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Original Article

Comparison of Alectinib/Crizotinib Data in First-Line Therapy in Patients with Anaplastic Lymphomakinase-Positive Nonsmall Cell Lung Carcinoma with Poor Prognostic Features for Alectinib

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Abstract

OBJECTIVE: Alectinib has a much better central nervous system transmission than crizotinib in patients diagnosed with anaplastic lymphoma kinase mutation-positive nonsmall cell lung carcinoma. We aimed to investigate alectinib's efficacy in the treatment and its place in the first-line treatment and report our real-life data.

MATERIAL AND METHODS: The data of 38 patients who were diagnosed with anaplastic lymphoma kinase-positive nonsmall cell lung carcinoma in our clinic between 2016 and 2021, who did not receive any treatment before were retrospectively analyzed.

RESULTS: Of the 19 patients who received alectinib, 14 had multiple, and 6 had pretreatment brain metastases. No newly emerging brain metastases were detected during the treatment period. The progression-free survival of patients was 23.5 ± 4.2 months, and overall survival was 24.6 ± 4.1 months. Progression was observed in 10 (52.6%) patients. Of the 19 patients who received crizotinib, 7 had multiple metastases, and brain metastases were detected in 1 patient before treatment and 6 patients during the treatment period. Progression-free survival of crizotinib patients was 17.1 ± 4.8 months and their overall survival was 26.5 ± 6.1 months. Progression was observed in 17 (89.5%) patients. The second line of alectinib could be given to 8 of these patients. Overall survival after second-line treatment of alectinib was 18.2 ± 7.0 months. Overall survival of the patients who could not receive second-line treatment of alectinib was 4.0 ± 2.0 months.

CONCLUSION: The progression rate was lower in alectinib than the crizotinib patients, although there were more patients with multiple metastases and brain metastases in the alectinib arm.

KEYWORDS: Nonsmall cell lung carcinoma, anaplastic lymphomakinase mutation, alectinib, crizotinib, brain metastasis
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INTRODUCTION

The survival of patients with metastatic nonsmall cell lung carcinoma (NSCLC) is very low. However, it has been significantly prolonged with the development of targeted therapies in anaplastic lymphoma kinase (ALK) mutation-positive patients with chromosomal rearrangements in the ALK gene.[1] This condition which is observed in 3%-7% of patients with NSCLC and is related to the second chromosome, increases tumor cell proliferation and survival by increasing the tyrosine kinase activity of the ALK receptor.[2] Anaplastic lymphoma kinase positivity, first described by Soda et al[3] in 2007, is found more frequently in young patients with adenocarcinoma who have never smoked or rarely smoked.[4]

Brain metastasis is observed in approximately 20%-30% of patients with ALK-positive NSCLC at the time of diagnosis and in 50% of the patients during the course of the disease.[5] During the progression of the disease, brain metastases are most common.[6] The presence of brain metastases is also closely associated with high morbidity and mortality.[7] With the targeted therapies, the overall survival (OS) has increased in this patient group with frequent brain metastases.[8]

Crizotinib, the first ALK receptor inhibitor, has been used successfully for a long time due to its superiority over standard chemotherapy.[9] However, brain metastases were commonly seen during the treatment course due to poor central nervous system (CNS) transmission.[10] As a result of the development of drug resistance and brain metastases under treatment, usually within the first year, new searches have started for treatment of these groups of patients.[2,11,12]

Alectinib, a second-generation tyrosine kinase inhibitor (TKI), has a very good CNS transmission due to its lipophilicity. Therefore, it prevents the development of brain metastases and the progression of existing metastases, provides

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a longer progression-free survival (PFS) than crizotinib and has lower toxicity.[13] Due to the absence of a substrate for the *p*-glycoprotein that maintains the flow in the blood–brain barrier, it can penetrate the CNS effectively.[14] Despite its very strong efficacy, resistance is definitely developing against alectinib, too.[15]

The aim of our study is to evaluate the efficacy of alectinib and crizotinib on survival and brain metastasis in first-line therapy in real life.

