Brief Report

THROMBOSIS AND HEMOSTASIS

Risk factors predictive of occult cancer detection in patients with unprovoked venous thromboembolism

Ryma Ihaddadene,[1,2] Daniel J. Corsi,[2] Alejandro Lazo-Langner,[3,4] Sudeep Shivakumar,[5,6] Ryan Zarychanski,[7,8] Vicky Tagalakis,[9,10] Susan Solymoss,[11,12] Nathalie Routhier,[13,14] James Douketis,[15,16] Gregoire Le Gal,[1,2,17] and Marc Carrier[1,2,17]

[1]Department of Medicine, University of Ottawa, Ottawa, ON, Canada; [2]Ottawa Hospital Research Institute, Ottawa, ON, Canada; [3]Department of Medicine, and [4]Department of Epidemiology and Biostatistics, University of Western Ontario, London, ON, Canada; [5]Department of Hematology, Queen Elizabeth II Health Sciences Centre, Halifax, NS, Canada; [6]Department of Medicine, Dalhousie University, Halifax, NS, Canada; [7]Department of Medicine, University of Manitoba, Winnipeg, MB, Canada; [8]Department of Hematology and Medical Oncology, CancerCare Manitoba, Winnipeg, MB, Canada; [9]Department of Medicine, Sir Mortimer B. Davis Jewish General Hospital, Montreal, QC, Canada; [10]Center for Clinical Epidemiology, Lady Davis Institute, Montreal, QC, Canada; [11]Department of Medicine, McGill University, Montreal, QC, Canada; [12]Division of Hematology, Montreal General Hospital and St. Mary's Hospital, Montreal, QC, Canada; [13]Department of Medicine, Université de Montréal, Montreal, QC, Canada; [14]Sacre Coeur Hospital, Montreal, QC, Canada; [15]St. Joseph's Healthcare Hamilton, Hamilton, ON, Canada; [16]Department of Medicine, McMaster University, Hamilton, ON, Canada; and [17]The Ottawa Hospital, Ottawa, ON, Canada

Key Points

- It remains unclear whether a subgroup of high-risk patients could potentially benefit from a more extensive screening strategy.
- Age, prior provoked VTE, and smoking status may be important predictors of occult cancer detection in patients with first unprovoked VTE.

Risk factors predictive of occult cancer detection in patients with a first unprovoked symptomatic venous thromboembolism (VTE) are unknown. Cox proportional hazard models and multivariate analyses were performed to assess the effect of specific risk factors on occult cancer detection within 1 year of a diagnosis of unprovoked VTE in patients randomized in the Screening for Occult Malignancy in Patients with Idiopathic Venous Thromboembolism (SOME) trial. A total of 33 (3.9%; 95% CI, 2.8%-5.4%) out of the 854 included patients received a new diagnosis of cancer at 1-year follow-up. Age ≥ 60 years (hazard ratio [HR], 3.11; 95% CI, 1.41-6.89; $P = .005$), previous provoked VTE (HR, 3.20; 95% CI, 1.19-8.62; $P = .022$), and current smoker status (HR, 2.80; 95% CI, 1.24-6.33; $P = .014$) were associated with occult cancer detection. Age, prior provoked VTE, and smoking status may be important predictors of occult cancer detection in patients with first unprovoked VTE. This trial was registered at www.clinicaltrials.gov as #NCT00773448. (*Blood*. 2016;127(16):2035-2037)

Introduction

Venous thromboembolism (VTE), which comprises deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common and potentially fatal condition.[1-3] Unprovoked events, which occur in the absence of a major thrombogenic risk factor, represent approximately 40% of all VTEs.[4] Unprovoked VTEs may be the earliest indication of cancer.[5,6] It was previously demonstrated that between 3.2% and 10.0% of patients presenting with unprovoked VTEs will be subsequently diagnosed with cancer, with the highest risk in the first year after the diagnosis of VTE.[7-9] This has led to a debate on whether an extensive screening for occult cancer in these patients is warranted. Two recently published studies have reported that using an extensive screening strategy is unlikely to provide benefit to all patients with unprovoked episodes of VTE.[9,10] However it remains unclear whether a subgroup of high-risk patients could potentially benefit from a more extensive occult cancer screening strategy. Identification of risk factors associated with early detection of occult cancers to stratify patients with higher risk of cancer detection after an unprovoked VTE might be of potential clinical

importance and provide a basis for effective screening and preventive strategies. We sought to assess the risk factors predictive of occult cancer detection in patients with a first objectively proven unprovoked symptomatic VTE.

