Original Article

Crizotinib in Metastatic ALK mutant Non-small Cell Lung Cancer Patients: A Single Centre Experience

Abstract

The goal of this study was to evaluate the efficacy of crizotinib in patients with ALK-positive metastatic lung cancer. The patients' data were analyzed retrospectively. Cox regression and Kaplan-Meier methods were used to perform survival analyses. A total of 25 patients were involved in the study. Thirteen (52%) patients were male, and the average age was 55 (range, 30-80). 23 (92%) of the patients were de-novo metastatic. Brain metastases were present in 32% and liver metastases in 20% of the patients. Before crizotinib treatment, 64% of the patients had received chemotherapy, and 20% had received palliative radiotherapy. Progression-free survival was found as 16.8 (CI 95%, 5.7-27.9) months. Grade 1-2 side effects were detected in 36% of the patients, and grade 3-4 side effects were observed in 12%. After progression, 13 (52%) patients received 2nd series ALK inhibitors (alectinib, ceritinib, and lorlatinib) or chemotherapy. The median overall survival (OS) was found as 44.2 (95% CI, 28.5-59.9) months. The four-year OS rate was 37.4%. In the multivariate analysis, the ALK positivity ratio (p=0.02) was determined as a statistically significant factor affecting OS. We showed efficacy data of crizotinib in patients with ALK mutant metastatic non-small cell lung cancer. Crizotinib is an effective and safe therapy for patients with ALK mutant metastatic non-small cell lung cancer. Also, we found that the ALK positivity ratio was prognostic for OS.

Keywords: *Non-small cell lung cancer, ALK mutation, Crizotinib, Prognosis*

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Introduction

Lung cancer is one of the most common and fatal malignancies in the world.[1] In recent years, with the advances in oncology at the molecular and genetic level, personalized treatments have started to be developed in the treatment of cancer. Many driver mutations have been identified in metastatic non-small cell lung cancer (mNSCLC), and drugs targeting these mutations have been developed.[2] The level of effectiveness of these targeted drugs varies according to the type of mutation and the type of drug targeting the same mutation.[3] In many studies, it has been shown that these personalized treatments have better results than conventional cytotoxic chemotherapy in terms of survival data and toxicity.[4] These mutations are examined by immunohistochemistry, next-generation sequencing, and in situ, hybridization methods and are detected rarely.

In mNSCLC patients, the anaplastic lymphoma kinase (ALK) mutation, which is found on chromosome 2, is found at a rate of about 4-6 percent.[5] ALK is a transmembrane tyrosine kinase receptor that activates cell growth and proliferation-related pathways such as PI3K-AKT, MAP kinase pathways, and Janus kinase (JAK)-STAT.[6] ALK mutation is detected more frequently in young people, non-smokers, and adenocarcinoma histology, and relatively more frequently in males than females.[7, 8] In patients with ALK mutant mNSCLC, 1st generation crizotinib, 2nd generation ceritinib, brigatinib alectinib, and 3rd generation lorlatinib are used in the treatment of the disease. 2th and 3rd-generation ALK inhibitors were determined to be superior to the first-generation ALK inhibitor crizotinib in terms of disease control and cranial nervous system penetration.[9] Crizotinib is a first-line treatment option in ALK mutant mNSCLC patients, and the survival efficacy of sequential treatments with the next generations of ALK inhibitors after progression under crizotinib has been demonstrated.[10] In the literature, studies examining the factors affecting prognosis in patients with ALK mutant mNSCLC treated with crizotinib are limited. In this study, we examined real-life outcomes in patients

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treated with crizotinib ALK mutant mNSCLC and the factors affecting prognosis in these patients.

Materials and Methods

Patients inclusion and data collection

The study was planned with a retrospective design. The study was performed according to good clinical practice guidelines. Patients were identified through the hospital registry system. Patients with mNSCLC with ALK mutation and who used crizotinib were involved in the study. The study excluded patients whose records did not provide sufficient data for statistical analysis. Pathological, clinical, and radiological data of the patients were noted. The chemotherapy agents, radiotherapy treatments, and other treatments given to the patients during the entire treatment process were noted from the hospital patient files. ALK positivity was evaluated in a standardized pathology center with a fluorescence in-situ hybridization method. ALK mutation was accepted to be positive in the presence of a signal greater than 15%.

