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ORIGINAL ARTICLE

Real-life Outcomes of ROS1 Fusion-positive Metastatic Lung Cancer Patients who were Treated with Crizotinib

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OBJECTIVE

ROS1 positivity is seen in 1-2% of patients with metastatic lung cancer. Targeted drugs such as crizotinib, lorlatinib, and entrectinib are used in the treatment. We aimed to evaluate the efficacy of crizotinib and the prognosis of patients with ROS1 fusion-positive metastatic non-small cell lung cancer (NSCLC) in this study.

METHODS

We analyzed data of the advanced NSCLC patients with ROS1 mutation retrospectively. We determined the clinicopathological features of the patients. We evaluated the parameters affecting the prognosis with survival analyzes.

RESULTS

The research enlisted the participation of 21 patients. Median progression-free survival with crizotinib treatment was found 26.1 (95% Confidence interval [CI], 8.1-44.1) months. Median overall survival was 35.2 (95% CI, 13.5-56.9) months. Treatment-related Grade 1-2 adverse effects were observed in 9 (42.9%) patients and Grade 3-4 adverse effects were detected in 1 (4.8%) patient. Clinicopathological parameters affecting survival were evaluated; age (p=0.02) and liver metastasis (p=0.03) were defined as prognostic parameters. ROS1 positivity rate (p=0.08) was not found to be a prognostic factor.

CONCLUSION

In patients with ROS1 fusion-positive metastatic NSCLC, crizotinib was shown to be both efficacious and safe. We also found that in this patient group, age and the existence of liver metastases are prognostic factors.

Keywords: Crizotinib; non-small cell lung cancer; prognosis; ROS1 fusion.

INTRODUCTION

Lung cancer is one of the most common malignancies in men and women across the globe, with a poor prognosis. Different subtypes have been defined in non-small cell lung cancer (NSCLC), including squamous cell cancer, adenocarcinoma, and large cell cancer. While the primary treatment is surgery in early-stage disease, multimodal treatment approaches including surgery, radiotherapy, and chemotherapy are used in locally advanced disease. In recent years, treatments in metastatic NSCLC have become increasingly individualized. A targetable mutation has been demonstrated in approximately 60% of lung cancer patients.[1] Drugs

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targeting driver mutations are being developed and preferred for the treatment of metastatic NSCLC at first-line. Fluorescence in-situ testing (FISH), immunohistochemistry, and next-generation sequencing (NGS) methods are used to detect driver mutations.[2] In the treatment of metastatic disease, detection and targeting of ROS oncogene 1 (ROS1), anaplastic lymphoma kinase (ALK), epidermal growth factor receptor (EGFR), mutations, and other driver mutations are improved survival results.[3]

ROS1 gene fusion was first detected in glioblastoma cells in 1987 and NSCLC cells in 2007 and is located on chromosome 6q21.[4] ROS1 is a tyrosine kinase receptor that functions as a driving oncogene. FISH break-apart test or some NGS panels can be used to detect ROS1 translocations. ROS1 positivity is detected in 1-2% of patients with NSCLC.[5] Furthermore, ROS1 positivity is detected more frequently in young people, women, adenocarcinoma subtypes, and non-smokers.[6] ROS1 inhibitor crizotinib and tropomyosin receptor kinase inhibitor entrectinib can be used first-line in patients with metastatic NSCLC with ROS1 mutation. In a Phase 1 study (PROFILE 1001) conducted in 2014, it was shown that crizotinib has significant antitumoral activity in patients with metastatic NSCLC.[7] Similar results were obtained in subsequent studies. In studies conducted in ROS1 positive metastatic NSCLC patients, crizotinib was found to be more beneficial than platinum and pemetrexed-based treatments in the first line.[8,9] There are limited data in the literature on the factors affecting the prognosis in patients with ROS1 mutation. The goal of this research was to assess the efficacy of crizotinib therapy and prognostic factors in patients with metastatic NSCLC who had a ROS1 fusion.

