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RESEARCH

Is there any prognostic significance in pleural involvement and/or effusion in patients with ALK-positive NSCLC?

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Abstract

Purpose Anaplastic lymphoma kinase (ALK) mutations occurs in approximately 3–5% of patients with non-small cell lung cancer (NSCLC). Pleural involvement/effusion is common in ALK-positive patients with NSCLC at baseline. The aim of the study was to evaluate the characteristics of ALK-positive patients who have Ple-I/E.

Methods In this multicenter study, patients with ALK-positive NSCLC who have Ple-I/E were retrospectively analyzed. Clinical and demographic characteristics of the disease, response rates, median progression-free survival (PFS), and overall survival (OS) were evaluated in 362 ALK-positive patients with NSCLC.

Results Of the patients, 198 (54.7%) were male. The median age at the time of diagnosis was 54 (range 21–85) years. All patients' histology was adenocarcinoma (100%). At baseline, 57 (15.7%) patients had Ple-I/E. There was no association between Ple-I/E and gender, lung metastasis, or distant lymphadenopathy (LAP) metastasis. The frequencies of liver, brain, and bone metastases were significantly higher in ALK-positive patients without Ple-I/E compared to those with Ple-I/E (respectively 18.2% vs 4.8%, p = 0.008; 19.1% vs 4.8%, p = 0.001; 20.6% vs 8.9%, p = 0.002). The median PFS was longer in ALK-positive patients who had Ple-I/E (18.7 vs 10.6 months, p = 0.017). Similarly, the median OS was longer in ALK-positive patients who had Ple-I/E (44.6 vs 22.6 months, p = 0.051).

Conclusion Brain, liver, and bone metastases were lower in ALK-positive patients with Ple-I/E. Patients presented with Ple-I/E were prone to have better PFS and OS.

Keywords NSCLC · ALK-positive · Pleural involvement · Pleural effusion · Prognosis

Introduction

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related deaths worldwide (Siegel et al. 2014). While conventional therapies including chemotherapy and radiation can be effective in many cases, targeted therapies that specifically address the molecular changes driving cancer growth have shown great promise in the treatment of particular types of NSCLC. The discovery of the EML4-ALK fusion gene in 2007 was a major breakthrough in NSCLC research, as the fusion protein is a constitutively active tyrosine kinase that triggers multiple signaling pathways associated with cell growth and survival, leading to uncontrolled cell proliferation and tumor growth (Choi et al. 2008; Pikor et al. 2013; Soda et al. 2007).

Several targeted therapies have been developed to inhibit the activity of the EML4-ALK fusion protein, including crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib. These drugs have demonstrated high efficacy in treating NSCLC patients with the EML4-ALK fusion gene, with response rates ranging from 60 to 90%. ALK mutation is predictive for tyrosine kinase inhibitors (Camidge et al. 2020; Peters et al. 2017; Shaw et al. 2020, 2017; Solomon et al. 2014).

ALK mutation occurs in approximately 3–5% of NSCLC patients, primarily in those with little or no smoking history, young women, and adenocarcinoma histology (Bilgin et al. 2021). Due to its low incidence, there is limited data about its clinical characteristics. Few real-world studies have been conducted on clinicopathological characteristics and

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treatment in advanced ALK-positive NSCLC patients (Soda et al. 2007).

Pleural involvement and/or effusion (Ple-I/E) is common in ALK-positive patients with NSCLC at the time of diagnosis (Doebele et al. 2012; Rizzo et al. 2016). In our study, we retrospectively analyzed advanced NSCLC patients with ALK rearrangements and evaluated clinicopathological characteristics, treatment response, and survival of ALK-positive patients who have Ple-I/E. Here, we present one of the largest nationwide series to date of EML4-ALK positive patients with NSCLC (Figs. 1, 2).

Material and methods

In this multicenter study, we aimed to investigate the clinicopathological characteristics, treatment response, and survival of ALK-positive NSCLC patients with Ple-I/E compared to those without Ple-I/E. To achieve this goal, the researchers retrospectively collected data from NSCLC patients diagnosed between 2015 and 2019. The patients' records and data were obtained retrospectively from the electronic databases of the participating hospitals. The study included only patients who were over 18 years old, had metastatic disease, and had measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. In our study, pleural involvement and/or effusion were defined if at least one of the following criteria existed: 1. Malignant pleural biopsy, 2. Malignant pleural effusion cytology, 3. Appearance consistent with metastatic pleural involvement/effusion on PET-CT. EML4-ALK gene rearrangements were detected by fluorescence in situ hybridization (FISH) analysis in all patients.

