Venous Thromboembolism Prophylaxis and Treatment in Cancer: A Consensus Statement of Major Guidelines Panels and Call to Action

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A B S T R A C T

Purpose

Venous thromboembolism (VTE) is an increasingly frequent complication of cancer and its treatments, and is associated with worsened mortality and morbidity in patients with cancer.

Design

The Italian Association of Medical Oncology, the National Comprehensive Cancer Network, the American Society of Clinical Oncology, the French National Federation of the League of Centers Against Cancer, and the European Society of Medical Oncology have recently published guidelines regarding VTE in patients with cancer. This review, authored by a working group of members from these panels, focuses on the methodology and areas of consensus and disagreement in the various clinical guidelines as well as directions for future research.

Results

There is broad consensus regarding the importance of thromboprophylaxis in hospitalized patients with cancer, including prolonged prophylaxis in high-risk surgical patients. Prophylaxis is not currently recommended for ambulatory patients with cancer (with exceptions) or for central venous catheters. All of the panels agree that low molecular weight heparins are preferred for the long-term treatment of VTE in cancer. Areas that warrant further research include the benefit of prophylaxis in the ambulatory setting, the risk/benefit ratio of prophylaxis for hospitalized patients with cancer, an understanding of incidental VTE, and the impact of anticoagulation on survival.

Conclusion

We call for a sustained research effort to investigate the clinical issues identified here to reduce the burden of VTE and its consequences in patients with cancer.

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INTRODUCTION

Cancer and its treatment are frequently complicated by thrombotic events including deep vein thrombosis (DVT) and pulmonary embolism (PE), collectively known as venous thromboembolism (VTE), as well as arterial events such as stroke and myocardial infarction. Although the association between cancer and thrombosis has been known for years,¹ there is now an increasing recognition among cancer providers of the impact of thrombotic complications on patients with cancer.² Several factors have contributed to this heightened awareness. Firstly, cancer-associated VTE is increasingly prevalent. In a recent analysis of more than 1 million hospitalized patients with cancer, the rate of VTE increased by 28% from 1995 to 2003 ($P < .0001$).³ Secondly, the consequences of VTE are better understood. Thrombosis is the second-leading cause of

death in patients with cancer and is associated with worsened mortality.⁴⁻⁶ In addition, patients with cancer who suffer VTE have an increased risk of recurrent VTE, bleeding complications, morbidity, and utilization of health care resources.^{7,8} Finally, newer anticancer agents particularly antiangiogenic drugs, appear to be more thrombogenic than conventional chemotherapy.^{9,10}

In response to the increasing concern regarding VTE in patients with cancer, multiple international cancer organizations have recently issued guidelines for providers regarding its prevention and treatment. These include the Italian Association of Medical Oncology (AIOM),¹¹ the National Comprehensive Cancer Network (NCCN),¹² the American Society of Clinical Oncology (ASCO),¹³ the French National Federation of the League of Centers Against Cancer (FNCLCC)^{14,15} and the European Society of Medical Oncology (ESMO).¹⁶ This

review, authored by a working group of members from these guideline panels, will focus on the methodology and areas of consensus in the clinical recommendations issued by these organizations. In addition, we will identify areas lacking clear evidence where further research is warranted to achieve the overarching goal of reducing the burden of thromboembolism in patients with cancer.

METHODS

AIOM Guidelines

The AIOM guidelines panel was organized in 2004 and focused on six distinct issues: VTE and occult cancer; VTE prophylaxis in cancer surgery; VTE prophylaxis during chemotherapy or hormone therapy; VTE prophylaxis and central venous catheters (CVCs); VTE treatment in cancer patients; and anticoagulation and prognosis of patients with cancer. The panel used a systematic review of the evidence as a basis for making recommendations. This process included adjudicating the strength of each recommendation after a systematic weighing and grading of the level of evidence. Greater weight was given to well-designed randomized controlled trials and meta-analyses than to studies with weaker internal validity. The panel scored as high-quality recommendations those that were derived from studies with false-positive rates of $\leq 5\%$ and false-negative rates of $\leq 20\%$. When evidence was lacking, the panel determined that it was inappropriate to reach conclusions based on expert opinion. The guidelines were first presented in October 2005 and subsequently published in 2006.¹¹

