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Venous thromboembolism is associated with increased all-cause mortality in ALK-positive non-small cell lung cancer

Magdalena Zaborowska-Szmit[1], Sebastian Szmit[2,3*], Marta Olszyna-Serementa[1], Katarzyna Zajda[1], Anna Janowicz-Żebrowska[1], Piotr Jaśkiewicz[1], Dariusz M. Kowalski[1] and Maciej Krzakowski[1]

Abstract

Background Venous thromboembolic events (VTE) are often diagnosed in ALK-positive lung cancer although it has not been demonstrated how their co-occurrence affects patients' survival.

Methods The study included patients with ALK-positive lung cancer recognized in metastatic stage in the period 2017–2022. All received treatment with ALK inhibitors at The Maria Sklodowska-Curie National Research Institute of Oncology in Warsaw. The main aim of the study was to assess overall survival (OS) in relation to VTE occurrence. The additional purpose was to define predictors of VTE and OS.

Results The study included 54 patients in median age 60 years, men were a minority (25 / 46.3%). VTE was diagnosed in 12 (22.2%) patients: 9 (16.7%) cases with pulmonary embolism (PE), 2 cases with thrombosis in vena cava superior, one case with deep vein thrombosis and thrombosis in vena cava inferior. Among patients with PE: 2 patients died directly due to the first PE episode and one due to a recurrent PE. Patients with VTE had significantly shorter overall survival (median 11.7 vs. 37.4 months, log-rank test $p=0.003$). The risk of all-cause mortality was increased significantly in both: VTE (HR = 3.47; 95%CI: 1.61—7.49; $p=0.0016$) or alone PE (HR = 2.41; 95%CI: 1.06—5.50; $p=0.037$). The risk of VTE diagnosis was significantly increased during active treatment with crizotinib (HR = 8.72; $p=0.0004$) or alectinib (HR = 21.47; $p=0.000002$). Metastases to liver and baseline leukocyte count > 11×10^9/L were significant predictors of VTE and OS. Khorana score ≥ 3 points predicted OS (HR = 2,66; 95%CI: 1,05—6,75; $p=0,04$), but remained insignificant for VTE.

Conclusion The diagnosis of any type of VTE or alone PE was associated with significantly worse overall survival in patients with ALK-positive non-small cell lung cancer.

Keywords Lung cancer, ALK inhibitors, Thromboembolism, Pulmonary embolism, Overall survival

*Correspondence:
Sebastian Szmit
s.szmit@gmail.com
Full list of author information is available at the end of the article

Introduction

Lung cancer predisposes to thromboembolic complications [1]. The Khorana score is used to assess the risk of a venous thromboembolic event (VTE), and diagnosis of lung cancer means one point on it [2].This scale is recommended for practical use by important guidelines published by American Society of Clinical Oncology (ASCO) [3] and European Society for Medical Oncology (ESMO) [4]. However, it must be highlighted in the case of lung cancer, the Khorana score does not take into account either the detailed molecular diagnosis of cancer disease or the type of anticancer treatment. Meanwhile, in practice, the highest risk of pulmonary embolism is observed in the case of ALK-positive non-small cell lung cancer [5]. It is unknown whether the effect of high prothrombotic readiness is only related to a specific histological and molecular type of lung cancer disease, or whether the type of therapy used, i.e. ALK inhibitors, plays an additional role.

The recent data confirm that the occurrence of venous thromboembolism in cancer is associated with an unfavorable prognosis, i.e. increased mortality, regardless of whether the VTE is diagnosed simultaneously with cancer or later during anticancer treatment [6]. VTE associated with immune checkpoint inhibitors therapy is also associated with a significantly shorter survival time [7]. This study included 24.1% of patients with non-small cell lung cancer.

The occurrence of VTE may be a consequence of the nature of the cancer disease and the type of anticancer treatment [8]. It is constantly being investigated whether the occurrence of VTE is always associated with a deterioration in survival. The main goal of the current study was designed to expand knowledge regarding the assessment of the impact of VTE on the overall survival (OS) of patients with ALK-positive non-small cell lung cancer (NSCLC). The additional purpose of the observation was to identify predictors of VTE and OS specific only for population of patients with ALK-positive NSCLC.

