphoma and myeloma. Recent studies have also demonstrated a considerable risk of VTE in patients with hematologic malignancies including malignant lymphomas [17-19]. Elevations in leukocyte and platelet counts and reductions in hemoglobin appear to increase the risk of VTE in patients with cancer. Finally, the risk of VTE is further increased in patients receiving systemic therapies including chemotherapy, hormonal therapy, and certain targeted agents. A number of new cancer therapies, especially the antiangiogenesis agents, appear to be associated with an increased risk of both arterial and venous thrombosis [20-25]. While the risk of arterial thrombotic events is increased with bevacizumab, it remains unclear whether the risk of VTE