NCCN Guidelines

The NCCN is a consortium of 21 leading academic cancer institutes in the United States. In 2005, the NCCN organized a multidisciplinary panel from its member institutions to develop an evidence-based guideline outlining diagnosis, prevention, and initial and long-term management of VTE in the patient with cancer. The guideline was based on a comprehensive search of the English language literature on the prevention, diagnosis, and management of VTE that was performed by network staff and provided to panel members before the first consensus conference in October 2005. Panel members were encouraged to supplement the literature review with additional data they deemed important for the committee to consider in the guideline development process. Guideline recommendations were graded according to the amount of available evidence to support the recommendation and the degree of consensus among panel members. The first version of the guideline was presented at the NCCN Annual Meeting in March 2006 and subsequently published.¹² The guideline subsequently has undergone annual revisions to reflect newly published research or address clinical management questions posed by member institutions.

ASCO Guidelines

A proposal to develop guidelines for the prevention and treatment of VTE in patients with cancer was approved by ASCO in 2005. The evidence basis of the ASCO guideline was established by a comprehensive systematic review of published and unpublished randomized controlled clinical trials of anticoagulation therapy in medical and surgical oncology patients, subsequently published separately.¹⁷ Shortly thereafter, a guideline panel of content and methodology

experts was convened. The entire panel met twice to discuss the results of the systematic review, resolve any differences in the interpretation of the results, and determine what practice recommendations should be made. Primary questions addressed by the ASCO VTE Guideline Panel included: should hospitalized cancer patients receive anticoagulation for VTE prophylaxis? Should 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 patients with cancer with established VTE to prevent recurrence? Should patients with cancer receive anticoagulants in the absence of established VTE to improve survival? The ASCO panel did not address catheter-related thrombosis, deferring to a separate panel focused primarily on catheter-related issues. The guideline was initially published in December, 2007, and an update is anticipated in 2010.¹³

FNCLCC Guidelines

In 2007, the guidelines department of the FNCLCC proposed to answer questions relating to treatment of VTE and prevention and treatment of CVC-related thrombosis in patients with cancer, based on evidence synthesis and experts' judgment in accordance with the Standards, Options, and Recommendations program procedure. The French guidelines did not address general prophylaxis in patients with cancer as it deemed the evidence to date insufficient to make recommendations. A multidisciplinary panel was assembled as part of a collaborative effort by the French National Institute of Cancer, the French Society of Internal Medicine (Société Française de Médecine Interne), the French Society of Vascular Diseases (Société Française de Médecine Vasculaire), and the French Society of Anesthesiology (Société Française d'Anesthésie-Réanimation). The Guideline was based on a systematic literature review and a critical appraisal performed by a multidisciplinary working group of experts using successive meetings over a 13-month period. Recommendations were classified as standards (defined as a clinical pathway unanimously recognized as the gold standard by clinical practitioners) or options (where many clinical pathways may be appropriate and one of the options can be preferred). The document was subsequently peer reviewed by 65 other independent experts and their comments were integrated into the final version first published online in February 2008 and in print thereafter.^{14,15}

ESMO Guidelines

The ESMO clinical recommendations are based on a narrative platform that briefly summarizes the state of the art. The panel used a systematic review of the evidence as a basis for recommendations. This process included a systematic weighting of the level of evidence and a systematic grading of the evidence for making a recommendation. Similar to the AIOM panel, greater weight was given to well-designed randomized controlled trials and meta-analyses and progressively less weight to studies with weaker internal validity. The ESMO guidelines were first published in 2008.¹⁶

PREVENTION AND TREATMENT OF VTE IN CANCER: AN INTERNATIONAL CONSENSUS

Each of the guideline panels broadly addressed the primary clinical problems of prevention and treatment of cancer-associated VTE. In

addition, individual panels focused on VTE and occult malignancy and the diagnosis of VTE. In general, there was broad agreement among the various panels regarding recommendations. This section provides an outline of the recommendations focusing on areas of consensus as well as disagreement.

