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Predictors of recurrent venous thromboembolism and bleeding on anticoagulation

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ABSTRACT

The impact of venous thromboembolism (VTE) in the cancer population remains substantial despite significant advances in detecting and treating thrombotic events. While there is extensive literature regarding predictors of first VTE event in cancer patients as well as a validated predictive score, less data exist regarding recurrent VTE in cancer cohorts and associated predictive variables. A similar paucity of data in regard to bleeding events in cancer patients receiving anticoagulation has been observed. This review article will highlight clinical risk factors as well as predictive biomarkers associated with recurrent VTE and bleeding in cancer patients receiving therapeutic anticoagulation. Predictive risk assessment models for cancer-associated recurrent VTE and bleeding are also discussed.

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Introduction

The impact of venous thromboembolism (VTE) in the cancer population remains substantial despite significant advances in detecting and treating thrombotic events. Deep venous thrombosis (DVT) and pulmonary embolism (PE) confer significant morbidity and mortality in patients with malignancy, and recent studies have demonstrated that even asymptomatic or incidentally detected thrombotic events may confer similar risk [1-3]. Thromboembolism in cancer patients is associated with reduced survival in a variety of settings [4]. Compared to cancer patients without VTE, those with VTE are three times more likely to die within 6 months [5].

Treating thrombotic events in cancer patients also confers a greater level of complexity given associated high rates of recurrent thromboembolism despite therapeutic anticoagulation as well as the paradoxical and heightened risk for major bleeding in such cohorts. Approximately 10-17% and 6-9% of cancer patients with VTE treated with a vitamin K antagonist (VKA) and low molecular weight heparin (LMWH) respectively will develop recurrent VTE during follow up [6,7]. In a prospective cohort of 842 patients receiving anticoagulation for VTE, patients with a diagnosis of active malignancy were found to have significantly increased rates of recurrent VTE or major bleeding within a 12 month time period as compared to those without cancer; metastatic disease also appeared to increase risk for such events [8]. Furthermore, recurrent VTE did not appear to correlate with intensity of anticoagulant therapy and often developed within the first month of treatment.

While there is extensive literature regarding predictors of first VTE event in cancer patients as well as a validated predictive score [9], less data exist regarding recurrent VTE in cancer cohorts and associated predictive variables. A similar paucity of data in regard to bleeding events in cancer patients receiving anticoagulation has been observed.

This review article will highlight clinical risk factors as well as predictive biomarkers associated with recurrent VTE and bleeding in cancer patients receiving therapeutic anticoagulation. Predictive risk assessment models groups for cancer-associated recurrent VTE and bleeding will also be discussed.

Predictors of recurrent cancer-associated VTE

Clinical risk factors

Determining recurrent VTE risk in cancer patients is complex and influenced by a number of clinical risk factors. Risk factors for recurrent VTE can be classified as patient-related, cancer-related and treatment-related (Table 1).

In a prospective study of 842 patients therapeutically anticoagulated for VTE, patients with cancer (n = 181) were found to have higher rates of recurrent PE and/or DVT over a 12 month observation period (20.7%, 95% Confidence Interval (CI), 15.6%-25.8% vs. 6.8%, 95% CI, 3.9% -9.7% in patients without a diagnosis of malignancy) [8]. Frequency of recurrent VTE in cancer patients with localized, Stage III, and Stage IV disease was 14.5, 44.1 and 54.1 per 100 patient-years respectively. Furthermore, lung and gastrointestinal cancers appeared to confer additional risk for recurrent VTE as compared to other primary sites with hazard ratios of 6.9 and 5.1, respectively. Of note, breast cancer was not observed to be associated with increased recurrent VTE risk in this cohort.

The presence of metastatic disease also appears to confer risk for recurrent thrombotic events in cancer patients. Louzada et al published a large systematic review which included four retrospective and

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Table 1
Clinical Risk Factors and Candidate Biomarkers for Cancer-Associated Recurrent VTE

Patient-Related Risk Factors	Cancer-Related Risk Factors	Candidate Biomarkers
Age < 65 years	Diagnosis of malignancy within 3 months of VTE event	Tissue factor (TF)
Female gender		D-dimer
	Locally advanced or metastatic cancer	
Prior history of VTE		C Reactive protein (CRP)
	Primary tumor site (lung, hepatobiliary)	
	Venous compression secondary to tumor or malignant adenioathy	

six prospective studies in an effort to determine which malignancy characteristics were associated with recurrent VTE in cancer cohorts [10]. Included studies were those in which patients were diagnosed with cancer excluding basal and squamous cell skin cancers within six months prior to or after objectively diagnosed DVT and/or PE. Therapeutic anticoagulation with either VKAs or LMWH was initiated after diagnosis of VTE. Primary outcome was documented VTE recurrence despite anticoagulation and association with malignancy characteristics. On pooled analysis of the ten studies (n = 4791), there were a total of 331 observed VTE recurrences (7%). Patients with metastatic cancer were observed to have a significantly increased recurrent VTE rate as compared to those with localized malignancy (RR 1.36; 95% CI 1.06-1.74, p = 0.01). Tumor site and histology were unable to be accurately analyzed as predictors of recurrent VTE in the review. In a subgroup analysis of the CLOT (Comparison of Low Molecular Weight Heparin Versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients With Cancer) trial which investigated the use of VKAs versus LMWH for prevention of recurrent VTE in patients with malignancy, metastatic cancer was also associated with risk of recurrent VTE with a hazard ratio (HR) of 3.5 [11]. Furthermore, CLOT subgroup analysis demonstrated that tumor primary site, specifically lung cancer, was an independent predictor of recurrent VTE.

