Original Study

ALK-Rearranged Non–Small-Cell Lung Cancer Is Associated With a High Rate of Venous Thromboembolism

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Abstract

We examined the rate of venous thromboembolism in a cohort of consecutive patients with *ALK*-rearranged non–small-cell lung cancer (NSCLC) at a single center and found it to be 3- to 5-fold higher than previously reported in the setting of advanced NSCLC. The results were comparable when we included a validation cohort of consecutive patients at 2 other centers, with an overall rate of 36%. Prospective confirmation is warranted.

Background: Patients with lung cancer are at increased risk for venous thromboembolism (VTE), particularly those receiving chemotherapy. It is estimated that 8% to 15% of patients with advanced non–small-cell lung cancer (NSCLC) experience a VTE in the course of their disease. The incidence in patients with specific molecular subtypes of NSCLC is unknown. We undertook this review to determine the incidence of VTE in patients with *ALK* (anaplastic lymphoma kinase)-rearranged NSCLC. **Patients and Methods:** We identified all patients with *ALK*-rearranged NSCLC diagnosed and/or treated at the Princess Margaret Cancer Centre (PM CC) in Canada between July 2012 and January 2015. Retrospective data were extracted from electronic medical records. We then included a validation cohort comprising all consecutive patients with *ALK*-rearranged NSCLC treated in 2 tertiary centers in Israel. **Results:** Within the PM CC cohort, of 55 patients with *ALK*-rearranged NSCLC, at a median follow-up of 22 months, 23 (42%) experienced VTE. Patients with VTE were more likely to be white ($P = .006$). The occurrence of VTE was associated with a trend toward worse prognosis (overall survival hazard ratio = 2.88, $P = .059$). Within the validation cohort (n = 43), the VTE rate was 28% at a median follow-up of 13 months. Combining the cohorts (n = 98), the VTE rate was 36%. Patients with VTE were younger (age 52 vs. 58 years, $P = .04$) and had a worse Eastern Cooperative Oncology Group performance status ($P = .04$). VTE was associated with shorter overall survival (hazard ratio = 5.71, $P = .01$). **Conclusion:** The rate of VTE in our *ALK*-rearranged cohort was 3- to 5-fold higher than previously reported for the general NSCLC population. This warrants confirmation in larger cohorts.

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Introduction

The overall risk of venous thromboembolism (VTE) in cancer patients is approximately 7- to 8-fold higher than in the general population.[1,2] VTE risk in cancer patients varies throughout the course of the disease, with increased risk in the first few months after diagnosis.[3,4] Tumor stage and treatment also are important factors, with chemotherapy and advanced disease associated with the greatest risk (relative risk = 16.2 and 17.1, respectively).[2] Furthermore, VTE in cancer patients is associated with worse prognosis.[5,6]

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In lung cancer, a pooled analysis of individual patient data from 3 randomized trials reported the incidence of VTE to range from 0% in patients with early stage disease not receiving systemic treatment to 8% in patients with advanced disease receiving chemotherapy.[7] Higher rates of VTE, up to 13% to 15%, also have been reported in retrospective studies of non–small-cell lung cancer (NSCLC) patients.[8,9] Within NSCLC, patients with adenocarcinoma have the highest rates of VTE.[10]

In recent years, there has been a transformation in the management of NSCLC. Although previously it was considered a homogeneous disease treated empirically with chemotherapy, genomically defined subsets of patients now are treated with specific molecularly targeted tyrosine kinase inhibitors (TKIs) that are associated with high response rates and prolonged progression-free survival.[11,12] Chromosomal rearrangement on the gene encoding anaplastic lymphoma kinase (*ALK*) are detected in 3% to 5% of all NSCLC and lead to constitutive activation of downstream signaling and tumor growth.[13] A typical pathologic feature for *ALK*-rearranged lung adenocarcinoma is the abundance of mucin-containing signet ring cells.[14] Three TKIs—crizotinib, ceritinib, and alectinib—now are approved for the treatment of this small subset of NSCLC patients.[12,15,16]

In this study, we examined the rate of VTE in the entire cohort of patients with *ALK*-rearranged tumors seen at the Princess Margaret Cancer Centre (PM CC).

