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Monocyte count associated with subsequent symptomatic venous thromboembolism (VTE) in hospitalized patients with solid tumors

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ABSTRACT

Background: Solid tumor is the strongest risk factor for VTE in Thai medical in-patients. This study aimed to identify the markers predicting symptomatic VTE in this group.
Methods: Solid tumor patients admitted to the medical wards from June 2007 to December 2009 were monitored for VTE symptoms, excluding patients with VTE on admission. Anticoagulant prophylaxis was not given. Cases were all symptomatic VTE within 6 weeks after discharge. The controls were active solid tumor in-patients admitted in 2009 and did not develop VTE. The cases and controls were compared for the risk factors of VTE and complete blood count (CBC) on admission.
Results: There were 28 radiology-confirmed VTE cases during the 2.5-year study period. There were 280 solid tumor patients without VTE as the controls. There was no difference in age (58.4 *vs.* 61.6 years), sex (53.6% *vs.* 64.3% male), presence of leg paralysis, acute infection and obesity between cases and controls, respectively. The cases showed higher absolute monocyte counts compared with the controls (0.76 *vs.* 0.56×10^9/L, p 0.013), but there were no differences in other CBC parameters. In a multivariate analysis, cancer of unknown primary (Odds ratio [OR] 13.7, 95% confidence interval [CI] 2.74-68.7, p 0.001), biliary cancer (OR 6.6, 95% CI 1.80-24.3, p 0.004) and a monocyte count over 0.5×10^9/L (OR 5.0, 95% CI 1.62-15.5, p 0.005) significantly associated with VTE.
Conclusion: Metastatic diseases with obscured primary sites, biliary carcinomas and higher monocyte counts on admission are related to subsequent VTE in hospitalized cancer patients.

Introduction

Without thromboprophylaxis, venous thromboembolism (VTE) causes significant morbidity and mortality to hospitalized medical patients. The American College of Chest Physicians, and other guidelines, recommends the use of anticoagulants in these high-risk medical patients [1]. The problem is, therefore, emerging in Asian countries where the VTE incidence is not low [2], but the preventive measures are scarcely employed [3].

One of the reasons of the under-utilization of the prophylaxis is the notion that the incidence of VTE in Asians is, although not trivial, not as high as that of the Caucasian [4,5]. Supporting this idea, a recent large randomized trial comparing enoxaparin versus placebo in mainly-Asian medical patients shows a remarkably low rate of symptomatic VTE in the placebo arm [6]. Due to a definite risk of bleeding from anticoagulants [7], this lower incidence may shift the risk-benefit ratio of heparins in Asian medical patients.

The other main reason is the questionable benefit of low molecular weight heparin in this group. Although pharmacologic prophylaxis can reduce the incidence of asymptomatic and symptomatic VTE, it is unable to decrease the overall mortality, which is the most important outcome [8,9]. This conclusion is further corroborated in a recent randomized trial containing a large number of Asian patients [6].

A potential approach to this problem is to identify subgroups of patients who have the greatest risks for hospital-acquired VTE. Focusing on the prophylaxis for this group may benefit the most to the patients. Our previous study has shown that the risk scores generated from Western patients could not categorize the probability of VTE in Thais [10]. Furthermore, we found that solid tumors, not hematological cancer, and autoimmune diseases are the 2 strongest VTE risk factors in Thai hospitalized patients. In addition, cancer was more common and attributed to over half of the hospital-acquired VTE. Therefore, this group should be the first target for preventive strategies [10].

The aim of this study is to further sub-classify the risk of VTE in solid tumor patients. Previous investigations of VTE risk scores were performed in Caucasian cancer patients receiving chemotherapy in ambulatory settings [11,12]. They revealed that certain sites of cancer, complete blood count (CBC) parameters and body mass indices (BMI)

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were independently predictive of VTE. In this study, we analyzed the VTE risks in Thai cancer patients who were admitted to the hospital.

Methods

Patients who were admitted to the internal medicine wards of Chulalongkorn Hospital for 3 days or more from June 2007 to December 2009 were monitored for VTE symptoms as part of the 2 previously published studies [2,10]. The purpose is to identify subgroups of patients who are the potential targets for VTE prophylaxis. Therefore, patients with symptoms of VTE before or on admission, although the diagnosis may be confirmed later, were excluded because these incidents were considered unpreventable. The study was approved by the Ethics Committee of the Faculty of Medicine, Chulalongkorn University before enrollment.

The objective of the first study from June 2007 to December 2008 was to determine the incidence of VTE. All 42 hospital-acquired VTE cases were enrolled and evaluated for potential VTE risk factors [2]. The denominator was the total number of medical patients who were admitted during the same period. The data on VTE risk factors were not prospectively gathered in patients who did not develop VTE.

The objective of the second study in 2009 was to identify the VTE risk factors. There were 2495 medical inpatients prospectively evaluated for VTE risk factors [10]. One hundred and fifty-three patients received anticoagulants and were excluded from the cohort. The common anticoagulant indications were cardiogenic embolism prevention, coronary disease or previously diagnosed VTE. Only 2 cases, which were not cancer, were excluded due to anticoagulant uses for VTE prophylaxis. Consequently, 1335 cases with at least one VTE risk factor were followed for signs and symptoms of VTE until 6 weeks after discharge. All patients were contacted by nursing staff on telephone and interviewed for VTE symptoms. If there were suspected DVTs or PEs, they would be asked to come for confirmatory investigations. The patients, whom we lost contact with, were excluded from the analysis. The flow diagram of the study was previously published [10]. Patients who did not develop VTE from this cohort were used as the controls to determine VTE risk factors because the complete information was available.