Methods

The study included all patients with confirmed metastatic ALK-positive non-small cell lung cancer consulted at The Maria Sklodowska-Curie National Research Institute of Oncology in Warsaw and started treatment with ALK inhibitors in the period 2017–2022.

The main objective of the study was to compare clinical characteristics and overall survival (OS) among patients experiencing venous thromboembolism (VTE) versus those without this complication in the ALK inhibitors-treated population of NSCLC.

The additional purpose of the study was to define possible predictors of VTE and OS unique for NSCLC patients treated with ALK inhibitors.

The overall survival (OS) was calculated from the beginning of treatment with first ALK-inhibitor to a moment of death from any reasons. Additionally the time from the beginning of first ALK inhibitor treatment to VTE occurrence and the time from a moment of a VTE-type complication development to the date of death from any cause were determined.

The STATISTICA package was used to calculate all results. The Kaplan–Meier curve was used to estimate OS in patients experiencing VTE or PE compared to patients without these complications. The chi-squared test with possible Yates correction was used to compare characteristics of patients with and without VTE (all characteristics features were expressed by nominal scale). All possible risk factors associated with the occurrence of VTE and predictors of OS were calculated by the Cox proportional hazards model.

Results

The study included 54 patients in mean age 58.35 ± 12.51 years (median 60 years, range: 31–81 years). The study group consist of 29 women (53.7%) and 25 men (46.3%).

As the first ALK inhibitor, patients received: alectinib (30 patients; 55.6%), crizotinib (19 patients; 35.2%) or brigatinib (5 patients; 9.3%). After lung cancer progression 20 patients received a second ALK inhibitor: alectinib (11 patients), lorlatinib (7 patients) or brigatinib (2 patients). The small group of 6 patients (11.1%) were treated with a third line of ALK inhibition and received lorlatinib.

Based on the Khorana Risk Score for VTE, as many as 30 patients (55.56%) had only 1 point for the diagnosis of lung cancer. Among others 16 patients (29.63%) had 2 points, 7 patients (12.96%) had 3 points and 1 patient (1.85%) had 4 points (Table 1).

The follow-up was finished on March 13th 2024. During observation 12 of all 54 (22.2%) patients experienced VTE: 9 cases with pulmonary embolism (PE), 2 cases with thrombosis in vena cava superior, one case with deep vein thrombosis (DVT) and concomitant thrombosis in vena cava inferior. Median time to VTE occurrence (in 12 patients) was 102 days (IQ: 28—293). Median time from VTE diagnosis to death was 142 days (IQ: 90—333 days).

Patients with VTE were significantly more likely to be men (10 / 83.33% vs 15 / 35.71%, $p=0.0035$), had liver metastases (5 / 41.67% vs 5 /11.90%, $p=0.019$) and had an elevated leukocyte count $>11\times10^9$/L (5 / 41.67% vs 6 / 14.29%, $p=0.038$). However, there were no differences

Table 1 Characteristics of 54 study patients and comparison between patients with and without VTE