The primary end-point was overall survival (OS), which was defined the time from diagnosis to death. The secondary end-point was progression-free survival (PFS), which was described as the time from initiation of crizotinib to RECIST-defined progression or death. The study also collected data on various patient characteristics, including age, gender, smoking status, histological diagnosis, metastases at diagnosis, initial Eastern Cooperative Oncology Group (ECOG) performance score, diagnostic stage, and treatment options.

All statistical analysis was performed using SPSS software version 22.0. We examined the relationship between clinicopathological variables and Ple-I/E status, as well as the relationship between Ple-I/E status and metastasis sites. We used the chi-square test or Fisher exact test for categorical data and independent-samples t-test for continuous data. To determine if the variables were normally distributed, we used visual methods such as histograms and probability plots, as well as analytic methods such as the Kolmogorov–Smirnov or Shapiro–Wilk's test. Additionally, we calculated Kaplan–Meier survival estimates and used a log-rank

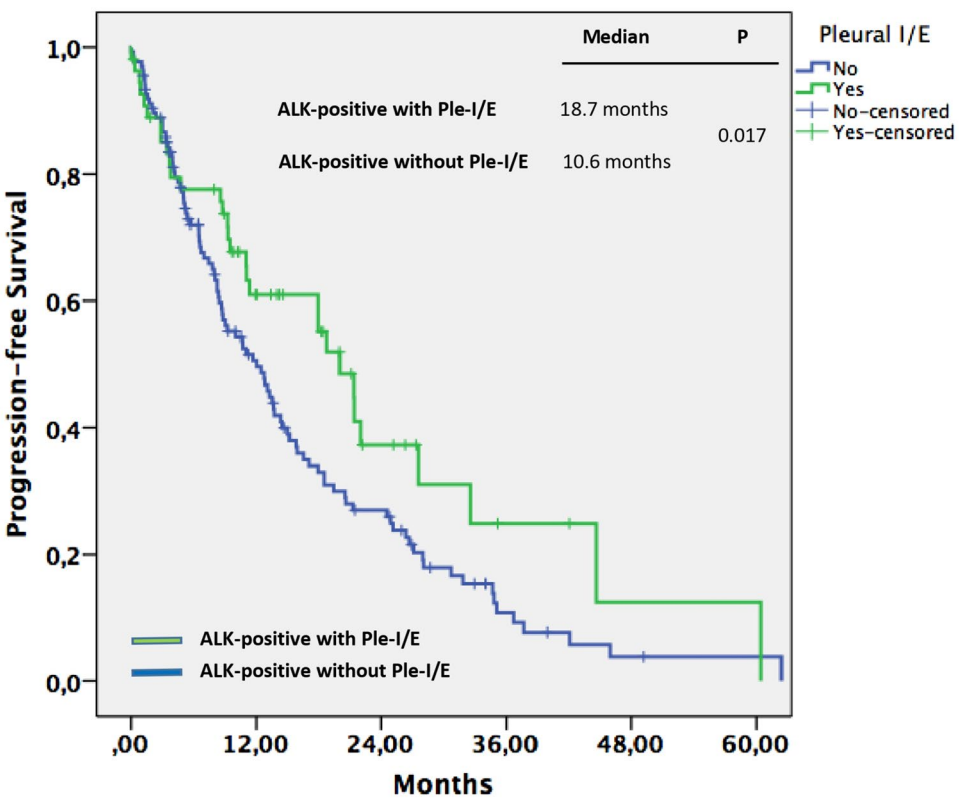

Fig. 1 Comparison of PFS between ALK-positive patients with Ple-I/E and ALK-positive patients with non-involvement. *I/E* Involvement/effusion, *PFS* Progression-free survival, *ALK* Anaplastic lymphoma kinase

