

Cancer Associated Thrombosis: Still many unanswered Questions



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Abstract

LMWH is recommended by major consensus guidelines for both initial and long-term anticoagulation in cancer-associated thrombosis. With improvements in imaging technology and extended survival duration of cancer patients, more unique challenges are encountering. These include optimal duration of anticoagulant therapy, management of incidental VTE, identifying biomarkers that can predict recurrent VTE, treatment of recurrent VTE after initial therapy, the treatment of patients with concurrent bleeding or those at a high risk of bleeding, management of VTE in intracranial malignancies and the limitations of the novel direct oral anticoagulants.

Abbreviations: VTE: Venous Thromboembolism; PE: Pulmonary Embolism; DOACs: Direct Oral Anticoagulants; LMWH: Low-Molecular-Weight Heparin; UFH: Un-Fractionated Heparin; CrCl: Creatinine Clearance; INR: International Normalized Ratio; ASCO: American Society of Clinical Oncology; FDA: Food and Drug Administration; VKAs: Vitamin K Antagonists; HIT: Heparin-Induced Thrombocytopenia.

Introduction

Patients with cancer have a high risk of developing manifestations of cancer-associated venous thrombosis including DVT and PE [1] as well as visceral or splanchnic vein thrombosis. All these together are described as VTE [2]. The risk of developing VTE in cancer patients is increased up to seven-fold as compared to the general population [3]. In addition to VTE, arterial occlusion with stroke and anginal symptoms is relatively common among cancer patients and is possibly related to genetic predisposition [2]. Symptomatic acute VTE is a common complication in cancer patients. It occurs in up to 15% of cancer patients during their disease course and is the second leading cause of death after the malignancy itself [4]. However, VTEs are incidentally detected in about one-half of all cancer patients without any clinical suspicion of VTE at the time of diagnosis [1]. A higher prevalence of incidental VTE has been reported in pancreatic, hepatobiliary, upper gastrointestinal tract, brain, or ovarian cancer and advanced or metastatic disease patients [5].

As many as two-thirds of affected patients report symptoms such as cough and fatigue or signs indicative of potential DVT which may be often regarded as a side effect of the underlying cancer or its associated treatment [1]. Incidental VTEs are mostly diagnosed by multidetector computed tomography scans requested for baseline staging, treatment response evaluation, or routine

surveillance while off anticancer treatment. Ultrasonography has potential usefulness to screen for incidental DVT in high-risk populations before chemotherapy with low yield in serial testing. The clinical significance of detecting incidental VTEs on screening ultrasonography is unknown [5].

Risk factors for VTE

VTE risk factors in cancer patients can be grouped into 3 general categories: intrinsic and extrinsic patient-related factors, cancer-related factors and treatment-related factors. The risk for VTE and recurrent VTE is highest among certain hematologic malignancies, such as lymphoma, acute leukemia and multiple myeloma. Patients with high-grade lymphoma and acute promyelocytic leukemia appear to be at higher risk than other forms of lymphoma or leukemia [6]. Lung cancer, gastrointestinal cancer (stomach/ colon), pancreatic cancer, kidney cancer, bone cancer, myelodysplastic disorder and patients with distant metastasis are also susceptible [7]. Several risk factors for developing venous thrombosis usually coexist in cancer patients including surgery, hospital admissions, immobilization; and the presence of an indwelling central catheter [2], older age, platelet count $\geq 350 \times 10^9 /L$, hemoglobin $< 100 \text{ g/L}$ or use of red cell growth factors, and leucocyte count $\geq 11 \times 10^9 /L$ or BMI $> 35 \text{ kg/m}^2$ [7].

Chemotherapy such as thalidomide/ lenalidomide/ pomalidomide in combination with high dose dexamethasone [7] (480 mg/month) or doxorubicin or multiagent chemotherapy in myeloma patients [6], exogenous hormonal therapies such as tamoxifen/ raloxifene, diethylstilbestrol [7] and new molecular targeted therapies are well-recognized risk factors for venous thromboembolism [2]. The risk of VTE in cancer patients is amplified by concomitant risk factors such as factor V Leiden mutation or prothrombin 20210A mutation [7] as well as by the presence of other comorbid features that influence the overall thrombotic complications in non-cancerous patients [2].

Assessment of the Thrombotic Risk In Cancer Patients

Risk predictors models include the Ottawa score which identify patients at highest risk of recurrent VTE and may benefit from prolonged anticoagulation treatment among those with cancer-associated VTE, and the Khoranna score for chemotherapy-associated VTE [7]. The Khoranna score is based on five predictive models including cancer sites, platelet counts, hemoglobin level or the use of erythropoiesis-stimulating agents, leucocyte count and body mass index [3].

VTE Thromboprophylaxis (inpatients and following discharge)

LMWH, fondaparinux or UFH (category 1 options) is recommended by NCCN guidelines panel for all hospitalized cancer patients with no contraindication to such therapy [6]. Cancer patients at a high risk setting for VTE is recommended to continue receiving VTE prophylaxis following hospital discharge with the duration of anticoagulation determined by the clinical situation. Myeloma patients receiving highly thrombotic chemotherapy are recommended for VTE thromboprophylaxis based on a risk-assessment model of International Myeloma Working Group. Aspirin 81-325 mg is recommended for lower risk myeloma outpatients with one or fewer individual or myeloma risk factor and warfarin or LMWH for high-risk myeloma outpatients with two or more individual or myeloma risk factors [6].