The patients used crizotinib at 250 mg twice daily. Clinical and radiological treatment response assessments were performed on patients every two or three months. Crizotinib-related treatment responses were categorized according to RECIST 1.1. Crizotinib-related adverse events were noted at each examination, and toxicity grading was performed.

Progression-free survival (PFS) was measured as the interval between starting crizotinib and progression. The patients' status as deceased was checked using the Ministry of Health's death notification system. The time from the development of metastasis to any cause was accepted as overall survival (OS). Univariable statistical analysis was done for parameters affecting OS. A multivariable analysis was carried out using parameters that were statistically significant for OS.

Statistical analysis

Study statistics were done using SPSS 25. Continuous variables were indicated by the median value (minimum-maximum). Categorical variables were indicated by numbers (%). Survival analyzes and curves were made by Kaplan Meier analysis, while a log-rank test was used for differences between groups. Multivariable analysis was done by the Cox regression method. Statistical significance was determined to be a p-value less than 0.05.

Results and Discussion

Patient features and treatment modality

The data of 25 patients were analyzed in the study. The patients' median age was 55 (30-80). The most diagnosed histopathological type was adenocarcinoma (96%) and twenty-three (92%) presented with de-novo metastatic disease. The most common extrapulmonary metastases site was bone (40%). **Table 1** is presented the features of the patients.

Table 1. Patients Characteristics

Characteristics	Number of patients Total number: 25	%
Gender		
Male	13	52
Female	12	48
Smoking history		
Yes	11	44
No	6	24
Unknown	8	32
Primary tumor location		
Right side	13	52
Left side	9	36
Unknown	3	12
De-novo metastatic disease		
Yes	23	92
No	2	8
Number of metastatic sites		
1	9	36
2	5	20
≥ 3	8	32
4	1	4
Unknown	2	8
Metastatic sites		
Lung	16	64
Bone	10	40
Brain	8	32
Liver	5	20
Adrenal gland	3	12
Treatments before crizotinib		
Palliative chemotherapy	16	64
Palliative radiotherapy	5	20

The median ALK positivity ratio was 42 (15-100). Sixteen (64%) patients received palliative chemotherapy, and 5 patients (20%) received palliative radiotherapy before crizotinib. Objective response was achieved in 17 (68%) patients, and disease control was achieved in 19 (76%) patients with crizotinib treatment **(Table 2)**. One (4%) patient could not continue treatment due to toxicity. Grade 1-2 adverse events were observed in nine (36%) patients, and grade 3-4 adverse events were observed in three (12%) patients. When the analysis was done, 20 (80%) patients discontinued crizotinib therapy because of progression or toxicity. Ten (50%) of these patients continued treatment with a different ALK inhibitor, one (4%) patient with chemotherapy, and one (4%) patient with an EGFR inhibitor.

Table 2. Responses of treatment to crizotinib in mNSCLC patients who were treated with crizotinib

	Number of patients (Total number: 25)	%	Valid-%
Response ratios			
Complete response	3	12	14.3
Partial response	14	56	66.7
Stable disease	2	8	9.5
Progresşon	2	8	9.5
Unknown	4	16	
Objective response ratio	18	68	71
Disease control ratio	20	76	80.5
Unknown	4	16	

Survival outcomes and prognosis

The average period of follow-up from the post-metastasis period was 39 months. Crizotinib-related PFS was 16.8 (95% CI, 5.7-27.9) **(Figure 1)**. In the analysis performed according to the ALK positivity ratio, the median PFS was found as 14.3 (95% CI, 2.1-26.6) months in patients who had ALK positivity <50% and 25.9 (95% CI, 0-60.8) months in patients had ALK positivity ≥50% **(Figure 2)**. This difference in PFS according to the ALK positivity ratio was not statistically significant (p=0.1). In patients treated with crizotinib, the one-year PFS rate was detected at 67.3%, while the three-year PFS rate was 33.3%. At the time of analysis, 14 (60.9%) patients had died. The median OS was observed at 44.2 (95% CI, 28-59) months after the post-metastasis period **(Figure 3)**. Five-year OS rate was found to be 37.4% in all patients. In the analysis performed according to the ALK positivity ratio, in the arm with an ALK positivity ratio ≥50% compared to the arm with an ALK positivity rate <50%, the median OS was statistically significantly higher (p=0.01) **(Figure 4)**. In the univariable and multivariable analysis for factors affecting OS, the ALK positivity ratio was determined as a statistically significant factor affecting OS **(Table 3)**.