MATERIAL AND METHODS

The data of 38 patients diagnosed with NSCLC patients with ALK-positive in our clinic between June 2016 and April 2021 were treated with ALK TKI as a first-line treatment. They did not receive any chemotherapy regimen retrospectively analyzed. Patients who were not followed up and treated in our oncology clinic were not included in the study.

Demographic characteristics of the patients, stages, metastasis status, treatments, PFS, and OS times of the patients were recorded. Patients were categorized according to crizotinib or alectinib administration in first-line therapy and whether they received second-line therapy in the event of progression. Progression-free survival and OS were calculated for patients who did not progress and survived until April 30, 2021, and all data were recorded.

The study is approved by the ethics committee of Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital at the 10th meeting dated May 26, 2021, with the first decision number. The study was conducted in accordance with the Helsinki Declaration. An informed consent form is not required due to the fact that it is a retrospective study.

Statistical Analyses

Analyses were performed with Statistical Package for Social Sciences (SPSS) software version 22 (IBM Corp.; Armonk, NY, USA). The normality of the data was evaluated with Shapiro–Wilk and Kolmogorov–Smirnov tests. After descriptive statistics, the chi-square test was used to compare categorical variables between groups. Mann–Whitney *U*-test and Student's *t*-test were used for comparing continuous variables. Results were given as median (min-max), mean ± SD, number, and percentage (%). Kaplan–Meier analysis was used to evaluate the effect of parameters on survival. Results were presented with both mean and median values, with 95% confidence intervals. *P*-value < .05 was considered statistically significant in all analyses.

MAIN POINTS

- In lymphoma kinase mutation-positive nonsmall cell lung carcinoma, alectinib is superior to crizotinib in the first-line treatment.
- Although the number of metastases is higher, alectinib provides more benefits than crizotinib.
- Alectinib is also effective in existing brain metastases.
- Alectinib reduces the risk of developing brain metastases.

RESULTS

Thirty-eight ALK-positive NSCLC patients who were treated with ALK TKI as a first-line treatment were included in the study. The mean age of the patients was 56.0 ± 11.5, 24 (63.2%) of them were male, and 8 (21.1%) of them had no history of smoking. All of the patients had adenocarcinoma type and were all in stage 4. The most common sites of metastasis were pleura in 15 patients (39.5%), bone in 11 (28.9%), and contralateral lung in 10 patients (26.3%), respectively. Brain metastases were detected in 7 (18.4%) patients at admission and 6 (15.8%) during the treatment period. Nineteen patients were each given crizotinib or alectinib as first-line therapy. For 8 patients who progressed after crizotinib therapy, alectinib had administered as second-line therapy. More detailed data of the patients are shown in Table 1.

A comparison of demographic and clinical findings between alectinib and crizotinib is shown in Table 2. There were 14 multiple metastatic patients in the alectinib therapy, while this number was 7 in the crizotinib therapy ($P = .022$). There were 6 patients with brain metastases before treatment with alectinib; no new brain metastases were observed during the treatment period. There was only 1 patient with brain metastases before treatment with crizotinib; 6 patients had developed brain metastases during the treatment period ($P = .006$).

Progression was observed in 10 (52.6%) patients in the alectinib group and in 17 (89.5%) patients in the crizotinib group ($P = .012$).

Although PFS was 23.5 ± 4.2 months, OS was 24.6 ± 4.1 months in the alectinib group, PFS was 17.1 ± 4.8 months and OS 26.5 ± 6.1 months in the crizotinib group, it was not statistically significant in terms of both PFS and OS ($P = .187$, $P = .383$, respectively) (Table 3).

