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EVALUATION AND MANAGEMENT OF VENOUS THROMBOEMBOLISM IN CANCER PATIENTS

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ABSTRACT

Venous thromboembolism (VTE) is a frequent complication of cancer associated with morbidity, mortality, increased hospitalizations and higher health care costs. The risk of VTE is 4- to 7-fold higher in patients with cancer than in those without cancer. 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. It is important to assess the risk of thrombotic events in cancer patients and administer effective prophylaxis and treatment to reduce morbidity and mortality, and improves patients' quality of life. Low molecular weight heparin is the first-line treatment for VTE, as an effective and safe means for prophylaxis and treatment. 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. Oral anticoagulation therapy with warfarin is preferable to no therapy. Use of novel oral anticoagulants for either prevention or treatment of VTE in cancer patients is not recommended at this time. Oncologists should educate patients regarding the warning signs and symptoms of VTE, including leg swelling or pain, sudden-onset chest pain, and shortness of breath.

KEYWORDS: Cancer, thromboembolism, risk assessment, prophylaxis, management.

INTRODUCTION

Venous thromboembolism (VTE), which includes deep-vein thrombosis (DVT) and pulmonary embolism (PE), is a common, life-threatening condition in many cancer outpatient populations. Without prophylaxis, up to 8% of ambulatory and almost 20% of hospitalized cancer patients develop VTE. The overall risk is 4–7-fold higher than in non-cancer patients. The risk of cancer-associated VTE varies during the course of the disease, being especially high during the first few months after diagnosis, surgical management, during systemic cancer treatment, immobility, advanced age, prothrombotic medications and in late-stage metastatic disease. In addition, tumors activate coagulation factors and platelets to a variable degree, which supports the growth and spread of tumor cells, thereby creating a positive feedback loop. Development of VTE in patients with cancer is associated with substantial morbidity and mortality, as well as higher health care costs.VTE in cancer patients is associated with a poorer prognosis compared to cancer patients without VTE and is the second leading cause of death in ambulatory patients with cancer. Furthermore, patients with cancer who develop VTE have a threefold increase in hospitalizations and length of hospital stay, as well as higher health care costs, compared with cancer patients without VTE ($p < 0.0001$). The occurrence of VTE also complicates the clinical management of cancer and may terminate or delay needed anticancer therapies.[1-3]

Cancer: A hypercoagulable state

It is common knowledge that cancer induces a hypercoagulable state, and this state is regarded as the main reason for the increased risk of VTE. It is not only the deep veins that may thrombose, but also the superficial veins, as was first noted by Trousseau, who described the association between thrombophlebitis and malignancy. Superficial vein thrombosis, deep vein thrombosis (DVT) and pulmonary embolism (PE) cause a number of symptoms, such as pain and swelling, and

thus have a major impact on the quality of life of cancer patients. Pulmonary embolism constitutes an immediate fatal risk. In the long term, patients may develop post-thrombotic syndrome after DVT, and those with PE may develop pulmonary hypertension. The primary medical objective is therefore, in the first place, to prevent VTE in cancer patients altogether and, if it occurs, to treat it safely, efficaciously, and easily without additionally burdening the patients. Anticoagulants used for patients with VTE in general, but cancer patients specifically, should fulfill all of these criteria.[4] Table-1 summarizes several patient-, cancer-, and treatment-related factors that adversely affect the risk of VTE.[5]

Risk assessment

Risk stratification tools have been developed to identify a subset of cancer patients in whom the risk of developing VTE is high enough to justify thromboprophylaxis. The best validated tool is a score proposed by Khorana and colleagues[2] which aims to identify cancer patients receiving chemotherapy at high risk of VTE based on the tumor type, hemoglobin concentration or use of erythropoietin stimulating agents, white blood cell count, platelet count, and Body Mass Index (BMI) (Table 2).[6,7] Conventionally, the Khorana score is a clinical prediction score developed to identify ambulatory cancer patients at high risk of VTE, who may be eligible for thromboprophylaxis.[8,9] Recent research has indicated that the Khorana score is predictive of in-hospital, symptomatic VTE development in cancer patients who are hospitalized for medical reasons and may be a useful tool for tailoring inpatient anticoagulant thromboprophylaxis.[10]