MATERIALS AND METHODS

Patients and Data Collection

The study was designed retrospectively. Institutional ethics review board approval was obtained before the study. The research was carried out in accordance with good clinical practice recommendations. The patients involved in the study consisted of patients who were followed up in the outpatient clinic of a single oncology center between 2015 and 2020. The patients involved in the study were identified through the hospital information system. All patients with ROS1 fusion-positive metastatic NSCLC who used crizotinib were involved in the study. Patients who did not have sufficient data for statistical analysis were excluded from the study. The pathological, clinical, radiological, and treatment-related data of the patients were noted from the patient data system. ROS1 positivity was evaluated from pathology specimens by the FISH method. A signal presence of 15% or more in the tumor was accepted as the cutoff value for ROS1 positivity.

The patients were given crizotinib 250 mg twice a day. The efficacy of the treatment was evaluated clinically and radiologically every 2 or 3 months. Treatment responses were analyzed according to the RECIST 1.1 guideline. The Common Terminology Criteria for Adverse Events standards were used to record and assess treatment-related adverse events.

The Ministry of Health's death notification system was used to verify the patients' death status. The time from onset of metastatic disease to death from any cause was defined as overall survival (OS). The period from the start of crizotinib to disease progression was used to calculate progression-free survival (PFS). The factors affecting OS were analyzed with clinical and pathological parameters. In addition, the relationship between ROS1 positivity rate and treatment response was evaluated.

Statistical Analysis

SPSS 25 was used to conduct all statistical analyses. Numbers and percentages were used to represent categorical data, whereas a median value (minimum-maximum) was used to represent continuous variables. The survival analysis and curve were calculated using the Kaplan-Meier technique. Prognostic univariate and multivariate analyses in terms of OS were obtained by applying the Cox-regression method. ROC analysis was performed to evaluate the effect of ROS1 positivity rate on treatment response. Statistical significance was accepted as $p<0.05$.

RESULTS

Patients and Data Collection

A total of 28 patients were identified and seven patients were excluded from the study due to insufficient data. The median age was 56 (23-79). The primary tumor origin was predominantly from the right lung (81%) in patients. The number of de novo metastatic patients was 13(61.9%). We found that the most common metastasis site outside the lung was the brain (28.6%). The clinical and treatment characteristics of the patients are listed in Table 1.

Table 1 Clinical and treatment features of the patients

Characteristics	Number of patients (Total number: 21)	%
Gender		
Male	11	52.4
Female	10	47.6
Smoking history		
Yes	12	57.2
No	5	23.8
Unknown	4	19
Primary tumor location		
Right side	17	81
Left side	4	19
Stage at diagnosis		
Stage 1	1	4.8
Stage 2	2	9.5
Stage 3	5	23.8
Stage 4	13	61.9
Primary lung surgery		
Yes	4	19
No	17	81
Number of metastatic sites		
1	8	38.1
2	7	33.3
≥3	6	28.6
Metastatic sites		
Lung	18	85.7
Brain	6	28.6
Liver	4	19
Adrenal gland	3	14.3
Bone	2	9.5
Other sites	3	14.3
Treatments before crizotinib		
Palliative chemotherapy	7	33.3
Palliative radiotherapy	7	33.3

The objective response rate with crizotinib treatment was found as 55.5% and the disease control rate was 83.3% after correction due to missing data (Table 2). Treatment-related Grade 1-2 toxicity was observed in 9 (42.9%) patients and Grade 3-4 toxicity was observed in 1 (4.8%) patient. Non-hematological side effects were more frequent and these were observed as bradycardia, myalgia, and dermatitis. As severe toxicity, only one patient had elevated liver function tests. The median ROS1 positivity rate was 21 (15-79) in the patients. In the ROC analysis, we found that the rate of ROS1 positivity did not predict the response. In addition, 3 (14.3%) patients received chemotherapy after progression under crizotinib.

