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Early venous thromboembolic events are associated with worse prognosis in patients with lung cancer

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ABSTRACT

Objectives: Venous thromboembolic events (VTE) are a leading cause of death in cancer patients. We hypothesized that early VTE (EVTE, within 3 months of diagnosis) in patients with lung cancer (LC) are associated with worse overall survival (OS).
Materials and methods: We identified 727 patients with LC between 1998 and 2011. Late VTE (LVTE) were defined as VTE occurring after 3 months from LC diagnosis. Advance disease (AD) was defined as patients with Stage IV non-small cell lung cancer (NSCLC) or extensive stage small cell lung cancer (SCLC), and non-advanced disease (non-AD) was defined as ≤Stage III NSCLC or limited stage SCLC.
Results: Out of 727 patients included in our review, 617 patients had NSCLC (85%), 94 (13%) SCLC, and 16 (2%) low grade neuroendocrine tumors. Ninety five patients (13%) experienced VTE, 44 (6%) experienced an EVTE and 49 (7%) had a LVTE. Patients with an EVTE had worse OS when compared to all other patients (medians 4 vs. 17 months, $p < 0.0001$). EVTE were associated with worse OS in patients with non-AD (medians 12 vs. 42 months, $p = 0.01$) and AD (medians 4 vs. 6 months, $p = 0.02$). When considering patients with NSCLC only, in a multivariate model that included age, stage, performance status >2, administration of chemotherapy and Charlson comorbidity index, EVTE were an independent predictor of increased mortality (HR 2.4; 95% CI 1.6–3.3).
Conclusions: EVTE are associated with worse OS, irrespective of stage of the disease. Our findings underscore the need for an efficient preventive strategy for VTE among patients with lung cancer.

1. Introduction

Venous thromboembolic events (VTE), which include deep venous thrombosis (DVT) and pulmonary embolism (PE), are a leading cause of morbidity and mortality among cancer patients [1,2]. As many as one in five patients with VTE also has a concurrent diagnosis of a malignancy [3]. Patients with lung cancer are at a particularly high risk for VTE when compared to other tumor types, and if one considers its high prevalence, lung cancer may be responsible for one of the highest incidence of thrombotic events associated with cancer [4].

VTE have been associated with worse prognosis among patients with solid malignancies [5,6], although it remains unclear whether VTE constitute an independent predictor of worse survival in this patient population or merely represent surrogates of more advanced malignancies overall. Primary prevention is effective in decreasing the incidence of cancer associated VTE [7]; however, the optimal timing and patient population that would most benefit from outpatient thromboprophylaxis is not well defined [8,9]. As a result, thromboprophylaxis is not routinely indicated in ambulatory patients with solid malignancies [10]. Furthermore, the majority of VTE events seem to occur within the first year after the diagnosis of cancer and there is evidence to suggest that early VTE might carry a worse prognosis in patients with newly diagnosed

Abbreviations: DVT, deep venous thrombosis; ESA, erythropoietin stimulating agents; EVTE, early venous thromboembolic events; LVTE, late venous thromboembolic event; NSCLC, non-small cell lung cancer; OS, overall survival; PS, performance status; PVTE, prior venous thromboembolic event; SCLC, small cell lung cancer; VTE, venous thromboembolic event.

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malignancies [11]. In an effort to clarify the impact of VTE on the prognosis of patients with lung cancer, we hypothesized that early VTE, occurring within 3 months of diagnosis, are associated with worse overall survival.

2. Methods

From a prospectively maintained lung cancer database, we retrospectively identified and reviewed 727 patients with lung cancer that were treated at the Mayo Clinic between January 1998 and December 2011. The Mayo Foundation Institutional Review Board approved the study, and all patients consented to have their medical records reviewed. The diagnosis of lung cancer was established after histological examination of biopsy specimens by a Mayo Clinic pathologist in all cases. Clinical and laboratory data as well as VTE occurrences were extracted after review of the electronic health records. The Charlson comorbidity index was calculated as previously described and comorbidities required to calculate the index were abstracted from the clinical charts [12]. ECOG performance status (PS) was considered as a dichotomous variable (>2 or ≤2), since there was not always enough clinical information available in the charts to classify patients with a PS ≤2 further. Medication use thought to be associated with a higher risk of VTE was also abstracted and included: erythropoietin stimulating agents (ESA) [13], estrogen and progestin containing medications [14], tamoxifen [15] and bevacizumab [16]. Overall survival follow-up was complete for all patients.