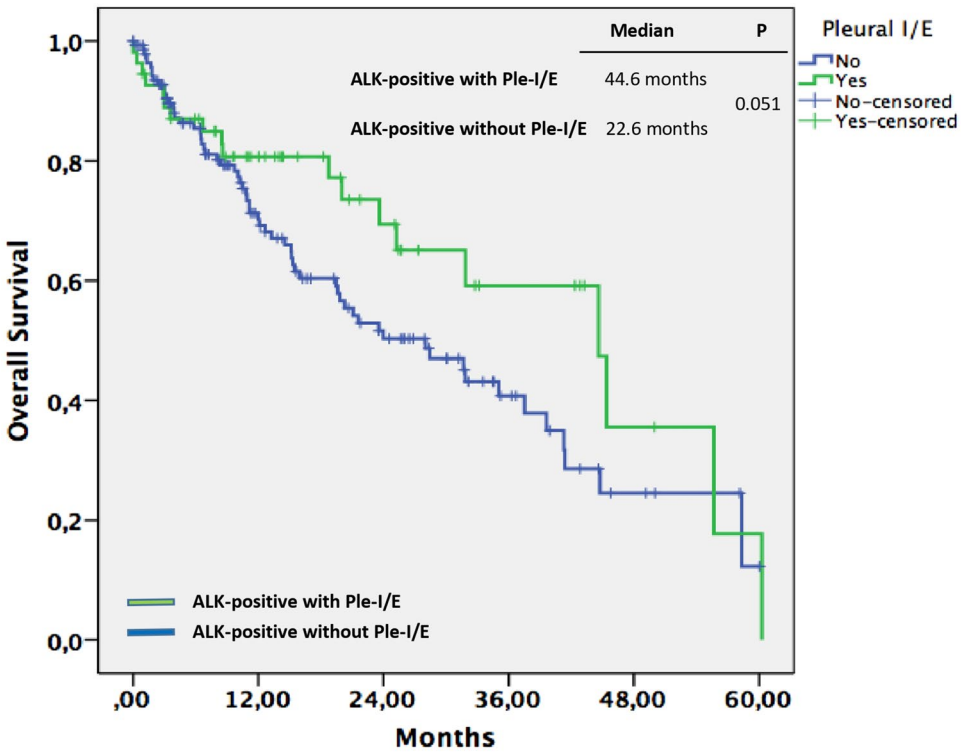

Fig. 2 Comparison of OS between ALK-positive patients with Ple-I/E and ALK-positive patients with non-involvement. *I/E* Involvement/effusion, *OS* Overall survival, *ALK* Anaplastic lymphoma kinase

test to compare survival times between the two treatment groups. A two-sided P-value < 0.05 was considered statistically significant.

Results

Patients' characteristics

A total of 362 patients were enrolled in the study, and their clinical characteristics were summarized in Table 1. Of the patients, 198 (54.7%) were male. The median age at diagnosis was 54 (range 21–85) years. The median age was higher in males than in females (57 vs 52 years; p = 0.011). The smoking rate was 43.4% (n = 157) in the patients. All patients' histology was adenocarcinoma (100%). At baseline, 57 (15.7%) patients had Ple-I/E.

Comparison of clinicopathological data and metastatic sites between Ple-I/E positive patients and negative ones

The median age of patients with Ple-I/E was similar to patients without Ple-I/E (53 vs 55 years; p = 0.541). There was no association between Ple-I/E and gender, lung metastasis, or distant LAP metastasis. Although pleural involvement was higher in non-smokers than in smokers (19.4% vs 13.4%; p = 0.077), it was not statistically significant.

The frequencies of liver, brain, and bone metastases were significantly higher in ALK-positive patients without Ple-I/E compared to those with Ple-I/E (respectively 18.2% vs 4.8%, p = 0.008; 19.1% vs 4.8%, p = 0.001; 20.6% vs 8.9%, p = 0.002). For lung and lymph node metastases, no significant difference was found between two groups (respectively p = 0.375, p = 0.118).

Survival analyses

During the study period, alectinib was not approved for first-line use. In the final period of the study, it obtained approval. Therefore, the number of patients is low. During the study period, according to Turkish reimbursment regulations, EGFR, ALK, and ROS could be sequentially evaluated in patients. First-line chemotherapy was initiated in symptomatic patients requiring urgent treatment. ALK-positive patients were continued on crizotinib as part of their treatment during follow-up. The number of patients who started first-line systemic treatment in ALK-positive without Ple-I/E was as follows: crizotinib, 161; chemotherapy, 131; alectinib 13. The number of patients who started first-line systemic treatment in ALK-positive with Ple-I/E was as follows: crizotinib, 40; chemotherapy, 15; alectinib, 2.