In a subgroup analysis published in 2008, Registro Informatizado de la Enfermedad Trombo Embolica (REITE) investigators focused on predictors of recurrent VTE in cancer patients [12]. As of May 2007, 3,805 cancer patients with acute VTE had been enrolled in the RIETE registry. Of these patients, 1,684 (44%) had metastatic disease and 1,464 (38%) had been diagnosed with cancer within three months prior to VTE presentation. Lung (n = 461, 12%), breast (n = 483, 13%), gastrointestinal (n = 813, 21%), and genitourinary (n=1096, 29%) cancers comprised the majority of solid tumor cases. Only 285 patients with hematologic malignancy were included. Long term anticoagulant therapy with LMWH was utilized in 1643 patients (43%) versus VKA drugs in 1855 (49%) patients; 146 patients had an inferior vena cava filter placed.

During the three month study period, 90 patients (2.4%) developed objectively verified recurrent PE with significant associated mortality [12]. Predictive variables potentially associated with recurrent PE included younger patient age, clinically overt PE on initial presentation, more recent diagnosis of cancer as well as lung or brain cancer. On multivariate analysis, only age <65 years (Odds Ratio (OR) 3.0, CI 1.9-4.9, p < 0.001), clinically overt PE on initial presentation (OR 1.9, CI 1.2-3.2, p = 0.01) or diagnosis of cancer within three months of VTE presentation (OR 2.0, CI 1.2-3.1, p = 0.005) were associated with increased risk for recurrent PE. A total of 100 patients (2.6%) were diagnosed with recurrent DVT during the three month follow up period. Upon multivariate analysis, only age <65 years (OR 1.6 CI 1.0-2.4, p = 0.04), or diagnosis of cancer within three months of VTE presentation (OR 2.4, CI 1.5-3.6, p < 0.001) were associated with increased risk for recurrent DVT.

Recent studies have demonstrated that additional risk factors, including female gender, history of prior VTE, hepatobiliary cancers and venous compression secondary to tumor burden or malignant adenopathy are associated with recurrent VTE in cancer patients and will be outlined later in this review [13,14].

Predictors of recurrent VTE from CATCH subgroup analyses

The CATCH trial was a large international randomized controlled trial which investigated the use of tinzaparin versus warfarin for treatment of acute symptomatic PE and/or DVT in patients with cancer [13]. Nine hundred patients were enrolled and randomized to receive systemic anticoagulation with either aforementioned agent for a treatment time period of 6 months as per CAT guidelines. Included patients were those with pathologically confirmed malignancy with exception of nonmelanoma or basal cell skin cancers, those diagnosed with cancer within the preceding 6 months, those who received cancer specific treatment during the preceding 6 months, patients with recurrent or metastatic disease as well as patients with hematologic malignancies not in remission. Exclusion criteria included pre-existing contraindications to systemic anticoagulation, therapeutic anticoagulation at time of VTE diagnosis, systemic anticoagulation greater than 72 hours prior to randomization, history of heparin induced thrombocytopenia (HIT) or documented sensitivity to study anticoagulants, significant renal dysfunction (creatinine clearance ≤20 mL/min/1.73 m^2), life expectancy of less than 6 months, and men and women of childbearing age not on contraceptives. Patients enrolled in other clinical trials or deemed high risk for protocol non-compliance were also excluded. A large proportion of enrolled patients had solid tumors (89.6%) and over half had metastatic disease; only 10.4% of patients had hematologic malignancies. A total of 57 patients (6.3%) had a history of prior VTE at time of enrollment.

Primary outcome measures included objectively verified recurrent symptomatic DVT, asymptomatic or incidental venous thrombotic events, specifically proximal DVT and PE, as well as non-fatal and fatal pulmonary embolism. Overall mortality, as well as clinically major and non-major bleeding events were also analyzed as safety outcomes.

A total of 31 (6.9%) and 45 (10%) patients in the tinzaparin and warfarin treatment groups developed recurrent VTE during 6 month follow up respectively (HR 0.65, 95% CI, 0.41-1.03, p = 0.07). There was no statistically significant difference in major bleeding between the two treatment groups although less non-major bleeding events were observed in the tinzaparin treatment arm (10.9% versus 15.3%; HR 0.58, 95% CI, 0.40-0.84, p = 0.004). There was no difference in overall mortality between the two groups.

A recently presented prespecified subgroup analysis of CATCH Trial data focused specifically on clinical predictors and biomarkers of recurrent VTE [15]. At time of randomization, the presence of metastatic disease (54.7%), active treatment with chemotherapy (32.0%), hospitalization within the previous 3 months (31.8%) and Eastern Cooperative Group (ECOG) performance status of 2 (23.2%) appeared to be the most prevalent clinical predictors of recurrent VTE. While recurrent VTE rates were similar amongst various racial and ethnic groups, a higher incidence of recurrent events was noted in Asian and Middle Eastern clinical centers (10.0%). At regression analysis, only two clinical variables were found to be significantly associated with recurrent VTE, hepatobiliary cancer and venous compression secondary to tumor bulk or malignant adenopathy.

Biomarkers

Readily available laboratory values and novel biomarkers have been investigated in predictive cancer associated thrombosis (CAT) models. For instance, multiple studies have demonstrated that

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