Methods

Study Population

The pathology department database and thoracic oncology clinical database were searched to identify all *ALK*-rearranged cases diagnosed and/or treated at PM CC since July 2012, when reflex *ALK* testing was introduced at University Health Network for all resected and newly diagnosed lung adenocarcinomas. Data cutoff was January 2015. The validation cohort consisted of all *ALK*-rearranged cases in patients diagnosed and treated in 2 Israeli tertiary medical centers (Rambam Medical Center and Rabin Medical Center) from July 2012, when *ALK* testing was reimbursed in Israel, until March 2016 (data cutoff).

Patients whose tumors were *ALK* positive by immunohistochemistry but negative by fluorescence in-situ hybridization were excluded.[17] The study was approved by the institutional review boards at all 3 centers.

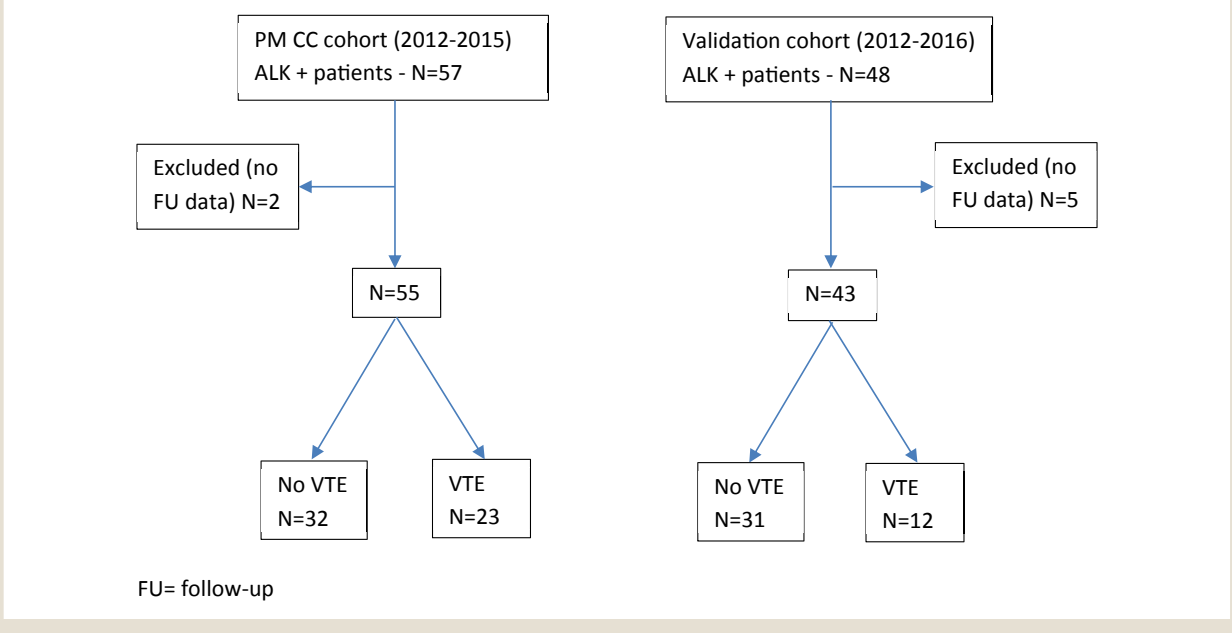
Data Collection and Statistical Analysis

VTE was defined as any deep vein thrombosis (DVT), pulmonary embolism (PE), or both documented by appropriate imaging studies (either Doppler ultrasound or contrast-enhanced computed tomography [CE-CT]). Asymptomatic VTE reported as an incidental finding by CE-CT was included as a VTE event.

Demographic and clinical characteristics evaluated for association with VTE included age, sex, ethnicity, smoking status, Eastern Cooperative Oncology Group (ECOG) performance status (PS), stage at diagnosis, types and lines of systemic treatment, body mass index, major comorbidities, prior VTE, baseline anticoagulation, baseline use of steroids or hormone therapy, and baseline hematology. Differences between the VTE and no-VTE groups were compared by the chi-square test, Fisher's exact test, or *t* test, as appropriate.

Overall survival (OS) was measured from the date of diagnosis of NSCLC until the date of death. The censoring date for patients on follow-up was the last clinic visit before January 1, 2015, for the PM CC patients and March 1, 2016, for the 2 centers in Israel. Survival

Figure 1 Study Design and Patient Distribution



Abbreviation: FU = follow-up.