The median PFS was longer in ALK-positive patients with Ple-I/E compared to those without Ple-I/E (18.7 vs 10.6 months, p = 0.017). The 1-, 2-, and 3- year PFS rates

Table 1 Clinicopathological characteristics and metastasis sites of patients with advanced ALK-positive NSCLC and their relationship with Pleural I/E status

Characteristics	Pleural I/E		p
	No (n = 305)	Yes (n = 57)	
Age, median (range)	55 (23–82)	53 (26–84)	
Gender, n			
Female	134	30	0.302
Male	171	27	
Smoking, n			
Never	146	34	0.025
Smoker	135	22	
Unknown	24	1	
Metastasis sites, n			
Liver	58	5	0.008
Brain	79	4	0.001
Bone	135	11	0.002
Lung	127	29	0.375
Lymph node	212	42	0.118
Pleural seeding	–	18	
ECOG PS, n			
0	86	11	0.052
1	158	30	
2	77	14	
Treatments, first-line, n			
Chemotherapy	131	15	
Crizotinib	161	40	
Alectinib	13	2	

ALK Anaplastic lymphoma kinase, *NSCLC* Non–small cell lung cancer, *I/E* Involvement/effusion, *n* Number, *ECOG PS*: Eastern Cooperative Oncology Group performance status

were 59%, 36%, and 24% in patients with Ple-I/E and 47%, 24%, and 8% in patients without Ple-I/E.

The overall survival analysis showed similar results, with the median OS longer in ALK-positive patients with Ple-I/E (44.6 vs 22.6 months, p = 0.051). The 1-, 2-, and 3- year OS rates were 78%, 67%, and 57% in patients with Ple-I/E and 66%, 48%, and 34% in patients without Ple-I/E.

Discussion

Molecular analysis of NSCLC identifies subsets with various oncogenic driver mutations, clinicopathological features and potential for targeted therapies (Tsao et al. 2016). Molecular profiling is crucial for improving first-line progression-free survival and overall survival (Barlesi et al. 2016). Additionally, there is an association between molecular oncogene status and patterns of metastatic spread in treatment-naive patients (Doebele et al. 2012). Here, we report an analysis of the prognostic significance of pleural involvement and/or effusion (Ple-I/E) in patients with ALK-positive NSCLC.

Metastasis is the leading cause of death in lung cancer (Dragoj et al. 2017). The brain is a common site for lung cancer metastasis, with about half of lung cancer patients developing brain metastases during the course of the disease (Gavrilovic and Posner 2005; Sørensen et al. 1988; Yousefi et al. 2017). The propensity to metastasize to the brain remains an important clinical barrier that adversely affects the survival rate of lung cancer patients (Yousefi et al. 2017). Several studies have shown that brain metastases tend to occur more frequently in ALK-positive advanced NSCLC during treatment compared with negative ones (Chen et al. 2017; Gupta et al. 2019; Johung et al. 2016). In our study, we found that ALK-positive patients with Ple-I/E had a significantly lower incidence of brain metastasis than ALK-positive patients without Ple-I/E (4.8% vs 19.1%, p = 0.001). Based on these results, maybe due to the earlier development of symptoms related to effusion in ALK-positive patients with Ple-I/E, they may receive an earlier cancer diagnosis before the development of brain metastasis.

Bone is a common metastatic site in advanced NSCLC, occurring in approximately 30 to 40% of patients during trajectory of disease, and resulting in significant adverse effects on both morbidity and survival (Coleman 1997; Quint et al. 1996). Bone pain caused by skeletal metastases is one of the most common types of pain reported by cancer patients, and this is particularly true for lung cancer patients with bone metastases (Mercadante 1997). In previous studies, the incidence of bone metastases was found to be similar in ALK-positive and negative patients (Chen et al. 2017; Doebele et al. 2012). However, in one study, patients in ALK-positive group had more multiple bone metastatic sites than ALK − group through stratified analysis (Chen et al. 2017). In our study, we found that ALK-positive patients with Ple-I/E had a significantly lower incidence of bone metastasis than ALK-positive patients without Ple-I/E (8.9% vs 20.6%, p = 0.002), which suggest that patients without Ple-I/E may be at a higher risk of experiencing skeletal-related events during the course of the disease, compared to those with Ple-I/E. Based on the results, we hypothesized that ALK-positive patients without Ple-I/E were prone to form distant metastasis through hematogenous dissemination, while ALK-positive patients with Ple-I/E were prone to invade locally through the lymphatic system.

Based on previous studies, it seems that patients diagnosed with liver metastasis have a poorer prognosis compared to those with other organ metastasis (Finkelstein et al. 1986; Hoang et al. 2005; Li et al. 2019). The majority of NSCLC patients with liver metastasis do not respond well to chemotherapy (Yamamoto et al. 1999). Additionally, some patients with liver metastases may not be able to tolerate chemotherapy due to liver dysfunction (Nakagawa et al.