	All 54 patients	VTE (12 patients)	No VTE (42 patients)	*p*-value
Male	25	10 (83.33%)	15 (35.71%)	$p=0.0035$
Age > 60 years	24	3 (25%)	21 (50%)	$p=0.23$
Co-morbidity	24	6 (50%)	18 (42.86%)	$p=0.66$
Cardiovascular disease	16	4 (33.33%)	12 (28.57%)	$p=0.97$
Other cancer disease	6	2 (16.67%)	4 (9.52%)	$p=0.86$
Smoking	23	8 (66.67%)	15 (35.71%)	$p=0.056$
eGFR < 60 ml/min/1.73m^2	7	1 (8.33%)	6 (14.29%)	$p=0.96$
Characteristic localization of metastases				
Brain	8	1 (8.33%)	7 (16.67%)	$p=0.8$
Lung	39	9 (75%)	30 (71.43%)	$p=0.81$
Liver	10	5 (41.67%)	5 (11.90%)	$p=0.019$
Bones	18	5 (41.67%)	13 (30.95%)	$p=0.49$
Pleura	23	7 (58.33%)	16 (38.10%)	$p=0.21$
Lymph nodes	16	3 (25%)	13 (30.95%)	$p=0.97$
Peritoneum	3	2 (16.67%)	1 (2.38%)	$p=0.23$
Pericardium	4	0	4 (9.52%)	$p=0.63$
BMI ≥ 35 kg/m^2	1	0	1 (2.38%)	$p=0.5$
Platelet count ≥ 350×10^9/L	19	4 (33.33%)	15 (35.71%)	$p=0.85$
Hemoglobin level < 10 g/dL	2	1 (8.33%)	1 (2.38%)	$p=0.92$
Leukocyte count > 11×10^9/L	11	5 (41.67%)	6 (14.29%)	$p=0.038$
Khorana score				
1point	30	6 (50%)	24 (57.14%)	$p=0.28$
2 points	16	3 (25%)	13 (30.95%)	
3 points	7	2 (16.67%)	5 (11.90%)	
4 points	1	1 (8.33%)	0	
Khorana score ≥ 2 points	24	6 (50%)	18 (42.86%)	$p=0.66$
Khorana score ≥ 3 points	8	3 (25%)	5 (11.9%)	$p=0.51$

in the risk assessment according to the Khorana score (Table 1).

The frequency of PE was 16.7% (9 cases in 54 patients). Only men experienced PE, they were in median age 54 years (IQ: 48—59). Median time to PE occurrence (in 9 patients) was 160 days (IQ: 28—441). Median time from PE diagnosis to death was 177 days (IQ: 23—364). In two cases, the episode of the first PE was the direct cause of death. Only one patient had a recurrence of PE, which was also the direct cause of death.

Patients with VTE had significantly shorter overall survival (median 351 days vs. 1121 days / 11.7 months vs 37.4 months, log-rank test $p=0.003$, Fig. 1). Similarly patients experiencing PE had significantly shorter overall survival (median 436 days vs. 1075 days / 14.5 months vs 35.8 months, log-rank test $p=0.04$).

The risk of all-cause mortality was increased significantly in patients with VTE compared to patients without VTE (HR = 3.47; 95%CI: 1.61—7.49; $p=0.0016$). Patients with PE had also significantly higher risk of premature all-cause mortality (HR = 2.41; 95%CI: 1.06—5.50; $p=0.037$).

Men had significantly higher risk of VTE occurrence (HR = 5.41; 95%CI: 1.18–24.76; $p=0.03$) and similarly patients with liver metastases (HR = 4.78; 95%CI: 1.46–15.58; $p=0.01$). Interestingly patients with baseline leukocyte count > 11×10^9/L had significantly higher risk of VTE development (HR = 4.85; 95%CI: 1.46–16.08; $p=0.01$), however there were no associations with other points of Khorana score (Table 2). There was the significantly increased risk of diagnosis of VTE during active treatment with crizotinib (HR = 8.72; 95%CI: 2.61–29.11; $p=0.0004$) or alectinib (HR = 21.47; 95%CI: 6.02–76.48; $p=0.000002$).

Among predictors of overall survival (Table 3), except for the occurrence of VTE or PE, there were found as significant: history of smoking (HR = 2.52; 95%CI: 1.19–5.36; $p=0.02$), presence of metastases to liver (HR = 3.91;