Study design

Post hoc predefined analyses of the Screening for Occult Malignancy in Patients with Idiopathic Venous Thromboembolism (SOME) trial[10] were performed. The SOME trial is a multicenter, open-label, randomized controlled trial of patients with a first unprovoked VTE that compared a limited evaluation for occult cancer screening (basic laboratory testing, chest radiography, and breast, cervical, and prostate cancer screening) with a more comprehensive strategy (limited evaluation plus computed tomography scan of the abdomen and pelvis).[10] Unprovoked VTE was defined as occurring in the absence of known malignant disease in the past 5 years, trauma of the leg or lower-extremity plaster cast,

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Table 1. Risk factors of occult malignancy among patients with a first unprovoked VTE

	Patients without cancer (n = 821) No. (%)	Patients with cancer (n = 33) No. (%)	Absolute risk (%)	Univariate analysis HR (95% CI)	P	Multivariate analysis HR (95% CI)	P
Age at diagnosis ≥ 60 y	288 (35.1)	20 (60.6)	6.5	2.90 (1.44-5.83)	.003	3.11 (1.41-6.89)	.005
Male sex	555 (67.6)	21 (63.6)	3.6	0.72 (0.35-1.46)	.358	—	—
Medical history							
Hypertension	176 (21.4)	11 (33.3)	5.9	2.06 (1.00-4.26)	.050	1.33 (0.60-2.96)	.485
Myocardial infarction	21 (2.6)	1 (3.0)	4.5	1.52 (0.21-11.17)	.679	—	—
Stroke	10 (1.2)	1 (3.0)	9.1	2.34 (0.32-17.18)	.402	—	—
Congestive heart failure	2 (0.2)	0 (0.0)	—	—	—	—	—
Diabetes mellitus	36 (4.4)	3 (9.1)	7.7	2.89 (0.87-9.55)	.082	2.09 (0.60-7.22)	.258
COPD	18 (2.2)	1 (3.0)	5.3	0.93 (0.13-6.84)	.945	—	—
Previous cancer	46 (5.6)	4 (12.1)	8.0	2.92 (1.03-8.33)	.045	1.87 (0.61-5.72)	.274
Prior provoked VTE	42 (5.1)	5 (15.2)	10.6	3.57 (1.38-9.25)	.009	3.20 (1.19-8.62)	.022
Current smoker	123 (15.0)	9 (27.3)	6.8	2.15 (1.00-4.63)	.050	2.80 (1.24-6.33)	.014
Past smoker	271 (33.0)	13 (39.4)	4.6	1.32 (0.66-2.66)	.435	—	—
Type of current VTE							
DVT only	447 (54.4)	24 (72.7)	5.1	1.89 (0.88-4.07)	.104	1.89 (0.87-4.10)	.108
PE only	271 (33.1)	7 (21.2)	2.5	0.60 (0.26-1.38)	.229	—	—
DVT + PE	103 (12.6)	2 (6.1)	1.9	0.54 (0.13-2.24)	.392	—	—
Medications							
Oral contraceptive pills	48 (5.8)	0 (0.0)	—	—	—	—	—
Exogenous estrogen	18 (2.2)	1 (3.0)	5.3	1.51 (0.21-11.07)	.685	—	—
Antiplatelet agent	39 (4.8)	1 (3.0)	2.5	0.62 (0.09-4.56)	.641	—	—

COPD, chronic obstructive pulmonary disease.

surgery using general anesthesia 3 months before the event, immobilization for 3 or more days, previous unprovoked VTE, thrombophilia (hereditary or acquired), and current pregnancy. Methods have previously been described in detail.[10]

All patients enrolled (n = 854) in the SOME trial were included in the analyses. The influence of the following potential risk factors was analyzed: (1) demographic characteristics (age and sex), (2) medical history (hypertension, myocardial infarction, stroke, congestive heart failure, diabetes mellitus, chronic obstructive pulmonary disease, previous cancer, previous provoked VTE, and smoking history), (3) qualifying episode of VTE (DVT only, PE only, DVT and PE), and (4) baseline medications (oral contraceptive pills, exogenous estrogen, antiplatelet agent). Cox proportional hazard models were used to analyze the effect of these specific risk factors on the outcome of occult cancer detection within 1 year of a diagnosis of unprovoked VTE. Multivariate analyses were performed using Cox proportional hazard models that included all variables that achieved a P value of ≤ .20 in univariate analyses.