Table 2 Responses of treatment to crizotinib in the patients

Response ratios	Number of patients (Total number: 21)	%	Valid, %
Complete response	None		
Partial response	10	47.6	55.5
Stable disease	5	23.8	27.7
Progression	3	14.3	16.6
Objective response ratio	10	47.6	55.5
Disease control ratio	15	71.4	83.3
Unknown	3	14.3	

Survival Outcomes and Prognosis

The average period of follow-up was 17 months. Ten (48.6%) patients died during the study period. Crizotinib-related median PFS was 26.1 (95% CI, 8.1-44.1) months (Fig. 1). The median OS was detected as 35.2 months (95% CI, 13.5-56.9) in patients after metastatic disease development (Fig. 2). In the analysis of clinicopathological parameters affecting OS, gender, smoking history, primary tumor site, presence of de novo metastatic disease, the number of metastatic sites, and ROS1 positivity rate were evaluated. The existence of liver metastases (p=0.03) and age (p=0.02) was identified to be prognostic variables for OS in multivariate analysis (Table 3).

DISCUSSION

The prognosis of patients with ROS1 fusion-positive NSCLC and the effectiveness of crizotinib in this patient group was proven in this research. Crizotinib was shown to be safe and effective in patients. In a Phase 2 study evaluating 34 patients with ROS1 fusion-positive metastatic NSCLC, the objective response rate with crizotinib treatment was found as 70% with a 20-month median PFS, and crizotinib was well tolerated.[10] The objective response rate in metastatic NSCLC patients treated with crizotinib was found to be 72% in a research that presented the long-term outcomes of the PROFILE 1001 investigation, with a median PFS of 19.3 months.[11] In this study, the median OS was found 51.4 months, with a 4-year survival rate of 51%. In addition, more than half of the patients enrolled in this study had received at least one series of chemotherapy before crizotinib and their performance status was good before the treatment. In our study,

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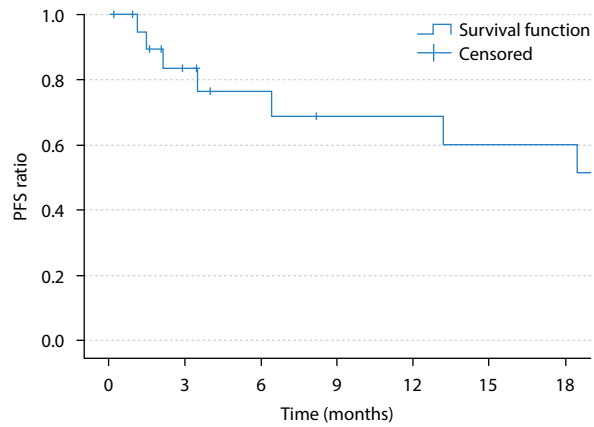

Fig. 1. Kaplan-Meier curve for PFS in the patients.
PFS: Progression-free survival.

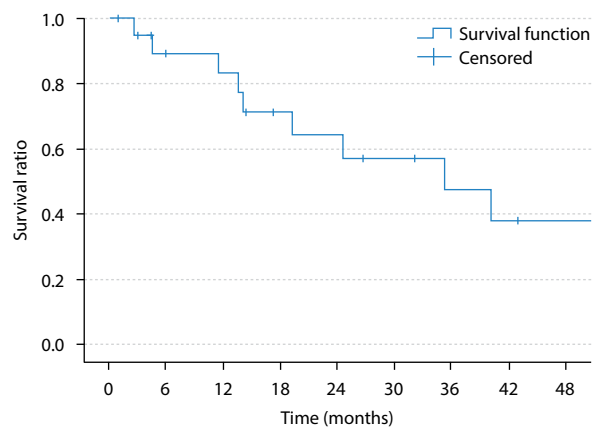

Fig. 2. Kaplan-Meier curve for OS in the patients.
OS: Overall survival.