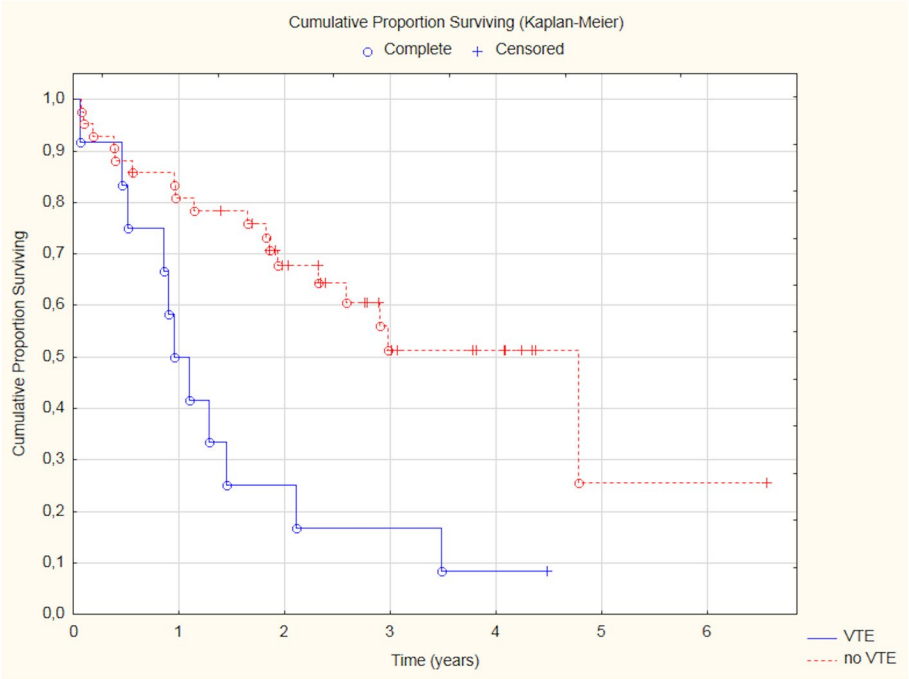

Fig. 1 Comparison of Overall Survival (OS) between patients with and without VTE (log-rank test $p=0.003$)

95%CI: 1.72–8.91; $p=0.001$) or bones (HR = 2.57; 95%CI: 1.19–5.53; $p=0.016$), baseline hemoglobin level < 10 g/dL (HR = 9.15; 95%CI: 1.96–42.66; $p=0.005$) or leukocyte count > 11×10^9/L (HR = 3.16; 95%CI: 1.34–7.47; $p=0.009$). Finally baseline Khorana score ≥ 3 points had negative impact on OS (HR = 2.66; 95%CI: 1.05—6.75; $p=0.04$).

Discussion

The current study is the first documented evidence revealed increased mortality in ALK-positive non-small cell lung cancer patients experiencing VTE. It is worth asking what determines such an unfavorable result. It is difficult to conclude that the response to ALK inhibitor therapy was worse in patients with VTE. There is evidence in the literature that the occurrence of VTE is associated with higher tumor grade [9]. The response anticancer treatment may be also worse, although this was clearly confirmed in pancreatic cancer [10]. The current study as the first in the literature confirmed the patients with ALK-positive lung cancer and metastases to liver are at significantly higher risk of both, VTE development and shorter overall survival. Additionally proinflamatory status defined by high number of leukocytes can also lead to VTE and premature mortality.

Different anticancer therapies like cisplatin-based chemotherapy, immunotherapy, selected targeted therapies, may cause an increased risk of VTE [11, 12]. The mechanism seems to be multifactorial, associated with the induction of coagulation disorders and damage to the vascular endothelium. Until recently, when analyzing the cardiac safety of ALK inhibitors, there have been no data that these drugs caused VTE [13]. In the case of crizotinib (ALK and ROS1 inhibitor), two types of electrocardiographic complications were reported: bradycardia and QT prolongation [14]. A relationship between the occurrence of bradycardia and the response to treatment with crizotinib has even been reported [15]. Alectinib (ALK and RET tyrosine kinase inhibitor) had a significantly lower effect on heart rhythm and conduction [16]. Brigatinib (an inhibitor of ALK and EGFR) has been connected with the problem of arterial hypertension [17]. Finally, lorlatinib mainly causes problems related to hypercholesterolemia and hypertriglyceridemia [18]. The current study as the first in the literature suggests a possible relationship between VTE and active treatment with crizotinib or alectinib. This certainly requires further research focused on prothrombotic activity of ALK-inhibitors.