Prevention of VTE in the Hospitalized Medical Patient With Cancer

Hospitalized patients with cancer are particularly at risk for VTE, although the risk varies significantly among various subgroups of patients with cancer.^{3,18-20} Three large randomized studies have demonstrated that hospitalized acutely ill medical patients derive benefit from thromboprophylaxis with either a low molecular weight heparin (LMWH) or fondaparinux.²¹⁻²³ Unfortunately, the study populations in these trials only included a minority of patients with cancer (range, 5% to 15%) and rates of major bleeding in the cancer subgroups were not reported. Given

the known high risk of VTE in the hospitalized patient with cancer, however, the guidelines recommend pharmacologic thromboprophylaxis in the absence of contraindications (Table 1). The ASCO guidelines recommend that hospitalized patients with cancer should be considered for thromboprophylaxis. The NCCN guidelines recognize that multiple intrinsic and extrinsic factors play a role in the risk of VTE during hospitalization and ask that clinicians take into account these risk factors. The NCCN panel therefore recommends that all patients with cancer or suspected to have cancer should receive risk-stratified VTE prophylaxis on hospital admission. The AIOM and ESMO guidelines focus on immobility as a major risk factor and recommend prophylaxis only in immobilized hospitalized patients with cancer with an acute medical illness. These guidelines all recommend either low-dose unfractionated heparin (UFH), LMWH, or fondaparinux as anticoagulants for thromboprophylaxis without expressing a preference for a particular agent or class of agents.

Table 1. Recommendations for Prevention of VTE in Patients With Cancer by the Guidelines Panels

Parameter	ASCO	NCCN	AIOM/ESMO	FNCLCC
Prevention of VTE in the hospitalized cancer patient				
Recommendation	Prophylactic anticoagulation considered for all hospitalized cancer patients in the absence of contraindications	Prophylactic anticoagulation for all hospitalized cancer patients in the absence of contraindications	Prophylactic anticoagulation in immobilized hospitalized cancer patients with acute medical illness	NA
Agent(s)	Low-dose UFH, LMWH, or fondaparinux			
Prevention of VTE in the surgical cancer patient				
Recommendation	Initial prophylaxis: prophylactic anticoagulation for patients undergoing laparotomy, laparoscopy, or thoracotomy lasting greater than 30 minutes; Prolonged prophylaxis: continue up to 4 weeks for major abdominal or pelvic surgery for cancer with high-risk features such as residual disease, obesity, or prior VTE	Initial prophylaxis: prophylactic anticoagulation is recommended; Prolonged prophylaxis: continue up to 4 weeks post-operation for high risk abdominal or pelvic cancer surgery	Initial prophylaxis: prophylaxis for cancer patients undergoing major cancer surgery; Prolonged prophylaxis: continue up to 28-35 days after major abdominal or pelvic surgery	NA
Agent(s)	LMWH or UFH; add mechanical methods in highest-risk patients	LMWH, UFH, or fondaparinux (± pneumatic venous compression)	LMWH or UFH	
Prevention of VTE in the ambulatory cancer patient				
Recommendation	Not recommended with the exception of patients with multiple myeloma receiving thalidomide-/lenalidomide-based combination regimens	Not recommended with the exception of patients with multiple myeloma receiving thalidomide-/lenalidomide-based combination regimens	Not recommended with the exception of patients with multiple myeloma receiving thalidomide-/lenalidomide-based combination regimens	NA
Prevention of VTE in cancer patients with central venous catheters				
Recommendation	NA	Prophylactic anticoagulation not recommended	Prophylactic anticoagulation not recommended	Prophylactic anticoagulation not recommended; CVC should be placed at the superior vena cava and right atrium junction

Abbreviations: VTE, venous thromboembolism; ASCO, American Society of Clinical Oncology; NCCN, National Comprehensive Cancer Network; AIOM, Italian Association of Medical Oncology; ESMO, European Society of Medical Oncology; FNCLCC, French National Federation of the League of Centers Against Cancer; NA, not addressed; UFH, unfractionated heparin; LMWH, low molecular weight heparin; CVC, central venous catheter.