Results and discussion

A total of 33 patients (3.9%; 95% CI, 2.8%-5.4%) received a new diagnosis of cancer at 1-year follow-up. In total, 471 (55.2%) had DVT only, 278 (32.6%) had PE only, and 105 (12.3%) had both DVT and PE. Among the participants included in the analysis, 187 (21.9%) had hypertension, 50 (5.9%) had a previous cancer, 47 (5.5%) had a previous provoked VTE, and 132 (15.5%) were current smokers (Table 1). In terms of baseline medications, 48 (5.8%) were taking oral

contraceptive pills, 19 (2.2%) an exogenous estrogen, and 40 (4.7%) an antiplatelet agent (Table 1).

Age ≥ 60 years was associated with cancer with a corresponding hazard ratio (HR) of 3.11 (95% CI, 1.41-6.89; P = .005). When age was explored as a continuous variable, an increase of 1 year of age was also associated with an increased hazard of occult cancer detection (HR, 1.06; 95% CI, 1.03-1.08; P < .0001). Patients with a previous provoked VTE (HR, 3.20; 95% CI, 1.19-8.62; P = .022) or current smoking (HR, 2.80; 95% CI, 1.24-6.33; P = .014) were associated with higher hazard of being detected with cancer during the 1-year follow-up period (Table 1). The combined effect of these 3 characteristics in the adjusted model was associated with an HR for occult cancer of 3.33 (95% CI, 1.73-4.92; P < .001). Sex and baseline medications were not associated with occult malignancy. Predicted risks at 2 and 5 years that were based on adjusting the baseline risk from the Cox proportional hazards regression model using different combinations of risk factors are reported in Table 2.

Our most salient finding is that simple characteristics of age at unprovoked VTE diagnosis, prior provoked VTE, and being a current smoker are important predictors of occult cancer diagnosis among patients with VTE. Some of our results are consistent with previously published literature. The increased risk in elderly patients has been reported in a subgroup analysis of a randomized controlled trial comparing extensive screening for occult cancer with no further testing in patients with acute unprovoked VTE.[11] Although a prior history of provoked VTE has never been described as an important risk factor for occult cancer detection, it is plausible that patients with

Table 2. Predicted 2-year and 5-year risk of occult cancer among patients with a first unprovoked VTE based on age, prior provoked VTE, and smoking

	Age < 60 y				Age ≥ 60 y			
	No VTE		Prior provoked VTE		No VTE		Prior provoked VTE	
Risk	Nonsmoker	Smoker	Nonsmoker	Smoker	Nonsmoker	Smoker	Nonsmoker	Smoker
2-y	0.2	0.6	0.7	1.8	0.6	1.8	2.0	5.5
5-y	1.8	5.0	5.7	15.2	5.6	14.8	16.8	40.2

prior provoked events (eg, postsurgery) might be more susceptible to VTE complications in the presence of an underlying occult cancer. Finally, smoking has been associated with oral, lung, colorectal, and urothelial cancers. Up to 25% of cancers diagnosed in this trial (colorectal [n = 5] and urothelial [n = 3]) might have been related to smoking. Our findings may help identify patients with first unprovoked VTE who are at particularly high risk and who may benefit from closer surveillance and additional testing. Our results need to be validated in other cohorts of patients, and further prospective studies are needed to assess whether occult cancer screening is beneficial in this high-risk group of patients.

Our study has a number of strengths, including prospective data collection within a multicenter trial and good measurement of a priori identified and potentially important predictors of cancer. Our study also has limitations. First, it has a relatively small number of events, which limits the ability to adjust for important confounders and to provide actual accurate absolute estimates for each possible combination of risk factors, although it is the largest trial population studied on this topic. Nevertheless, we were able to identify clinically relevant predictors for occult cancer. Second, potentially relevant risk factors, such as laboratory measurements, were not collected at study baseline. Finally, the definition of unprovoked VTE is heterogeneous, and other clinical settings might have different patient demographics (eg, older patient population), and therefore our results might not be generalizable to all clinical practices.

In conclusion, age, prior provoked VTE, and smoking may be predictors of occult cancer in patients presenting with a first unprovoked VTE. Our results might help identify patients with acute unprovoked VTE at high risk of underlying cancer.

Authorship

Contribution: R.I. designed and performed the research, analyzed and interpreted data, performed statistical analysis, and wrote the manuscript; D.J.C. analyzed and interpreted data, performed statistical analysis, and wrote the manuscript; M.C. designed the research, interpreted data, and wrote the manuscript; and A.L.-L., S. Shivakumar, R.Z., V.T., S. Solymoss, N.R., J.D., and G.L.G. collected and interpreted the data and provided vital reviews of the manuscript.

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Correspondence: Marc Carrier, University of Ottawa, 501 Smyth Rd, Box 201A, Ottawa, ON, Canada K1H 8L6; e-mail: mcarrier@toh.on.ca.

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