Initial Management of A First Episode Of Cancer-Associated VTE

a. Choice of Anticoagulant

Options for the initial treatment of cancer-associated thrombosis include LMWH, UFH, fondaparinux [8] and warfarin [7]. UFH can be considered for patients with severe renal insufficiency [7] (CrCl < 30 mL/min) given its shorter half-life, reversibility with protamine sulfate, and dependence on hepatic clearance [8]. Fondaparinux can be considered for patients with heparin induced thrombocytopenia (7). Barriers to fondaparinux use in oncology patients include a relatively long half-life of 17 to 21 hours, the lack of a reversal agent, and 100% dependence on renal clearance [8]. Patients with hepatic cancer or metastasis may not do well on warfarin whereas patients with renal cancer may not be well suited for LMWH therapy [7].

b. Treatment of Pulmonary Embolism

Anticoagulant therapy is recommended for all acute PE patients with no contraindication to such therapy. An IVC filter should be strongly considered in PE patients due to lower extremity, pelvic or abdominal DVT if contraindication to anticoagulation is present. Thrombolytic therapy is a therapeutic consideration in patients with submassive PE and evidence of moderate or severe right ventricular enlargement or dysfunction [6].

Long-Term Management of A First Episode Of Cancer-Associated VTE

a. Choice of Anticoagulant

The overall results of several trials provide consistent evidence of improved efficacy of LMWH vs VKA in the prevention of recurrent VTE in patients with cancer-associated VTE [8]. VKAs use is problematic in oncology patients. VTE recurrence rates in cancer patients, is threefold higher than in patients without cancer despite maintenance of the INR within the therapeutic range. Advantages of LMWH include (a) no need for laboratory monitoring of its anticoagulant activity; (b) a shorter half-life that facilitates temporary interruption for procedures or thrombocytopenia; (c) limited drug interactions; and (d) no food interactions or reliance on oral intake or gastrointestinal tract absorption [8]. If LMWH is unavailable, the ASCO 2013 VTE Prevention and Treatment Guideline recommends VKA use with a target INR of 2 to 3 as an acceptable alternative [8].

b. Optimal Duration of Anticoagulant Therapy

All current guidelines recommend LMWH for at least 3-6 months in cancer-associated symptomatic VTE [7]. The decision to continue or withdraw treatment after this initial period as well as the type and dose of anticoagulant should be evaluated case-by-case considering the benefit-to-risk ratio, drug availability, and patient preference [5]. Very little published data is available on the epidemiology of cancer-associated VTE beyond the initial 6 months [1]. Continuing anticoagulation treatment indefinitely beyond the acute treatment period of 3 to 6 months with periodic reassessment of the risks and benefits is suggested in patients with active malignancy and ongoing cancer treatment [7].

Management of Recurrent VTE in Cancer Patients

Once recurrent VTE is confirmed, HIT has to be excluded in patients who were first exposed to LMWH or UFH within the past 10 to 14 days. Compliance should also be reviewed [8].

a. Identifying Biomarkers that can Predict Recurrent VTE

D-dimer, prothrombin fragment 1+2, soluble P-selectin, and tissue factor appear to influence the risk for a first episode of VTE during the first year after cancer diagnosis. However, the CATCH trial did not find an association between baseline levels of D-dimer, factor VIII, or soluble P-selectin at VTE diagnosis and VTE recurrence, but the highest quartile of circulating tissue factor

antigen level was independently associated with a threefold risk of recurrence [1].

b. Treatment of Recurrent VTE in Cancer

The options for recurrent VTE in patients on VKA therapy and a subtherapeutic INR include continuation of VKA after a bridging period with LMWH (or UFH) or switching to LMWH monotherapy. The latter is likely preferred, especially in patients who had unstable INR values and the time-in-therapeutic range was low [8]. Patients with recurrent VTE and a therapeutic INR while on warfarin therapy can be switched to intravenous heparin (LMWH preferred). Patients with VTE recurrence and a therapeutic a PTT while receiving UFH can be switched to intravenous LMWH or fondaparinux or increase their intravenous UFH dose. A switch to heparin-based therapy is an option following failure of fondaparinux to prevent VTE recurrence and vice versa [6].

