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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

is increased after adjustment for treatment duration [26]. The use of the erythropoiesis-stimulating agents, epoetin alfa and darbepoetin alfa, as well as blood transfusions have also been associated with an increased risk of VTE [16,27,28].

Predictive risk models for VTE in ambulatory cancer patients receiving systemic chemotherapy have been developed [29,30]. A risk score for cancer-associated VTE based on clinical and laboratory measures has been developed and validated in multiple studies [29,31-33], (Table 2). Retrospectively, evaluation in large prospective randomized trials found that the risk of VTE in high-risk patients defined on the basis of the risk score was significantly reduced in those randomized to prophylactic thromboprophylaxis [34,35]. The updated ASCO Guidelines recommend that patients with cancer be educated about the symptoms and signs of VTE and that VTE risk be assessed at the time of chemotherapy initiation and periodically over the course of treatment.

Table 2
Risk Score for Predicting Outpatient VTE in Cancer Patients [29]

Patient Characteristics	Risk Score
Site of cancer	
Very high-risk (stomach, pancreas)	2
High-risk (lung, lymphoma, gynecologic, bladder, testicular)	1
Prechemotherapy platelet count 350000/mm^3 or more	1
Hemoglobin level less than 10g/dL or use of red cell growth factors	1
Prechemotherapy leukocyte count more than 11000/mm^3	1
Body mass index 35kg/m^2 or more	1

High-risk score ≥ 3; Intermediate risk score =1-2; Low-risk score =0. Primary brain tumor and myeloma patients were not part of this study. Information on the impact of prior VTE is also not available in this study.

Treatment of Established VTE in Cancer Patients

The initial treatment of established VTE in cancer patients is generally patterned after therapeutic approaches in other, non-cancer settings. However, the duration of therapy to prevent early recurrence is often extended in cancer patients with persistent disease or continuing on cancer treatment [36]. The ASCO Guidelines recommend low molecular weight heparin for the initial 5 to 10 days of anticoagulation in cancer patients with established VTE, as well as for secondary prevention of recurrence for at least six months**.** In high-risk patients with active malignancy continuing on chemotherapy, extended anticoagulation to prevent VTE recurrence is encouraged. A number of new oral and parenteral antithrombotic agents are currently under development which are likely to have future application to patients with malignant disease [37,38].

Of importance, the risk of recurrence, bleeding, and mortality in cancer patients with incidental or unsuspected VTE appears to be similar to those with symptomatic VTE [39]. Most patients with previously unsuspected pulmonary embolism (PE) found at the time of staging computerized tomography scans are actually symptomatic and are likely of clinical significance [40]. Based on consensus, the ASCO Guideline panel recommends that incidental VTE be treated the same as symptomatic VTE with the potential exception of peripheral subsegmental PE, especially if it is thought to be an imaging artifact.

Prophylaxis of Hospitalized Cancer Patients

It has long been recognized that thromboembolism is a major cause of death in hospitalized cancer patients [3,41]. Nevertheless, the reported frequency of VTE in hospitalized cancer patients varies widely [17,42-44]. Cancer patients hospitalized with neutropenia and presumed infection with documented thromboembolism have more than a two-fold increase in risk of mortality [17]. Three large RCTs of hospitalized acutely ill medical patients have demonstrated that enoxaparin, dalteparin, and fondaparinux are effective in preventing screen-detected VTE utilizing venography or ultrasound [45-48]. However, none of these trials were specifically conducted in patients with cancer who represented only a small proportion of the overall trial population. Nevertheless, the additional risk for VTE in hospitalized cancer patients and the efficacy and reasonable safety of prophylactic anticoagulation in seriously ill medical patients has provided the basis for consideration of thromboprophylaxis in most hospitalized cancer patients in the absence of contraindications to anticoagulation. The updated systematic review identified three recent randomized controlled trials (RCTs) of thromboprophylaxis in seriously-ill medical inpatients [49-51]. Despite limited cancer-specific data across these trials, the ASCO Guidelines continue to recommend that hospitalized patients with major medical illnesses or reduced mobility without serious bleeding risk receive prophylactic anticoagulation. Hospitalized cancer patients without additional risk factors may also be considered for prophylactic anticoagulation. However, there are inadequate data to support routine prophylaxis in patients admitted for chemotherapy or for minor procedures [52].

Prophylaxis in Surgical Cancer Patients

Cancer patients undergoing major surgical procedures are at increased risk for VTE as well as for bleeding complications [53]. Prophylactic anticoagulation with low molecular weight heparin (LMWH) in cancer patients undergoing major surgery has been shown to reduce the risk of venographically detected deep venous thrombosis (DVT) but not symptomatic VTE [54]. A variety of approaches for reducing the risk of VTE in the perioperative period are available including graduated compression stockings or intermittent pneumatic calf compression devices as well as medical thromboprophylaxis with low dose UFH, LMWH, or vitamin K antagonists [55-60]. The optimal duration of prophylactic anticaogulation in the postoperative setting continues to be discussed and studied [61,62]. Patients undergoing major surgical procedures for cancer should receive VTE prophylaxis unless contraindicated. In addition, combined mechanical prophylaxis and anticoagulation may be considered in high-risk patients [63].

Three additional RCTs evaluating perioperative prophylaxis in patients undergoing major abdominal or pelvic surgery were identified by the updated systematic review [64-66]. Prophylactic anticoagulation in patients undergoing major cancer surgery is recommended beginning preoperatively when appropriate and continuing for at least 7-10 days. Systematic reviews have been conducted of extended prophylaxis for up to four weeks [67-69]. Extended postoperative prophylaxis for up to four weeks is recommended in high-risk patients undergoing major cancer surgery such as those with restricted mobility, obesity, or a history of VTE.