As seen in Table 4, PFS was 34.9 ± 6.8 months in female patients and was 13.5 ± 3.2 months in males, and OS was 43.4 ± 7.2 months in females and 22.2 ± 5.1 months in males for all patients who received alectinib or crizotinib ($P = .021$ and $P = .035$). However, when analyzed by drug arms, female patients had longer PFS and OS in both drug arms, while PFS was significantly longer in female patients using only crizotinib ($P = .042$).

The mean OS was 18.2 ± 7.0 in 8 patients treated with alectinib treatment as second-line therapy after progression, while the mean OS of 12 patients who could not be treated with alectinib was 4.0 ± 2.0 months, which was significantly shorter ($P = .004$) (Table 5).

DISCUSSION

Many studies showed that TKIs used in ALK-positive patients with NSCLC were superior to chemotherapy, and alectinib was more effective on both PFS and OS than crizotinib.[16] In our patient group, we tried to answer whether alectinib, which we have used so far in first-line therapy, is superior to crizotinib and whether alectinib is effective against brain metastases or, more importantly, does it prevent their occurrence.

Table 1. Clinical Features of the Patients

Age, mean ± SD (minimum–maximum)	**56.0 ± 11.5 (32.0-75.0)**
Sex, n (%)	
Female	14 (36.8)
Male	24 (63.2)
Smoking status, n (%)	
Current	17 (44.7)
Ex-smoker	8 (21.1)
Never	13 (34.2)
Disease stage at baseline, n (%)	
Stage IV	38 (100)
Metastases, n (%)	
Solitary	17 (44.7)
Multiple organs	21 (55.3)
CNS metastasis, n (%)	7 (18.4)
Bone metastasis, n (%)	11 (28.9)
Liver metastasis, n (%)	7 (18.4)
Surrenal metastasis, n (%)	9 (23.7)
Contralateral lung metastasis, n (%)	10 (26.3)
Pleura metastasis, n (%)	15 (39.5)
LAP metastasis, n (%)	6 (15.8)
The other organ metastasis, n (%)	9 (23.7)
CNS metastasis, n (%)	
No	25 (65.8)
At admission	7 (18.4)
After treatment	6 (15.8)
First-line treatment, n (%)	
Alectinib	19 (50.0)
Crizotinib	19 (50.0)
Second-line treatment, n (%)	
No	30 (78.9)
Alectinib	8 (21.1)
Crizotinib	0 (0.0)
Progression, n (%)	27 (71.1)
Mortality, n (%)	22 (57.9)

CNS, central nervous system; LAP, lymphadenopathy.

Table 2. Comparison of Demographic and Clinical Features Between Drug Groups

	Alectinib (n = 19)	Crizotinib (n = 19)	*P*
Age (mean ± SD)	58.1 ± 10.4	53.9 ± 12.4	.276
Sex, n (%)			
Female	7 (36.8)	7 (36.8)	1.000
Male	12 (63.2)	12 (63.2)	
Smoking status, n (%)			
Current	6 (31.6)	11 (57.9)	
Ex-smoker	6 (31.6)	2 (10.5)	.167
Never	7 (36.8)	6 (31.6)	
Disease stage, n (%)			1.000
Stage IIIB	0 (0.0)	0 (0.0)	
Stage IV	19 (100.0)	19 (100.0)	
Metastasis, n (%)			
Solitary	5 (26.3)	12 (63.2)	.022
Multiple organ	14 (73.7)	7 (36.8)	
CNS metastasis, n (%)	6 (31.6)	1 (5.3)	.042
Bone metastasis, n (%)	7 (36.8)	4 (21.1)	.283
Liver metastasis, n (%)	5 (26.3)	2 (10.5)	.405
Surrenal metastasis, n (%)	7 (36.8)	2 (10.5)	.124
Contralateral lung metastasis, n (%)	5 (26.3)	5 (26.3)	1.000
Pleura metastasis, n (%)	8 (42.1)	7 (36.8)	.740
LAP metastasis, n (%)	3 (15.8)	3 (15.8)	1.000
Other organ metastasis, n (%)	4 (21.1)	5 (26.3)	1.000
CNS metastasis, n (%)			
No	13 (68.4)	12 (63.2)	
At admission	6 (31.6)	1 (5.3)	.006
After treatment	0 (0.0)	6 (31.6)	
Progression, n (%)	10 (52.6)	17 (89.5)	.012
Mortality, n (%)	9 (47.4)	13 (68.4)	.189

CNS, central nervous system; LAP, lymphadenopathy.