Prevention of VTE in the Surgical Patient With Cancer

The risk of VTE in the immediate postoperative period has long been recognized. Multiple randomized clinical trials in the surgical setting have demonstrated the benefit of pharmacologic prophylaxis.²⁴⁻²⁷ Based on this large body of literature, the AIOM, NCCN, ESMO, and ASCO guidelines all recommended prophylactic anticoagulation in the surgical oncology setting. The ASCO guidelines panel recommended that patients undergoing laparotomy, laparoscopy, or thoracotomy lasting greater than 30 minutes should receive pharmacologic thromboprophylaxis with either low-dose UFH or LMWH unless contraindicated because of a high risk for or active bleeding. Mechanical methods may be added to pharmacologic methods, but should not be used as monotherapy for VTE prevention unless pharmacologic methods are contraindicated. A combined regimen of pharmacologic and mechanical prophylaxis may improve efficacy, especially in the highest-risk patients. These recommendations are echoed by the NCCN and AIOM guidelines.

Cancer surgery patients remain at elevated risk for VTE for an extended period of time following hospital discharge.²⁸ Two recent randomized studies suggest that prolonging the duration of prophylaxis up to 4 weeks is effective and safe in reducing postoperative VTE.^{29,30} One study enrolled only abdominal or pelvic cancer surgery patients, while cancer surgery patients constituted over 50% of the participants in the second study. Based on these findings, the ASCO guidelines panel recommended that prolonged prophylaxis for up to 4 weeks be considered in patients undergoing major abdominal or pelvic cancer surgery with high-risk features, such as residual malignant disease postresection, obesity, or a previous history of VTE. The NCCN guidelines also recommend that all patients with high-risk cancer undergoing major surgery should be considered for extended VTE prophylaxis. Characteristics used by the NCCN guidelines to identify patients at high risk for VTE include age 60 years or older, advanced cancer, operative times more than 2 hours, previous VTE, and more than 3 days of bed rest.²⁸ The AIOM and ESMO guidelines take an even stronger stance by recommending that prolonged prophylaxis be considered the new standard of care for patients undergoing elective cancer surgery.

Prevention of VTE in the Ambulatory Patient With Cancer

Several clinical trials of thromboprophylaxis have been performed in ambulatory patients with cancer, with conflicting results.³¹⁻³⁴ The guidelines panels are again in broad agreement in not recommending routine thromboprophylaxis in this setting. Currently, outpatient VTE prophylaxis is recommended by the AIOM, NCCN, ASCO, and ESMO panels only for medical oncology patients receiving highly thrombogenic thalidomide- or lenalidomide-based combination chemotherapy regimens. Recommendations in this setting may change in the near future with the availability of a validated thrombosis risk assessment tool for ambulatory patients receiving chemotherapy that should facilitate the execution of randomized trials of VTE prophylaxis in higher-risk patients.³⁵ The panels are also likely to consider the results of a large, randomized clinical trial presented in abstract form recently that demonstrated a benefit for thromboprophylaxis in this setting.³⁴

CVC-associated VTE affects approximately 4% of patients with cancer.^{36,37} However, anticoagulant prophylaxis has yet to be proven effective in reducing the incidence of CVC-related DVT.³⁸⁻⁴¹ Therefore, until effective regimens are identified, the AIOM, NCCN, French, and ESMO guidelines do not recommend routine prophylaxis

for this purpose. The AIOM and ESMO guidelines suggest tailoring prophylaxis based on individual risk profiles without specifying a method of risk assessment in this setting. The French guidelines emphasize the importance of positioning the catheter tip at the superior vena cava–right atrial junction.

Initial and Long-Term Treatment of VTE in the Patient With Cancer

The ASCO guidelines recommend LMWH as the preferred approach to the initial treatment of VTE in patients with cancer whereas the NCCN guidelines suggest that agent selection should be based on the characteristics of the individual agents and the patient's clinical situation (Table 2). The AIOM guidelines also do not identify a preferred agent, although they recommend use of UFH or LMWH with anti-Xa activity monitoring in patients with severe renal failure (creatinine clearance < 25–30 mL/min).