The fundamental question arising from our study is whether we could prevent the occurrence of VTE and thus reduce mortality through primary antithrombotic prophylaxis. The European Society of Cardiology (ESC) guidelines on cardio-oncology state that primary thromboprophylaxis may be considered in high-risk cancer patients if an expected benefit outweighs the

Table 2 Univariate Cox proportional hazard model of predictors of VTE

	HR	95% CI (lower—upper)		*p*-value
Male	**5.41**	**1.18**	**24.76**	**0.03**
Age > 60 years	0.46	0.12	1.71	0.25
Co-morbidity	1.44	0.46	4.49	0.53
Cardiovascular disease	1.19	0.36	3.95	0.78
History of other cancer disease	1.83	0.40	8.49	0.44
History of smoking	3.15	0.95	10.47	0.06
eGFR < 60 ml/min/1.73m^2	0.80	0.10	6.25	0.83
D-dimer > upper quartile (> 4850 ng/mL)	2.88	0.66	12.57	0.16
Localization of metastases				
Brain	0.39	0.05	3.05	0.37
Lung	1.06	0.28	4.02	0.93
Liver	4.78	1.46	15.58	0.01
Bones	1.97	0.60	6.52	0.27
Pleura	1.63	0.50	5.37	0.42
Lymph nodes	0.89	0.24	3.36	0.86
Peritoneum	3.44	0.67	17.79	0.14
Pericardium	-	-	-	-
Khorana score				
BMI ≥ 35 kg/m^2	-	-	-	-
Platelet count ≥ 350 × 10^9/L	0.91	0.27	3.03	0.88
Hemoglobin level < 10 g/dL	3.04	0.39	23.85	0.29
Leukocyte count > 11 × 10^9/L	4.85	1.46	16.08	0.01
Khorana score ≥ 2 points	1.54	0.49	4.79	0.46
Khorana score ≥ 3 points	2.58	0.68	9.78	0.16
Diagnosis during treatment with				
Crizotinib	8.72	2.61	29.11	0.0004
Alectinib	21.47	6.02	76.48	0.000002

Table 3 Univariate Cox proportional hazard model of predictors of overall survival

	HR	95% CI (lower—upper)		*p*-value
VTE occurrence	3.47	1.61	7.49	0.0016
PE occurrence	2.41	1.06	5.50	0.037
Male	1.37	0.66	2.86	0.40
Age > 60 years	1.64	0.79	3.41	0.18
Co-morbidity	1.45	0.70	3.02	0.32
Cardiovascular disease	1.14	0.52	2.51	0.75
History of other cancer disease	0.78	0.23	2.60	0.69
History of smoking	2.52	1.19	5.36	0.02
eGFR < 60 ml/min/1.73m^2	2.30	0.87	6.12	0.09
D-dimer > upper quartile (> 4850 ng/mL)	2.04	0.68	6.08	0.20
Localization of metastases				
Brain	0.31	0.07	1.33	0.12
Lung	0.96	0.42	2.18	0.92
Liver	3.91	1.72	8.91	0.001
Bones	2.57	1.19	5.53	0.016
Pleura	1.40	0.67	2.95	0.37
Lymph nodes	0.95	0.43	2.12	0.91
Peritoneum	1.42	0.34	6.01	0.63
Pericardium	1.90	0.53	6.85	0.33
Khorana score				
BMI ≥ 35 kg/m^2	2.97	0.39	22.49	0.29
Platelet count ≥ 350 × 10^9/L	0.98	0.46	2.12	0.97
Hemoglobin level < 10 g/dL	9.15	1.96	42.66	0.005
Leukocyte count > 11 × 10^9/L	3.16	1.34	7.47	0.009
Khorana score ≥ 2 points	1.50	0.72	3.13	0.28
Khorana score ≥ 3 points	2.66	1.05	6.75	0.04

risk of bleeding [19]. Patients with ALK-positive lung cancer may be understood as very high risk population, the frequency of VTE is very high and most of patients may die prematurely. Our study showed three patients died in acute phase of pulmonary embolism what confirms high mortality rate (PE-related mortality was about 30%). Some data indicate that generally the strongest risk factor for poor prognosis in PE is cancer [20]. Another ESC guideline document dedicated to the diagnosis and treatment of PE strongly emphasizes the role of cancer as a predictor of early mortality [21]. Therefore, primary thromboprophylaxis remains the only preventive measure in these patients to reduce VTE-related mortality. The second is certainly not to interrupt ALK inhibitor therapy, but if cancer disease progression is detected, it is necessary to immediately introduce another ALK inhibitor. If VTE development is significantly associated with premature all-cause mortality, an intensification of anticancer therapy together with thromboprophylaxis become necessary.