2008). Previous studies have reported a higher incidence of liver metastases in ALK-positive patients (Doebele et al. 2012; Varella-Garcia 2011; Yang 2011). In our study, we found that ALK-positive patients with Ple-I/E had a significantly lower incidence of liver metastasis than ALK-positive patients without Ple-I/E (4.8% vs 18.2%, p = 0.008). Ple-I/E may have prognostic significance in patients with ALK-positive NSCLC. These factors make it challenging to treat and manage liver metastases in ALK-positive patients without Ple-I/E. Therefore, alternative treatment options may need to be explored for these patients, and personalized treatment strategies should be developed to improve outcomes..

It is interesting that our study revealed a significant difference in the incidence of brain, liver, and bone metastases between ALK-positive patients with and without Ple-I/E. ALK-positive patients without Ple-I/E were prone to form distant metastasis through hematogenous spread, while ALK-positive patients with Ple-I/E were prone to invade the local region through lymphatic system. However, further validation research is indeed necessary to test our hypothesis.

To the best our knowledge, the incidence of lung metastases is similar in both ALK-positive and negative patients. A previous study found no significant difference in incidence between ALK-positive patients and patients from the triple negative cohort (ALK, EGFR, ROS-1) (Doebele et al. 2012). In our study, we found no association between Ple-I/E and lung metastasis, possibly due to the infrequent spread of lung cancer to the contralateral lung (Onuigbo 1974). In a previous study, patients with ALK mutation had a slightly higher incidence of intrathoracic and extrathoracic lymph node spread compared to patients from the triple-negative cohort (ALK, EGFR, ROS-1), but the difference was not statistically significant (Doebele et al. 2012). In our study, we found no association between Ple-I/E and distant lymph node metastasis.

Regarding the survival analysis, ALK-positive patients with Ple-I/E had a longer median PFS compared to those without Ple-I/E (18.7 vs 10.6 months, p = 0.017). Similarly, the median OS was longer in ALK-positive patients with Ple-I/E (44.6 vs 22.6 months, p = 0.051). Previous studies have identified liver (HR 1.45, 95% CI 1.40–1.50), bone (HR 1.21, 95% CI 1.18–1.24) or brain metastases (HR 1.18, 95% CI 1.15–1.21) as poor prognostic factors for OS, with the highest hazard ratio value seen in patients with liver metastasis (p < 0.001) (Campos-Balea et al. 2020). In another study, Li et al. reported that patients with lung metastases had the best survival outcome, followed by bone metastases and brain metastases, while patients with liver metastases had the worst survival among those diagnosed with isolated metastases (Li et al. 2019). Our findings are consistent with these studies, suggesting that ALK-positive patients with Ple-I/E have better outcomes due to the lower incidence of brain, liver, and bone metastases. Thus, we can assume that pleural involvement and/or effusion (Ple-I/E) has prognostic significance in patients with ALK-positive NSCLC. However, it is important to note that these results are based on a specific study population and may not be generalizable to all patients with NSCLC. Further research is needed to confirm these findings and explore the underlying mechanisms of these associations..

Our study has some limitations. First, the retrospective design of our study is a significant limitation, potentially leading to selection bias in patient inclusion. Another limitation is that the number of patients with Ple-I/E group is relatively small, and none of the significant associations identified are absolute. Therefore, this data should not be used as the sole criterion for deciding if there is prognostic significance in Ple-I/E in patients with ALK-positive NSCLC. Further prospective studies evaluating the characteristics of ALK-positive patients who have Ple-I/E are needed.

Conclusion

In conclusion, our findings suggest that brain, liver, and bone metastases are less common in ALK-positive patients with Ple-I/E, and that ALK-positive patients with Ple-I/E have better outcomes compared to those without Ple-I/E. The presentation of Ple-I/E in patients with ALK-positive NSCLC is associated with longer overall and progression-free survival. However, it is important to note that these associations are not absolute, and other factors may also impact patient outcomes. Therefore, the presence of Ple-I/E in patients with ALK-positive NSCLC should be considered in the context of other clinical factors, and further research is needed to better understand its prognostic significance.

Author contributions All the authors contributed substantially to the study conception, design. Material preparation and data collection were performed by GG, BYA, FBB, AD, PG, UD, PFY, FÇŞ, BÇ, İÇ, AÖ, HŞC, EÇ, AI, ÖFÖ, AMT, MK, TŞ, YE, TK. Statistical analysis was performed by SK. The first draft of the manuscript was written by GG and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was conducted in accordance with the Declaration of Helsinki and approved by the institutional review boards at each of the participating centers.

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