Prophylaxis of Ambulatory Cancer Patients

The risk of VTE in ambulatory cancer patients appears to vary widely with the type of cancer and treatment, and any comorbid conditions present. Given the average low risk of VTE in this setting along with possible bleeding, anticoagulant prophylaxis has not been routinely recommended. Nevertheless, the emergence of more aggressive interventions and a number of new cancer therapies as well as supportive care agents associated with an increased risk of VTE has resulted in increased interest in the potential value of VTE prophylaxis in this setting [21,70-81].

Several RCTs of thromboprophylaxis in ambulatory cancer patients have been reported including nine with LMWHs. The PROTECHT trial presented at the 2008 Meeting of the American Society of Hematology reported a significant reduction in the composite outcome of arterial and venous thrombosis [82]. The most dramatic impact on the absolute risk of VTE was observed in patients with advanced pancreatic cancer receiving specified chemotherapy [83-85]. Most recently, a RCT of the ultra-low molecular weight heparin, semuloparin, reported a hazard ratio for VTE in 1608 cancer patients of 0.36 (95% CI: 0.21-0.60; P<0.001) [86]. A meta-analysis estimated an overall relative risk for symptomatic VTE of 0.47 (0.36-0.61; P<0.001) but with an absolute reduction in VTE risk of only 2.8% (1.8%-3.7%; P<0.001) [87]. Due to the small incremental benefit observed in most trials of ambulatory patients and the limitations in these trials, the ASCO Guideline panel concluded that routine anticoagulation prophylaxis is not yet warranted with the exception of patients with multiple myeloma receiving thalidomide or lenalidomide along with chemotherapy and/or dexamethasone where the risk of VTE is sufficient to justify routine thromboprophylaxis. Nevertheless, the panel did conclude that based on limited data from recent RCTs, LMWH prophylaxis may be considered on a case-by-case basis in highly selected high-risk patients with solid tumors receiving chemotherapy after thoroughly considering the potential benefits and harms [14].

Anticoagulation as Cancer Treatment to Improve Survival

The potential impact of treatment with anticoagulants on overall survival in patients with cancer without other indication for their use has gained considerable attention [4]. It is recognized that heparins may inhibit tumor cell growth, invasion, and distant metastasis [88]. LMWHs may also inhibit angiogenesis, block platelet aggregation, and inhibit platelet interaction [89]. The impact of anticoagulation on the survival of patients with cancer has been studied in RCTs of anticoagulants for the treatment or prevention of VTE as well as a component of overall cancer therapy. Meta-analyses of trials comparing initial treatment of VTE with UFH versus LMWH have shown a survival benefit in cancer patients receiving LMWH [90-93]. In addition, several RCTs in cancer patients without VTE have studied whether anticoagulants improve overall survival and reported mixed results [94-100].

A significant reduction in 1-year mortality was observed in a meta-analysis of 11 randomized controlled trials of patients treated with anticoagulants vs no anticoagulants [13]. The overall relative risk for all-cause mortality was 0.88 [95% CI: 0.79-0.98; P=0.015] and 0.94 [95% CI: 0.85–1.04; P=0.239] among LMWH and warfarin trials, respectively. However, major bleeding complications were greater in patients randomized to anticoagulation reaching statistical significance in warfarin studies (P<0.001) [13]. Overall these data provide some evidence that anticoagulation improves survival in patients with advanced cancer. However, small study sample sizes and the low power of these studies preclude a definitive conclusion on the efficacy of anticoagulants in the treatment of patients with cancer. Therefore, anticoagulation for cancer treatment is not currently recommended in the updated guidelines due to the limitations of the trials reported to date and concern over an increased risk for major bleeding complications [14]. Patients with cancer should be encouraged to participate in clinical trials designed to evaluate anticoagulant therapy as an adjunct to standard anticancer therapies. A number of additional trials are underway to better define the clinical value of anticoagulants as cancer therapy [4].

Conclusions

Patients with cancer, especially those hospitalized and those undergoing major surgery or systemic treatment are at increased risk for VTE and should be considered for routine thromboprophylaxis. Primary prevention of VTE in high-risk patients, as well as secondary prevention of recurrent VTE represent continuing clinical challenges. Additional studies are needed to better define the optimal role of anticoagulation in high-risk cancer patients including those receiving cancer chemotherapy in the ambulatory. While the need for more efficacious, safe, and convenient anticoagulants has sparked the development of a number of new agents, further clinical trials specifically including patients with cancer are needed. In the meantime, the optimal application of currently available agents based on clinical practice guidelines in patients with cancer must remain a high priority. In addition, the potential role of anticoagulants in improving cancer patient survival represents an intriguing opportunity that will require further clinical trials.

ASCO and other professional organizations based on rigorous systematic reviews and evidence appraisals can provide clinicians with a balanced resource for the use of anticoagulants in the specific management of patients with cancer. It should be noted that there is a high level of concurrence in recommendations across currently available clinical practice guidelines internationally. Nevertheless, further efforts are needed to improve the dissemination, implementation, and compliance with available guidelines to improve the overall quality of cancer patient care. Greater awareness and considerably more research are also needed to improve our ability to safely and effectively treat and prevent thromboembolic complications in patients with cancer. While the use of recently validated clinical risk models for VTE among ambulatory cancer patients is promising, identification and validation of new clinical and molecular biomarkers for VTE are awaited to further improve selection of high-risk patients for more personalized prophylactic strategies. Through optimal application of current strategies along with increased investment into basic and translational clinical research, further reductions in the morbidity and mortality associated with thromboembolic complications in patients with cancer can be realized.

Conflict of interest statement

The authors have no financial or personal conflicts of interest related to the subject matter of this review.

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