Diagnosis of DVT was confirmed in all cases by venogram, computed tomographic (CT) scan or magnetic resonance imaging scans. Diagnosis of PE was confirmed in all cases by pulmonary angiography, or CT angiography. Early VTE (EVTE) were defined as VTE occurring within 3 months from lung cancer diagnosis [11,17]. Late VTE (LVTE) were defined as VTE occurring after 3 months from lung cancer diagnosis and prior VTE (PVTE) as VTE occurring 3–12 months prior to their diagnosis of lung cancer. Patients who were already on anticoagulation prior to their lung cancer diagnosis were excluded, with the exception of patients with a PVTE on anticoagulation. Advanced disease was defined as patients with Stage IV non-small cell lung cancer (NSCLC) or extensive stage small cell lung cancer (SCLC), and non-advanced disease was defined as ≤Stage III NSCLC or limited stage SCLC. For patients diagnosed after January of 2010, the 7th edition of the tumor node metastasis (TNM) staging system was used [18].

Survival was estimated by the Kaplan–Meier method. The Pearson chi-square test and the Kruskal–Wallis test were used to ascertain differences between nominal and continuous variables, respectively. A Cox proportional hazard regression model was used for multivariable analysis. p values less than 0.05 were considered significant. All statistics were done using JMP software (SAS, Carey, NC).

3. Results

Out of 727 patients, 617 patients had NSCLC (85%), 94 had SCLC (13%) and 16 had low grade neuroendocrine tumors (2%). Ninety five patients (13%) experienced VTE, of which 44 (6%) experienced an EVTE and 49 (7%) had a LVTE. Two patients had a PVTE 5 and 9 months prior to lung cancer diagnosis. The timing of VTE occurrence is shown in Fig. 1. Approximately two-thirds of VTE occurred within a year from diagnosis. The patients' clinical and laboratory features with and without EVTE are shown in Table 1. Patients with EVTE were more likely to have advanced disease (67% vs. 39%, $p < 0.001$), a higher Charlson comorbidity index (8 vs. 6, $p = 0.02$) and to have received chemotherapy within 60 days from lung cancer diagnosis (55% vs. 39%, $p = 0.04$). When considering the whole cohort, 13 VTE (14%), were discovered incidentally during imaging and were not associated with any symptoms. With a median follow-up of 15 months (range 0–191 months), overall survival of patients with incidental VTE was not significantly different from that of patients with symptomatic VTE (18 months vs. 11 months, p = NS). Thirty four VTE (36%) were PE, 35 (37%) DVT, 6 (6%) both PE and DVT, 15 (16%) upper extremity DVT and 5 (5%) were VTE of other venous systems. Seven (7%) patients had a major surgery within 4 weeks of their VTE and 8 (8%) patients had venous compression from masses (primary tumor or, more frequently, metastatic disease) resulting in venous stasis in the thrombosed venous system. Twenty-six (27%) patients had an acute infection within 2 weeks from VTE diagnosis and 6 patients with an upper extremity VTE had a central venous catheter at the time of VTE.

Patients with an EVTE had worse OS when compared to the rest of the group (medians 4 vs. 17 months, $p < 0.0001$) (Fig. 2a). EVTE were associated with worse OS in patients with non-advanced disease (medians 12 vs. 42 months, $p = 0.01$) and advanced disease (medians 4 vs. 6 months, $p = 0.02$) (Fig. 2b and c, respectively). Since Stage IIIB disease is frequently considered together with Stage IV in NSCLC as advanced disease, in a separate set of analyses, we found that EVTE were associated with worse OS in patients with Stage IV/IIIB/extensive SCLC as well as Stage I/II/limited SCLC disease (data not shown). When considering patients with non-advanced disease, 60% of patients with early VTE had died within a year of diagnosis as opposed to only 30% of patients without an early VTE. Patients with non-advanced disease and EVTE included mostly Stage III patients (5 Stage IIIB, 4 Stage IIIA) and 1 patient with limited stage SCLC. In patients with advanced disease a similar trend was noted, with 6 month mortality in the EVTE group of 48% as opposed to 30%. Although the exact cause of death for each case was not abstracted, none of the 40 deaths were clinically attributed to VTE and all were clinically attributed to progressive disease. No patients had autopsies performed and 6 patients died within a month of VTE. Out of 44 patients, 10 were on chemotherapy when EVTE were diagnosed; out of these only 2 had to interrupt chemotherapy because

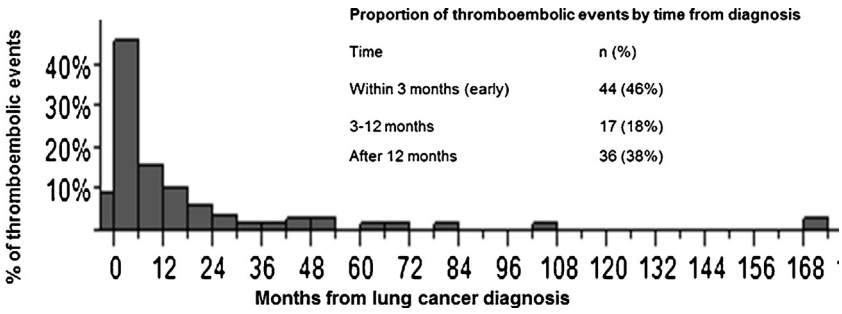

Fig. 1. Timing of thrombosis from diagnosis of lung cancer.