We retrospectively analyzed the data of 38 ALK-positive NSCLC patients who were diagnosed, treated, and followed up in our oncology clinic. The presence of 19 patients in both the alectinib and the crizotinib group was a good coincidence, in our opinion, in terms of ensuring homogeneous distribution. Patients in the alectinib group had a greater mean age, higher metastasis rates ($P = .022$), and more patients who had brain metastases before treatment ($P = .006$). However, progression was observed in 10 (52.6%) patients in the alectinib arm and 17 (89.5%) patients in the crizotinib arm ($P = .012$). This shows that alectinib administered to the older group, which had more brain metastases and multiple metastases, was more successful than crizotinib in disease control. Our results are consistent with Alex's study; the incidence of progression or death was 41% with alectinib and 68% with crizotinib, following the administration of alectinib and crizotinib for similar durations.[6]

There was only 1 patient who had brain metastasis before treatment, and 6 patients had developed brain metastases during the treatment in the crizotinib group, while in alectinib group there were 6 patients with brain metastases before treatment; no new brain metastases were detected during the treatment period $P = .006$). This difference shows alectinib is a lipophilic agent, and it can easily cross the CNS barrier, which prevents the formation of new metastases in the CNS. Our data showing the superiority of alectinib in brain metastasis showed similarity with Alex's study evaluating the CNS efficacy.[14]

Table 3. Comparison of PFS and OS Between Drug Groups

	PFS Mean		PFS Median		
	Estimated	**95% CI**	**Estimated**	**95% CI**	***P***
Alectinib	23.5 ± 4.2	15.4-31.7	39.3	6.4-72.2	.187
Crizotinib	17.1 ± 4.8	7.8-26.5	5.8	1.6-9.9	
	OS Mean		OS Median		
	Estimated	95% CI	Estimated	95% CI	*P*
Alectinib	24.6 ± 4.1	16.5-32.7	-	-	.383
Crizotinib	26.5 ± 6.1	14.6-38.4	9.2	0.0-24.6	

OS, overall survival; PFS, progression-free survival.

Table 4. The Effect of Gender, Smoking, and Metastasis Status on PFS and OS

	PFS Mean		PFS Median		
	Estimated	**95% CI**	**Estimated**	**95% CI**	***P***
Sex					.021
Female	34.9 ± 6.8	21.5-48.2	39.3	6.9-71.7	
Male	13.5 ± 3.2	7.3-19.7	4.1	0.0-8.5	
Smoking status					.062
Current	12.8 ± 3.6	5.7-19.9	4.9	0.7-9.1	
Ex	18.9 ± 6.5	6.2-31.6	4.1	0.0-24.9	
Never	35.7 ± 7.4	21.1-50.3	54.5	6.6-102.3	
Metastasis					.412
Solitary	24.5 ± 6.0	12.7-36.3	15.6	1.7-29.4	
Multiple	20.2 ± 5.2	10.0-30.3	10.0	0.0-21.6	
	OS Mean		OS Median		
	Estimated	95% CI	Estimated	95% CI	*P*
Sex					.035
Female	43.4 ± 7.2	29.3-57.4	-	-	
Male	22.2 ± 5.1	12.2-32.1	9.2	0.0-19.9	
Smoking status					.235
Current	22.9 ± 6.1	10.9-34.8	9.2	2.1-16.2	
Ex	20.4 ± 6.1	8.5-32.3	17.9	0.0-39.1	
Never	41.5 ± 7.7	26.5-56.5	-	-	
Metastasis					.689
Solitary	31.5 ± 6.5	18.8-44.3	22.0	0.0-44.7	
Multiple	29.6 ± 6.3	17.2-42.0	14.8	5.2-24.4	

OS, overall survival; PFS, progression-free survival.