Deep vein thrombosis (DVT) was diagnosed by Doppler ultrasonography, while pulmonary embolism (PE) was by computerized tomographic angiography (CTA) or ventilation/perfusion (V/Q) scan.

The subgroups with active solid tumors from these 2 studies were subjected to a case–control analysis. Because hematological malignancy was not a significant VTE risk factor in our study [10], it was not included. The cases were cancer patients with VTE developing during or within 6 weeks after hospitalization from June 2007 to December 2009. The controls were cancer patients in the 2009 cohort who did not develop VTE or expired without symptomatic VTE up to 6 weeks after discharge.

The recorded risk factors for VTE were acute infection, congestive heart failure (New York Heart Association's functional class III or IV), chronic respiratory diseases with acute exacerbations, hemiparesis or paraparesis (motor power grade 0–3), a bed ridden or vegetative state, respiratory failure requiring invasive or non-invasive assisted ventilation, compression fracture, arthritis of lower extremities, a previous history of VTE, a family history of VTE, a previous history of cancer, presence of varicose veins, an estrogen use, history of thrombophilia, thrombocytosis (platelet count $>600\times10^9$/L), obesity (BMI $\geq$ 30 kg/m^2) and nephrotic syndrome. Acute infections also included febrile neutropenic episodes that required antibiotics irrespective of culture results. In addition, the sites and cell types of cancer, CBC parameters and administrations of chemotherapy during admission were evaluated. Automated CBC was performed at the hospital laboratory using ADVIA120 automated hematology analyzer on the day of admission.

Descriptive data were expressed as means $\pm$ standard deviations (SD) or percents. The differences between continuous variables were determined using Student's *t* test. Risk factors of VTE and mortality were expressed as odds ratios with 95% confidence interval (CI) and *p* values from Chi square tests. The factors that showed the *p* values under 0.10 from univariate analyses were subsequently put in a multivariate analysis using a binary logistic regression model. All statistical analyses were computed using SPSS 16.0 program for Windows.

Results

Baseline characteristics and outcomes of the patients

There were a total of 308 patients. The mean ($\pm$SD) age was 61.3 $\pm$ 14.6 years ranging from 16 to 94 years and 63.3% of them were male. The most common primary sites were lung (25.6%), gastrointestinal tract (20.8%), hepatocellular (15.3%) and biliary tract cancers (7.8%). Biliary carcinomas comprised 21 cholangiocarcinomas and 3 gallbladder cancers. Prostate cancer was not included in the urogenital tract tumors due to the lower risk. Tumors of unknown primary sites were found in 2.9% (Table 1). Among the 264 patients who had staging information, 181 (68.6%) showed distant metastasis. Stage 1, 2 and 3 diseases were reported in 6.1%, 7.6% and 17.8%, respectively.

During the 2.5-year study period, there were a total of 28 confirmed VTE patients. Thirteen were PE, 12 were DVT and 3 were DVT with PE. The median time to develop VTE was 9.5 days after admission, ranging from 2 to 68 days. Three VTE cases were diagnosed on day 10, 22 and 40 after discharges. In the last year of the study period, there were 280 cancer patients who did not develop VTE as a control group. Twelve symptomatic VTE cases were diagnosed in 2009 yielding the VTE incidence rate of 4.1% in this solid tumor cohort.

Comparing cases and controls, the age (58.4 $\pm$ 12.1 *vs.* 61.6 $\pm$ 14.9 years, *p* 0.27) and sex (53.6% *vs.* 64.3% male, *p* 0.26) were not statistically different. The in-hospital mortality rate was 28.6% (88/308). The VTE cases showed longer mean hospital stay (25.5 $\pm$ 10.8 vs. 18.1 $\pm$ 23.9 days, *p* 0.11) and higher mortality rates (35.7% vs. 27.9%, *p* 0.38) than those of the controls, but there was no statistical significance.

Primary sites in the cases and the controls are shown in Table 1. Metastatic cancer from obscured primary sites and biliary carcinoma appeared to be over-represented in the VTE cases. Notably, 23.8% (5/21) of cholangiocarcinoma and 33.3% (1/3) of gallbladder cancer developed VTE. On the other hand, hepatocellular carcinoma showed a low VTE rate. The 3 other primary sites that had VTE were hemangiopericytoma, melanoma and thymoma.

Factors associated with venous thromboembolism (VTE)

The comparisons of body mass index (BMI) and CBC parameters on the days of admission between cases and controls were shown in Table 2. Obese patients were uncommon. Only 1 patient in the control group had BMI of over 30 kg/m^2. There were no significant

Table 1
The primary sites of cancer and venous thromboembolism (VTE).

Primary sites	Total (%)*	VTE (%)†	Primary sites	Total (%)*	VTE (%)†
Lung	79 (25.6)	8 (10.1)	Urogenital tract	13 (4.2)	1 (7.7)
Gastrointestinal tract	64 (20.8)	3 (4.7)	Pancreas	12 (3.9)	0 (0)
Hepatoma	47 (15.3)	1 (2.1)	Unknown	9 (2.9)	5 (55.6)
Biliary tract	24 (7.8)	6 (25.0)	Brain	4 (1.3)	0 (0)
Breast	22 (7.1)	1 (4.5)	Other	20 (6.5)	3 (15.0)
Head and neck	14 (4.5)	0 (0.0)	Total	308	28

* Percentage of the primary sites out of the total patients.
† Percentage of VTE out of the patients with respective primary sites.