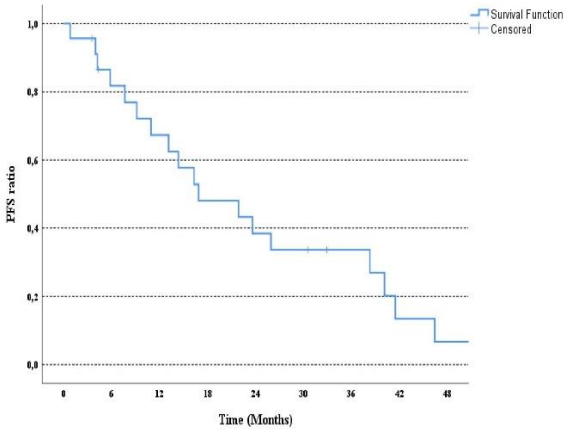

Figure 1. Kaplan Meier Curve for PFS in mNSCLC patients who were treated with crizotinib

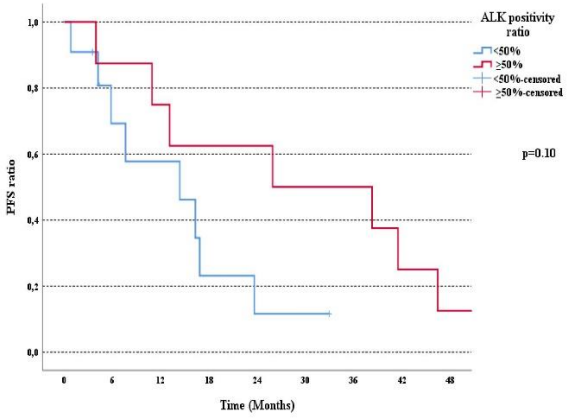

Figure 2. Kaplan Meier Curve for PFS by ALK positivity ratio in mNSCLC patients who were treated with crizotinib

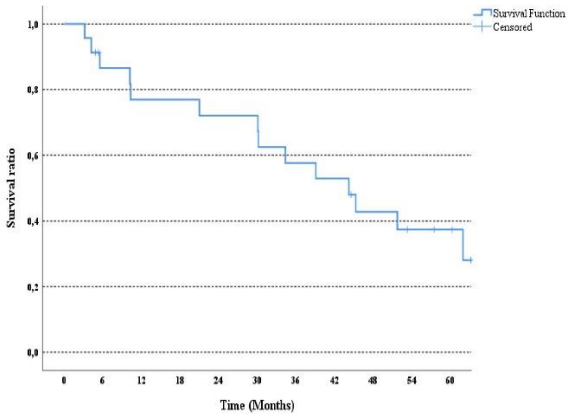

Figure 3. Kaplan Meier curve for OS in the ALK mutant mNSCLC patients who were treated with crizotinib

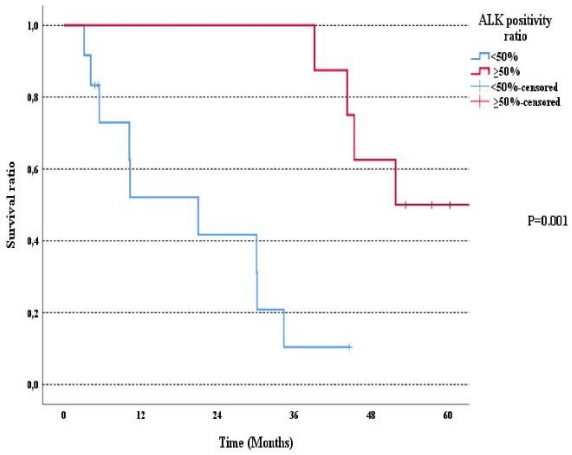

Figure 4. Kaplan Meier curves for OS by ALK positivity ratio in the ALK mutant mNSCLC patients who were treated with crizotinib

Table 3. Univariate and multivariate analysis for OS in the mNSCLC patients who were treated with crizotinib

	Univariate analysis	Multivariate analysis
	P-value	**P-value HR-CI 95%**
Age (<50 vs. ≥50)	0.57	
Gender (Male vs. Female)	0.55	
Smoking history (Yes vs. No)	0.52	
Primary tumor site (Right vs. Left)	0.41	
ALK positivity ratio (≥50% vs. <50%)	**0.001**	**0.022** 9.3 (1.3-63)
Brain metastasis (Yes vs. No)	0.70	0.66
Liver metastasis (Yes vs. No)	**0.007**	0.29
Adrenal gland metastasis (Yes vs. No)	**<0.001**	0.054