For long-term treatment, multiple clinical trials including one large, randomized study, have demonstrated the benefit of LMWH therapy over oral anticoagulation with vitamin K antagonists.⁴²⁻⁴⁶ All of the guidelines prefer LMWH for long-term anticoagulant therapy. The ASCO and French guidelines allow for vitamin K antagonists with a targeted international normalized ratio (INR) of 2 to 3 for long-term therapy when LMWH is not available or contraindicated. The NCCN guidelines further recommend that if vitamin K antagonists are to be used for chronic therapy, initial cotherapy with a parenteral agent (eg, UFH) should last at least 5 to 7 days and not be discontinued until the INR is 2 or more for at least 24 hours. The duration of anticoagulation is addressed by the ASCO guidelines, which recommend continuing LMWH treatment for at least 6 months. After 6 months, indefinite anticoagulant therapy should be considered for selected patients with active cancer such as those with metastatic disease and those receiving chemotherapy. This recommendation is based on panel consensus reflecting the lack of data in this area. The NCCN guidelines recommend that therapy should continue for at least 3 months for a DVT and 6 months for a PE or for as long as there is evidence of active cancer or the patient is under therapy for cancer, whichever is longer. The French guidelines also recommend 6 months as the optimal duration and 3 months as the minimal duration of LMWH therapy in this setting. The AIOM guidelines recommend that treatment continue indefinitely in the presence of active cancer. The ASCO panel calls for close monitoring but no dose adjustments in special populations such as the elderly, those with brain tumors, or those at risk for bleeding.

Although thrombolytic therapy can rapidly reduce thrombus burden and may reduce the incidence of post-thrombotic syndrome, it is associated with a greater risk of major and rarely fatal bleeding.⁴⁷ Therefore, the ASCO, NCCN, and French guidelines recommend that thrombolytic therapy be restricted to patients with life- or limb-threatening thromboembolic events.

The AIOM, NCCN, and ESMO guidelines address treatment of recurrent VTE in patients with cancer. The panels recommend that patients on long-term anticoagulation with vitamin K antagonists who develop VTE at the time of a subtherapeutic INR be re-treated with UFH or LMWH until a stable therapeutic INR has been reached, or switched to a parenteral agent such as LMWH or fondaparinux. If VTE recurrence occurs while the INR is in the therapeutic range, the recommendations are to either shift to parenteral anticoagulation with either LMWH, fondaparinux, or subcutaneous UFH maintaining a therapeutic activated partial thromboplastin time (ratio from 1.5

Table 2. Recommendations for Treatment of VTE in Patients With Cancer by the Guideline Panels

Parameter	ASCO	NCCN	AIOM/ESMO	FNCLCC
Initial treatment of VTE in patients with cancer	LMWH is the preferred approach for the initial 5-10 days	LMWH, UFH, or fondaparinux according to patient's characteristics and clinical situation	Weight-adjusted dose LMWH if creatinine clearance < 25-30 mL, either UFH or LMWH with anti-Xa monitoring	LMWH, UFH, or fondaparinux for the first 10 days if severe renal failure, UFH, and early VKA
Long-term treatment of VTE in patients with cancer	LMWH for at least 6 months is preferred; VKA are acceptable when LMWH is not available; indefinite anticoagulation in patients with active cancer	LMWH is preferred; indefinite anticoagulation in patients with active cancer or persistent risk factors	LMWH for at least 3-6 months; long-term LMWH for patients with active cancer	LMWH for 3-6 months; LMWH or VKA beyond 6 months
Thrombolytic therapy in the initial treatment of VTE in patients with cancer	Restricted to patients with life- or limb-threatening thrombotic events	Restricted to appropriate candidates with massive DVT or massive or sub-massive PE with moderate to severe right ventricular dysfunction	NA	Restricted to PE with hemodynamic collapse
Inferior vena cava filters	Restricted to patients with contraindications to anticoagulation or recurrent VTE despite adequate long-term LMWH	Restricted to patients with contraindications to or failure of anticoagulation, cardiac or pulmonary dysfunction severe enough to make any new PE life-threatening or multiple PE with chronic pulmonary hypertension	Contraindications to anticoagulation or PE despite adequate long-term LMWH	Contraindications to anticoagulation or PE despite adequate long-term LMWH; start anticoagulation as soon as possible
Treatment of catheter-related thrombosis	NA	LMWH or VKA for as long as catheter is in place and for at least 3 months after catheter removal	NA	LMWH for up to 6 months; consider VKA after 6 months as long as cancer is active or catheter in place; anticoagulate for up to 6 weeks after catheter removal if cancer is not active

