



Incidence, predictors and prognostic significance of thromboembolic disease in patients with advanced *ALK*-rearranged non-small cell lung cancer

To the Editor:

Thromboembolic disease is fairly common in patients with lung cancer [1–3]. This incidence seems to be higher in patients with lung adenocarcinomas [4], with approximately 15% of those with advanced stage disease developing venous thromboembolisms (VTE) during the whole course of their disease [5–7]. Pulmonary adenocarcinomas are a heterogeneous group of diseases that can be stratified according to the presence of major oncogenic driver alterations. Anaplastic lymphoma kinase (*ALK*) rearrangements are detected in approximately 4% of these cases [8]. Isolated reports have suggested that patients bearing *ALK*-rearranged tumours might have a higher than expected incidence of thromboembolisms [9, 10]. In the present study, we have analysed the incidence, predictors and prognostic significance of thromboembolic events in a large, multi-institutional and homogeneous cohort of advanced stage patients with *ALK*-rearranged lung cancers from Spain and Portugal. Our primary objective was to estimate the incidence of thromboembolic events and their association with overall survival in these patients.

A centralised institutional ethics committee approval at the 12 de Octubre University Hospital valid for all Spanish centres, and an institutional ethics committee approval at the Portuguese Institute of Oncology of Porto, were obtained before the study was initiated. We retrospectively selected all consecutive patients diagnosed with advanced stage (stages III and IV) *ALK* fusion positive non-small cell lung cancers (NSCLCs) between January 2012 and December 2016. Data were contributed by 29 Medical Centres from Spain and one from Portugal. *ALK* positivity was determined according to local standard protocols in each institution. We excluded patients with neuroendocrine tumours and patients on therapeutic doses of anticoagulants prior to advanced stage cancer diagnosis. We defined a thromboembolic event as any venous or arterial thromboembolism, documented by imaging studies, that occurred at the time or after advanced stage cancer diagnosis. In addition to thromboembolic events, collected during the whole patients' follow-up period, we collected baseline information (within 1 month of advanced stage cancer diagnosis) of several clinical and analytical variables of interest.

We included 241 *ALK*-rearranged NSCLCs in this study. The median age was 56 years (range 17–84 years). Half of the patients were never smokers (52%), and most had stage IV pulmonary adenocarcinomas (n=204, 85%). Baseline brain and liver metastasis were detected in 22% and 25% of the patients, respectively. 17 patients (7%) and 185 patients (77%) had high and intermediate Khorana risk scores (KRS) [11] respectively. The median follow-up of our study population was 19 months (range 0–59 months), and 127 (53%) of the patients died. The median follow-up of alive patients was 30 months (range 4–49 months). The estimated median overall survival was 26 months for the entire series, and 31 months for those patients that received *ALK* tyrosine kinase inhibitors (TKIs) (n=207, 86%).

73 patients (30%) experienced thromboembolic complications. 71 out of 73 patients (97%) had VTE, with pulmonary embolism as the most frequent location (n=30; 41%). Four patients (5%) developed arterial thromboembolisms, two of them with concurrent VTE. Thromboembolic events occurred within the first 6 months from cancer diagnosis in 54 patients (74%), of whom 24 (33%) were detected within the first

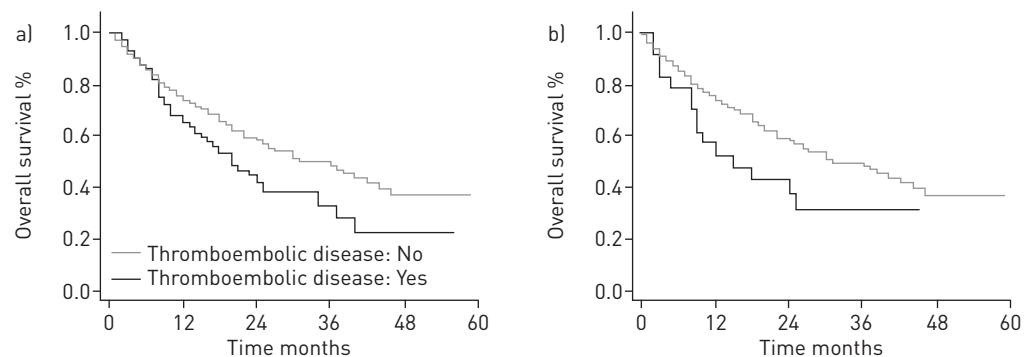
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High incidence and prognostic relevance of thromboembolic disease in patients with *ALK*-rearranged NSCLCs <http://ow.ly/DEZr30j6kC8>

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month from diagnosis. 22 patients (30%) were deemed to have incidental (asymptomatic or clinically unsuspected) thromboembolisms. 12 patients (16%) developed recurrent thrombosis (seven while receiving appropriate therapeutic anticoagulation). The mortality directly attributed to thromboembolic disease in this series was 2% (n=5).