Palliative Chemotherapy (Yes vs. No)	0.89
Palliative Radiotherapy (Yes vs. No)	0.73

Multivariate analysis model p-value <0.001

In this study, we demonstrated that the first-generation ALK inhibitor crizotinib is effective and safe in patients with ALK mutant mNSCLC. In the PROFILE 1014 study published in 2014 that compared crizotinib and chemotherapy in patients with ALK mutant mNSCLC in the first-line, median PFS was found to be 10.9 months in the patients who used crizotinib and 7 months in the patients who used chemotherapy.[11] The PROFILE 1014 study's final analysis was published in 2018, the median OS was not defined in the crizotinib arm, and it was found to be 47.5 months in the chemotherapy arm; also, patients with the longest median OS were identified as those receiving subsequent ALK inhibitors.[12] In our study, although the median PFS duration was longer, the median OS was found to be approximately 44 months. This can be explained by the retrospective nature of our study and the heterogeneity of our patient group. Also, in retrospective real-life studies, patients with low performance often receive treatment and are included in the analysis process. Better survival results have been obtained in patients with ALK mutant mNSCLC with new generation ALK inhibitors. In the phase 3 ALEX study comparing the efficacy of crizotinib and alectinib, median PFS was found to be 34.8 months in the patients who used alectinib and 10.8 months in the patients who used crizotinib.[13] In the phase 3 ALTA-1L trial study comparing the efficacy of crizotinib and brigatinib, the median PFS was found as 24 months in the brigatinib arm and 11.1 months in the crizotinib arm.[14] Alectinib and brigatinib were founded superior to crizotinib in terms of OS in both studies. The sequential use of ALK inhibitors can be beneficial in terms of survival outcomes after progression under crizotinib. In the phase III ALUR study, alectinib was found superior to standard chemotherapy in crizotinib-refractory disease, both in systemic and CNS efficacy.[15] Similar results were obtained in favor of brigatinib in the Phase 2 ALTA trial.[16] In addition, lorlatinib, a third-generation ALK inhibitor, has activity against ALK inhibitor resistance mutations, including G1202R; it is effective even in patients who progress under first and second-generation ALK inhibitors.[17] During treatment, new ALK gene mutations and activation of other tyrosine kinase inhibitors (EGFR, KIT) leading to crizotinib resistance can be seen, which leads to disease progression.[18] The prognostic variables related to crizotinib treatment in patients with ALK mutant mNSCLC were investigated in this study. We showed that the ratio of ALK positivity was prognostic. Similar to our results, in an analysis published by Soria *et al*. in 2018, a correlation was found between the increase in the percentage of ALK positivity and the prolongation of PFS.[19]

In this study, although there was a trend for better PFS, statistically significantly better OS was detected in patients who had an ALK positivity ratio above 50% and were treated with crizotinib. The fact that there was no statistically significant difference in PFS could be a result of the small number of patients in this study and the statistically significant difference in OS could be a result of the fact that the patients continued treatment with other ALK inhibitors after progression with crizotinib. In addition, ALK variants affect the duration of crizotinib response, and crizotinib was found to be more effective in patients with ALK variant 1.[20] In a study evaluating the clinical factors affecting progression under crizotinib treatment, it was shown that performance status and metastatic disease burden statistically significantly affected PFS, and gender, age, smoking history, and brain metastases did not affect PFS.[21] Our study showed that gender, age, smoking history, and brain metastases did not affect OS in patients receiving crizotinib. Although the presence of liver and adrenal gland metastases was found to affect OS in univariate analysis, this effect could not be confirmed in multivariate analysis. Our study had a few limitations. Since our study was of a retrospective nature, the patient group was heterogeneous. Some data were missing, and the number of patients was limited.

Conclusion

In our study, we showed the outcomes of crizotinib treatment in patients with ALK mutant mNSCLC. Crizotinib was effective and safe in patients with ALK mutant mNSCLC. We found that patients with an ALK positivity ratio above 50% have a better prognosis. ALK mutation is rare, and the number of studies examining prognostic data is limited. Multicenter studies included large numbers of patients are needed to identify the mechanisms of resistance to ALK inhibitors and to identify patient groups that benefit more from ALK inhibitors.

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Conflict of interest
None.

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Ethics statement
The local ethics committee approved this study at the Istanbul University Faculty of Medicine (Number:266748).

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