Abbreviations: VTE, venous thromboembolism; ASCO, American Society of Clinical Oncology; NCCN, National Comprehensive Cancer Network; AIOM, Italian Association of Medical Oncology; ESMO, European Society of Medical Oncology; FNCLCC, French National Federation of the League of Centers Against Cancer; UFH, unfractionated heparin; LMWH, low molecular weight heparin; VKA, vitamin K antagonist; DVT, deep vein thrombosis; PE, pulmonary embolism; NA, not addressed.

to 2.5), or to increase the target INR to 3.5. Full-dose LMWH can be resumed in patients who develop a VTE recurrence while receiving a reduced dose of LMWH as long-term therapy. Alternatively, patients may be shifted to anticoagulation with vitamin K antagonists. The panels recognize that these are empirical and not evidence-based recommendations and that further clinical research is needed to address this important clinical problem.

SPECIAL TOPICS: DIAGNOSIS OF VTE AND SCREENING FOR OCCULT MALIGNANCY

The NCCN guidelines address the issue of diagnosis of VTE in the patient with cancer. The panel notes that although the use of clinical prediction rules such as the Wells criteria in conjunction with d-dimer testing can reduce the need for objective radiologic testing in patients without cancer, these approaches are less rewarding in patients with cancer because few patients have a low probability of VTE and/or negative d-dimer assays.⁴⁸ Therefore, objective radiologic studies such as duplex ultrasound and multidetector spiral CT scanning remain the most effective diagnostic approach in patients with cancer with suspected DVT or PE. Ventilation/perfusion scans should be reserved for patients with contrast allergy or renal insufficiency and in pregnant patients in whom pulmonary scintigraphy probably results in a frac-

tionally lower fetal radiation doses compared with spiral CT angiography.⁴⁹ CT or MR venography remain important for diagnosis of venous thrombosis in areas poorly visualized by duplex ultrasound (eg, thorax, abdomen, cerebral vasculature).

The AIOM panel addresses the issue of screening for occult malignancy in patients presenting with idiopathic VTE. Several studies have demonstrated that there is a higher risk of occult cancer in patients with idiopathic VTE.⁵⁰⁻⁵³ Although some of these cancers can be identified by routine assessments at the time of the thrombotic event, approximately 10% of patients subsequently develop overt malignant disease over 24 months after the thrombotic event.⁵⁴ A prospective trial to assess the value of extensive screening did not identify a survival benefit.⁵⁵ Consequently, the AIOM panel does not recommend extensive cancer screening using CT scans, endoscopy, or tumor markers in patients with idiopathic VTE.

UNANSWERED QUESTIONS: A CALL TO ACTION FOR FUTURE RESEARCH

The past decade has seen important strides in the field of cancer-associated thrombosis. Dedicated clinical investigations into the prevention and treatment of this illness have resulted in a better

understanding of risk stratification and an emerging science of prognostic and predictive biomarkers. Despite these advances, however, many clinical questions remain unanswered. This section attempts to highlight gaps in evidence in areas of highest clinical priority.

Prevention of VTE in the Ambulatory Patient With Cancer: A Role for Targeted Prophylaxis

Systemic cancer treatment is increasingly offered in the outpatient setting where an increasingly large proportion of VTE events currently occur. The risk for VTE, however, must be counterbalanced by concern for increased bleeding with use of prophylactic anticoagulation as well as quality-of-life issues related to anticoagulant use in patients already burdened with demanding chemotherapy regimens. As discussed above, there have been several recent randomized clinical trials evaluating prophylactic anticoagulation for ambulatory patients with cancer. While the results of these studies have been inconsistent, it is clear that subgroups of patients with cancer may have rates of VTE as high as those observed in hospitalized medical or surgical patients. Using a risk model- and/or biomarker-based targeted prophylaxis approach may better identify patients with rates of VTE high enough to justify thromboprophylaxis. Patients receiving chemotherapy regimens that incorporate antiangiogenic agents are uniquely at high risk for both VTE and bleeding complications^{10,56,57}; prophylaxis studies are needed in this specific population as well. To reduce the overall public health burden of VTE in patients with cancer, it is vital that funding agencies support further studies of VTE prophylaxis in the outpatient setting.