To study the association between baseline characteristics and thromboembolic disease, we first conducted a univariate competing risk regression analysis [12] including gender, age, body mass index, performance status, smoking history, histology, tumour stage, central nervous system metastasis, liver metastasis, number of metastatic sites, haemoglobin, leukocyte, platelet and albumin counts, INR range and KRS. In this analysis, the presence of baseline liver metastases, leucocyte counts >11 000 cells per mm³, three or more metastatic organ involvement and a high KRS (HR 2.82, CI 95% 1.48–5.37; p=0.002) were significantly associated with increased risk of thromboembolic disease. In the multivariate model (in which we did not include KRS because it already incorporates leukocyte counts), only liver metastases and leukocytosis remained as independent predictors of thromboembolic disease, with corresponding HR of 1.85 (CI 95% 1.09–3.15; p=0.021) and HR of 2.34 (CI 95% 1.43–3.82; p=0.001), respectively.

Patients that experienced thromboembolic events at any time point had shorter median overall survival (20 months) than patients without thrombosis (36 months) (p=0.035) (figure 1a). Patients with thromboembolic events at baseline (n=24) had a median overall survival of 15 months (figure 1b). Patients that experienced recurrent thromboembolisms (n=12) had a median overall survival of 10 months, without statistically significant differences when compared with those without recurrent thromboembolism (n=61; 21 months) (p=0.369). Considering the development of thrombotic events as a time-dependent covariate, thromboembolic disease was significantly associated with an increased risk of death (HR 2.22, CI 95% 1.53–3.21; p=0.000). We conducted a multivariate Cox regression analysis including smoking history, comorbidities, leukocytosis, liver metastasis, performance status and ALK TKI treatment as fixed covariates, and thromboembolic disease as a time-varying covariate. In this analysis, thromboembolic disease remained as an independent predictor of overall survival with HR 1.70 (CI 95% 1.10–2.62; p=0.016) (figure 1c). The presence of thromboembolic disease at baseline (n=24) was associated with a numerically nonsignificant increased risk of death (HR 1.67, CI 95% 0.96–2.91; p=0.068).



Number at risk

No	167	123	70	35	12	0
Yes	73	48	27	11	2	0

Number at risk

No	168	123	70	35	12	0
Yes	24	12	8	2	0	0

c)

Variable	Multivariate HR (95% CI)	p-value
Thromboembolic disease	1.70 (1.10–2.62)	0.016
Tyrosine-kinase inhibitor treatment	0.60 (0.37–0.97)	0.041
Smoking history	1.60 (1.11–2.31)	0.011
>1 comorbidities	2.20 (1.31–3.71)	0.003
>11 000 leukocytes per mm ³	1.68 (1.09–2.59)	0.019
Liver metastasis	1.49 (0.99–2.25)	0.054
Performance status	1.76 (1.36–2.27)	0.000

FIGURE 1 Prognostic significance of thromboembolic disease in advanced ALK-positive non-small cell lung cancer patients. a) Kaplan–Meier curve for overall survival for patients with and without thromboembolic disease. b) Kaplan–Meier curve for overall survival for patients with baseline thromboembolic disease. c) Multivariate analysis showing the association of thromboembolic disease and overall survival.

In the present study, we show that thromboembolic disease is a frequent complication in patients with advanced-stage *ALK*-positive NSCLCs (30%), particularly in the presence of baseline liver metastasis or leukocytosis (~50%), and it is associated with a lower overall survival in this particular subtype of lung cancer. This study was not designed to compare the incidence of thromboembolic events between different molecular subtypes of lung cancers. However, the high incidence observed here is consistent with what has been reported in smaller *ALK*-positive cohorts [9, 10], and exceeds the observed in other subtypes of lung cancers [2, 3, 5–7]. We found that thromboembolic disease was an independent prognostic factor in advanced *ALK*-positive NSCLCs. Although the mortality rate of thromboembolic complications might have been underestimated in this study [13], the differences in survival do not seem to be directly related with the fatality of thromboembolic events themselves (2% of mortality attributed to thromboembolic disease in this cohort). In the present study, both leukocytosis and liver metastasis significantly predicted both the occurrence of thrombotic complications and reduced overall survival (figure 1c). A relatively low proportion of patients had progressive disease at the time of thromboembolic complications (22%), but we cannot definitely exclude that the association of thromboembolic disease with lower overall survival was confounded by subsequent development of liver metastasis and/or leukocytosis in some patients, as we only had baseline information for these variables.

Our findings have relevant implications for clinical practice. First, physicians should actively examine for the presence of signs or symptoms of thrombosis at diagnosis and during follow-up of these patients, and accordingly rule out the existence of thromboembolic disease with appropriate imaging studies. Additional surveillance strategies in high risk patients, including those with leukocytosis or liver metastasis, would need to be eventually considered. Second, these results justify investigation, in the context of a randomised trial, of the clinical benefit, in terms of thromboembolisms risk reduction and potentially in overall survival improvement, of adding prophylactic doses of anticoagulants to standard anticancer treatments in these patients. And ultimately, with median overall survival estimates exceeding 4 to 5 years with the incorporation of novel-generation *ALK* TKIs into the clinic [14, 15], thromboembolic disease will be one of the main cancer-related complication during the whole course of the disease in these patients.

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