although median PFS was found to be longer than in the literature, the median OS duration was found to be less. This can be explained by the fact that the patients in our study consisted of patients with poor real-life performance status and that a significant portion of the patients received chemotherapy before crizotinib. In addition, the limited number of patients may have affected the results. In a retrospective study in which 21 patients with ROS1 fusion-positive NSCLC treated with crizotinib were evaluated, the median PFS was 10.6 months, and similar to our study, the median OS was found 33.1 months.[12] In another retrospective analysis performed by Masuda et al.,[13] the median PFS was found 10 months, and the median OS was 28.7 months with crizotinib in patients with ROS1 positive metastatic NSCLC. Some specific additional genetic features may affect crizotinib-related treatment outcomes. In a study examining the response of different types of ROS1 fusion partners to crizotinib treatment, it was shown that in the presence of the CD 74 molecule gene, brain metastases are more common, and survival outcomes are negatively affected.[14] Resistance mutations such as G2032R, S1986F, and D2033N develop around 50% during crizotinib treatment in patients with NSCLC who are positive for ROS1 mutations.[15] However, the overall response rate with lorlatinib was found to be 35%, and the intracranial response rate was 50% in patients with brain metastatic ROS1 fusion-positive NSCLC who progressed under crizotinib therapy.[16]

Table 3 Univariate and multivariate analysis for OS in the patients

Characteristics	Univariate analysis p	Multivariate analysis p
Age	0.18	0.02
Gender		
(Male vs. Female)	0.72	0.31
Smoking history		
(Yes vs. No)	0.78	
Primary tumor site		
(Right vs. Left)	0.37	
De-novo metastatic disease		
(Yes vs. No)	0.16	
Number of metastasis		
(1-2 vs. ≥3)	0.06	
Brain metastasis		
(Yes vs. No)	0.06	0.39
Liver metastasis		
(Yes vs. No)	0.04	0.03
Adrenal gland metastasis		
(Yes vs. No)	0.09	
ROS1 positivity ratio	0.06	0.08

Multivariate analysis model p=0.004. OS: Overall survival; ROS1: ROS oncogene 1

The presence of brain metastasis is an indication of poor prognosis in lung cancer. The brain metastases incidence in NSCLC patients with ROS1 mutation is around 30-40%, and this rate was similar to that of other driver mutations.[17] In brain metastatic ROS1 fusion-positive patients, new agents such as lorlatinib, entrectinib, and rapotrectinib have started to be used, with an objective response rate of around 60% and higher intracranial activity.[18] In our study, we evaluated the parameters affecting the prognosis and determined that age and the presence of liver metastases were prognostic factors. In addition, the rate of

ROS1 positivity was not found to be prognostic. In a study presenting the real-life results of patients with metastatic NSCLC treated with crizotinib, median OS was detected for 36 months, similar to our study, and it was determined that current smoking and poor performance adversely affected the prognosis.[19] In another study evaluating the prognosis in metastatic NSCLC patients with ROS1 mutation treated with crizotinib, smoking history was not found to be a statistically significant factor for OS similar to our study, while the presence of more than two organ metastases was found a poor prognostic factor.[20]

Study Limitations

Some data were missing due to the fact that it was a retrospective study, and the number of patients was low due to the fact that ROS1 mutation is a rare mutation. The small number of patients limited the multivariate analysis for OS by evaluating more parameters. All these situations were limitations of the study.

CONCLUSION

In our study, we demonstrated the real-world results of crizotinib in patients with ROS1 fusion-positive metastatic NSCLC. Furthermore, in metastatic NSCLC patients with ROS1 fusion-positive, crizotinib was shown to be an effective and safe therapy. Age and liver metastases were prognostic parameters for OS. The ROS1 mutation positivity rate was not found to be prognostic for OS. Our results need to be confirmed by other study results. ROS1 mutation is rare and multicenter studies with large numbers of patients are needed to determine parameters predicting crizotinib-related treatment response.

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Conflict of Interest: All authors declared no conflict of interest.

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