Prevention of VTE in the Hospitalized Patient With Cancer: A Need for Cancer-Specific Studies

Although all panels recommended prophylactic anticoagulation for the hospitalized patient with cancer if no contraindications exist, this is based on clinical trials that included only a minority of patients with cancer and with little data on rates of bleeding complications in the cancer subgroups. There is abundant evidence from recent studies of hospitalized patients with cancer that the risk of VTE varies significantly across different cancer subgroups (eg, rates are only 2.3% per admission in hospitalized patients with breast cancer as compared with 8.1% in pancreatic cancer or 7.6% in patients with renal cancer).³ It will be difficult, however, to design future randomized clinical trials in hospitalized patients with cancer with a control group receiving no prophylactic anticoagulation given the current consensus. Data regarding both VTE and bleeding risk from well-designed, prospective observational studies may be more helpful in this regard. Data regarding the optimal duration of prophylaxis and the benefit of extended prophylaxis in this setting are also needed.

Treatment of Recurrent VTE

Although the evidence and consensus strongly favor LMWH treatment for up to 6 months in patients with cancer with established VTE, evidence is lacking to support continuing treatment beyond 6 months. It is likely that anticoagulation can be safely discontinued in certain patients (eg, patients who developed a VTE while on adjuvant chemotherapy and are in complete remission with no plans for further treatment). Conversely, certain patients will continue to be at risk for recurrent VTE (eg, a patient with cancer with metastatic disease with plans for indefinite chemotherapy). Data from well-designed randomized clinical trials are essential for clinicians to make evidence-based recommendations in these varied settings.

Issues Regarding the Epidemiology of Cancer-Associated Thrombosis

The advent of multidetector row computer tomography has led to an increased recognition of incidental or unsuspected pulmonary emboli and venous thromboses. Varying prevalence rates of these events have been reported and it has been questioned whether all of these events are truly asymptomatic.⁵⁸⁻⁶⁰ Furthermore, little is known regarding the clinical significance of incidental VTE and the risk/benefit ratio associated with prophylactic or therapeutic anticoagulation in this setting. This area certainly warrants further research. Likewise, arterial thromboembolism is associated with cancer, appears to be increasing in frequency, and is a recognized toxicity of bevacizumab, an antiangiogenic agent.^{56,61} Much work needs to be done to understand the true incidence and prevalence of arterial thromboembolism in patients with cancer and the optimal approach to prevention of life-threatening arterial events, including stroke and myocardial infarction. Finally, rates of VTE reported in clinical trials may underestimate the actual rate by as much as 10-fold.⁶² It is exceedingly important that data regarding venous and arterial thromboembolism in clinical trials, particularly those evaluating new therapies, be collected and reported in a standardized fashion.

Impact of Anticoagulation on Survival of Patients With Cancer

Activation of the hemostatic system promotes tumor growth, angiogenesis, and metastasis.⁶³⁻⁶⁵ Antithrombotic agents could therefore potentially influence tumor biology and outcomes in patients with cancer.^{64,66,67} Multiple recent studies have evaluated the effect of anticoagulants on survival, with encouraging but inconclusive results.¹⁷ Evidence continues to accumulate, however, that VTE in patients with cancer is associated with worsened short-term and long-term mortality.⁶⁸ Given that anticoagulant prophylaxis could have dual benefits for patients with cancer—reducing VTE and prolonging survival—it is vital to pursue well-designed clinical trials of thromboprophylaxis focusing on survival. In this context, it is important to note that several novel antithrombotic agents are on the horizon, some of which may impact tumor biology as well. It is imperative that the oncology community partner with industry and governmental funding organizations to efficiently evaluate the efficacy of these agents with regards to both thrombotic and cancer outcomes.

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