The strongest limitation of our study is the small size of the assessed population. However, it should be noted that the current study was conducted in the largest Polish oncology center and it is a summary of experience involving therapy with ALK inhibitors in really rare disease. ALK-positive is a specific molecular subtype of lung cancer recognized only in 3–8% of patients with NSCLC [22–24]. The largest analysis of this population regarding VTE risk includes 155 patients (3.2% of all identified patients with non small cell lung cancer) [25]. During 5-year of observation the frequency of VTE was 15.7%. ALK-positive lung cancer was significantly associated with increased risk of VTE but not with arterial thromboembolic events. The cited study did not present mortality rate related to VTE like it has been shown in our

study. All studies available in the literature, which indicated the increased VTE rate by a 3- to fivefold in ALK positive lung cancer, were small with 55 patients [26], 58 patients [27], 46 patients [28], respectively. The absolute incidence of VTE in ALK-positive lung cancer is very high: initial VTE 42.7% and recurrent VTE 13.5% [29]. The available meta-analysis of 8 clinical trials covering 766 patients with ALK positive lung cancer indicates beyond any doubt that the incidence of VTE is very high in these patients [30]. Therefore, the result we showed in a population of 54 patients and the presented significant relationship between VTE and premature all-cause mortality should become a new step in planning of clinical research focused on an improvement of prognosis in ALK-positive non-small lung cancer.

The authors of the manuscript are oncologists focused on modern molecular testing which became the basis of personalized cancer therapy [31]. We believe the molecular characteristics of cancer disease help to understand the risk of cardiovascular toxicity of targeted therapy in modern oncology [32]. ALK-positive NSCLC has a very specific biology: rapid dynamics of clinical development, usually recognized at a high stage of the disease advancement, predilection for metastases to the central nervous system (often diagnosed synchronously at the beginning of the disease), often central location in the lungs, often mediastinal lymph nodes involvement, more often presence in the pleura and pericardium, implants in the peritoneum [33–35]. The studies with assessment of the prognosis in lung cancer should not analyze ALK-positive patients together with other molecular types of NSCLC. In ALK-positive NSCLC the prognosis is completely different and our study in unique way supplements current knowledge by data with new predictors of OS. We included in the analyses not only typical risk factor for VTE defined by Khorana score but we calculated a risk of VTE and all-cause mortality in relation to localizations of metastases, co-morbidities, renal function, age and sex. In our opinion there is no similar study in the medical literature and everything above defines the novelty of the current study.

The treatment of ALK-positive NSCLC is based on personalized approach with ALK inhibitors which improved significantly prognosis [36–39]. The algorithm of therapy in ALK-positive NSCLC has been created based on the results from clinical trials dedicated only to this group of patients [40]. The future will depend on an appropriate sequence of the using of the most effective ALK inhibitors [41]. Additionally unacceptable toxicity should be avoided [42, 43]. It seems important our study showed the increased VTE risk during active treatment with crizotinib and alectinib. The use of immune checkpoint inhibitors can lead to the occurrence of VTE and sometimes to increased mortality, but not all studies have confirmed this [44]. As first researchers we found the occurrence of VTE is associated with an increased risk of all-cause mortality in patients with ALK-positive NSCLC under targeted therapy.

Authors' contributions

M.Z.S and S.S. wrote the main manuscript text and S.S. prepared Fig. 1. All authors edited and approved the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was approved by the Bioethical Committee of the Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland: opinion number 6/2024, date: January 18th, 2024.
The patients did not sign informed consent to participate in the study, because it based on retrospectively collected administrative data from the National Research Institute of Oncology in Warsaw, Poland.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Lung Cancer and Thoracic Tumors, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland. [2]Department of Cardio-Oncology, Chair of Hematology and Transfusion Medicine, Centre of Postgraduate Medical Education, Warsaw, Poland. [3]Department of Cancer Diagnostics and Cardio-Oncology, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland.

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