Management of Selected Cases of Cancer-Associated VTE

a. Management of VTE in Intracranial Malignancies

Management of VTE in patients with intracranial malignancies is particularly challenging because of the fear of intracranial hemorrhage [8]. The ASCO 2013 VTE Guideline recommends treating patients with intracranial malignancies with standard anticoagulation. Small retrospective studies indicate that anticoagulation can be safely used. There is improvement in survival duration of glioma or metastatic brain tumors patients with LMWH. Intravenous UFH followed by VKA or subcutaneous UFH has been associated with rates of symptomatic intracranial hemorrhage between 0% and 7% [8].

b. Treatment of Cancer Patients with Concurrent Bleeding or at High Risk of Bleeding

Cancer patients have a higher bleeding risk than non-cancer patients because they are uniquely at risk of malignant vascular or mucosal invasion and cancer- or chemotherapy-induced thrombocytopenia. They also have a high prevalence of comorbidities commonly associated with bleeding, including older age, frailty, renal impairment, and liver dysfunction [1]. Anticoagulation may be continued in patients with minor bleeding as long as close follow-up is available. If anticoagulation is absolutely contraindicated, follow-up imaging should be performed to assess for thrombus progression, and IVC filter insertion can be considered. Platelet transfusions may be used in severe cancer- or chemotherapy-induced thrombocytopenia, to allow anticoagulation [8].

c. Treatment of Incidental DVT

Anticoagulant treatment is recommended for incidental proximal DVT and incidental PE that involves multiple subsegmental or more proximal pulmonary arteries. The clinical relevance of isolated subsegmental PE without concomitant DVT is uncertain and either a watchful approach or a shorter anticoagulation course may be considered. Preliminary evidence suggests that incidental distal DVT and SVT may benefit of anticoagulant treatment [5].

Adverse Effect of Anticoagulation

a. HIT: It has been associated with the use of both LMWH and UFH. Platelet monitoring is recommended at baseline and then every 2 weeks thereafter or more frequently as clinically indicated. If HIT is suspected, the patient should be evaluated using the 4Ts score (thrombocytopenia, the timing of the onset of platelet fall, the presence of thrombosis or other clinical sequelae and evidence of other potential causes of thrombocytopenia [6].

b. Bleeding: It is the most serious adverse effect of anticoagulation. Anticoagulants do not cause bleeding, but they intensify the severity of any bleeding by interfering with hemostasis [1]. Similar to non-cancerous patients, the most common sites of bleeding in cancer patients are the gastrointestinal and genitourinary tracts [1]. Therapeutic anticoagulation with LMWH may be administered if the platelet count can be maintained above $50 \times 10^9/L$. Half-dose LMWH can be administered for platelet counts between 20 and $50 \times 10^9/L$, with close follow-up for possible bleeding. Therapeutic anticoagulation should be held if platelet count is $<20 \times 10^9/L$ [8]. VKA therapy should be avoided in patients with severe thrombocytopenia from the prolonged anticoagulant effect and unpredictable dose response [8]. However, unlike patients without cancer, bleeding events in cancer patients do not correlate with the intensity of warfarin anticoagulation. This finding may reflect exacerbation of bleeding at tumor sites even at a low intensity of anticoagulation [1].

c. Therapeutic Anticoagulation Failure: anticoagulant failure is defined as extension of DVT or PE or new DVT or PE while on recommended anticoagulation therapy. Causes include catheter-related hypercoagulability such as trousseau syndrome, HIT, cancer-related anatomic causes such as vascular compression and acquired and/ or familial thrombophilia. Anticoagulation failure of warfarin or UFH can occur in the setting of a therapeutic INR or aPTT value [6].

The Efficacy and Safety of DOACs in Patients with Cancer-Associated VTE

Since 2010, the US FDA has approved four DOACs: dabigatran (a direct thrombin inhibitor), rivaroxaban, apixaban, and edoxaban (all direct Xa inhibitors) to reduce the risk of stroke and systemic embolism in non valvular AF patients [9]. These new anticoagulants do not present some of the limitations associated with warfarin use, such as frequent INR monitoring and drug interactions [10]. The incidence rates of recurrent VTE in cancer patients varied from 1.8% to 5.8%, in patients treated with a new DOAC and varied from 2.8% to 7.4% in those treated with a VKA [4]. DOAC's (especially edoxaban and rivaroxaban) were more effective than LMWHs in preventing recurrent VTE in cancer associated thrombosis[10]. Concerns have been raised about the safety and efficacy of DOACs in cancer patients [9]. DOAC's (especially edoxaban and rivaroxaban) were associated with a small significant increased risk of major bleeding as well as a trend toward more clinically relevant non-major bleeding. Subgroup analysis from randomized controlled trials and observational studies suggest that gastrointestinal cancer

patients receiving DOACs may be at the highest risk of bleeding. DOACs should be used carefully in these patients [10].

However, evidence supporting the use of DOACs in cancer patients for any indication is extremely limited (9). Patients with cancer are complicated by inability to tolerate oral intake as adverse effects of chemotherapy can include loss of appetite, emesis and mucositis. There is currently no mechanism of monitoring DOAC levels in the presence of drug-drug interactions or gastrointestinal adverse effects resulting from chemotherapy [7]. Due to the dearth of data, the ASCO does not recommend use of DOACs for VTE patients with cancer [9]. New DOAC are likely to have a major impact in the next few years changing clinical practice of anticoagulation therapy [11].

Conclusion

Still there are many clinical questions remain unanswered about the use of DOAC in cancer patients. DOAC medications are not currently supported by guidelines but ongoing clinical studies will provide much needed evidence to guide clinical use.

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