Role of thromboprophylaxis

Current standard guidelines uniformly recommend thromboprophylaxis for hospitalized cancer patients, while routine thromboprophylaxis is not recommended for ambulatory patients. If VTE occurs, treatment recommendations differ between non-cancer and cancer patients. The former usually receive a rapid-acting, parenteral anticoagulant (unfractionated heparin (UFH), low-molecular weight heparin (LMWH), or fondaparinux) overlapping with and followed by an oral vitamin K antagonist (VKA). The new non-VKA oral anticoagulants (NOACs) have also been approved for this indication. The treatment of cancer-associated VTE is different in the way that LMWHs should be given initially and as long term treatment because of their improved efficacy over VKAs. The use of NOACs is currently not recommended for patients with malignancy and VTE. VKAs have also been useful and used for many decades in cancer patients. However, patients with cancer have a higher risk of recurrent VTE despite sufficient anticoagulation with VKAs. Moreover, treatment of cancer patients with VKAs has turned out to be more unstable than for noncancer patients, which is mainly due to impaired ability to take VKAs on a regular basis and decreased effectiveness of VKAs because of other medications.[1,4]

Management of established VTE

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. 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. 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. 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. 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.[11]

Most hospitalized patients with active cancer require thromboprophylaxis throughout hospitalization. Routine thromboprophylaxis is not recommended for patients with cancer in the outpatient setting. It may be considered for selected high-risk patients. Patients with multiple myeloma receiving antiangiogenesis agents with chemotherapy and/or dexamethasone should receive prophylaxis with either low–molecular weight heparin (LMWH) or low-dose aspirin. Patients undergoing major surgery should receive prophylaxis starting before surgery and continuing for at least 7 to 10 days. Extending prophylaxis up to 4 weeks should be considered in those undergoing major abdominal or pelvic surgery with high-risk features. LMWH is recommended for the initial 5 to 10 days of treatment for deep vein thrombosis and pulmonary embolism as well as for long-term secondary prophylaxis (at least 6 months). Use of novel oral anticoagulants is not currently recommended for patients with malignancy and VTE because of limited data in patients with cancer. Anticoagulation should not be used to extend survival of patients with cancer in the absence of other indications. Patients with cancer should be periodically assessed for VTE risk. Oncology professionals should educate patients about the signs and symptoms of VTE.[12]

Table I: Factors associated with venous thromboembolism in patients with cancer.[5]

Patient-related	Increased age
	Ethnicity (higher risk in African Americans)
	Comorbid conditions (infection, renal and pulmonary disease, arterial thromboembolism, venous thromboembolism history, inherited prothrombotic mutations)
	Obesity
	Performance status
Cancer-related	Site of primary cancer
	Stage (risk increases with higher stage)
	Comorbid conditions
	Histology
	Time since diagnosis (risk increases during first 3-6 months)
Treatment-related	Chemotherapy, antiangiogenesis agents, hormonal therapy
	Radiation therapy
	Surgery lasting 60 minutes or more
	Erythropoiesis-stimulating agents, transfusions
	Indwelling venous access
Biochemical	Leucocyte count exceeding $11x10^9$/L
	Hemoglobin below 100g/L

Table 2: Khorana's Risk Stratification Tool.[2]

Covariate	**Points**
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynaecological, bladder, testicular)	1
Prechemotherapy platelet count $350x10^9$/L or more	1
Hemoglobin level less than 110g/L or use of red cell growth factors	1
Prechemotherapy leucocyte count more than $11x10^9$/L	1
Body mass index (BMI) 35kg/m^2 or more	1
Risk score (points)	**VTE rate (%)**
Low (0)	0.3-0.8
Intermediate (1-2)	1.8-2.0
High (≥3)	6.7-7.1

RECOMMENDATIONS AND CONCLUSION

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.[11]

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