Table 5. OS Between Second-Line Treatment Groups

	OS Mean		OS Median		
	Estimated	**95% CI**	**Estimated**	**95% CI**	***P***
Best supportive treatment (n = 12)	4.0 ± 2.0	0.3-8.0	0.2	0.0-1.1	.004
Alectinib (n = 8)	18.2 ± 7.0	4.4-32.0	4.0	0.0-8.0	
Overall	8.3 ± 3.1	2.3-14.3	1.2	0.4-1.9	

OS, overall survival.

In the alectinib group, PFS was calculated as 23.5 ± 4.2 months, and in crizotinib group, PFS was 17.1 ± 4.8 months. Although alectinib provided a greater PFS like 6 months, this time was not statistically significant. However, we still think that this period should not be underestimated and may be marked by an increase in the number of patients.

In ALEX study[1], the independent investigator evaluated PFS 34.8 versus 10.9 months HR = 0.43, and alectinib has been shown to be superior to crizotinib. The lack of statistically significant difference between the 2 groups in our study is related to the higher number of patients with baseline brain metastases and multiple metastases with poor prognostic features in the alectinib arm and the low number of patients in both arms. Also, there were 9 patients in the alectinib arm, while 2 patients in the crizotinib arm did not progress at the time of data entry. This is also related to the fact that we were able to give alectinib to the last patients despite the fact that crizotinib treatment was given to the first patients because alectinib was reimbursed too late by the government so that the crizotinib data were finalized. However, the alectinib data needed more time to be finalized. Our real-life data for alectinib will be more accurate in the coming years. Khan et al, in a meta-analysis of 12 studies involving 3297 patients showed that alectinib and other new-generation ALK inhibitors were significantly superior to crizotinib in PFS.[17]

In our study, OS was 24.6 ± 4.1 months in the alectinib group and 26.5 ± 6.1 months in the crizotinib group. When Mok et al[1] updated the OS data of ALEX study, the mean OS for alectinib was 48.2 months versus 23.3 months for crizotinib, which made alectinib significant in patients with and without CNS metastases. Moreover, 34.9% of the patients in the alectinib group and 8.6% in the crizotinib group were still on treatment. The difference between this study and ours was that patients who progressed with crizotinib were not received alectinib.[1] Although it was not statistically significant, the reasons for the poor survival in the alectinib group in our study were thought to be due to the high number of patients with poor prognostic features such as brain metastases. Also, approximately half of the patients in the crizotinib arm had received alectinib treatment after progression.

When we evaluated the PFS and OS of both alectinib and crizotinib together by gender, it was statistically significantly better in female patients (P = .021 for PFS and P = .035 for OS). However, when we examined it separately according to the drug groups, we found this positive effect in the female gender only for PFS in crizotinib patients (P = .042). The female gender created the fact that we could not find statistically significant in other groups in both PFS and OS for all the remaining cases of the inadequacy of the number of patients, which was the most critical limiting factor in our study. Similar to our research, Zou et al[18] also defined crizotinib as an influential factor for longer PFS in women (P = .003), but they could not find the same relationship with alectinib.

Of the 38 patients in our study, we found that 10 (52.6%) of them progressed while using alectinib during treatment and 17 (89.5%) while using crizotinib (P = .012). Alectinib could be given to 8 of 17 patients who progressed with crizotinib as second-line therapy. The remaining 19 patients did not receive any treatment. Overall survival of the patients was 18.2 ± 7.0 months who received alectinib after progression, while it was 4.0 ± 2.0 months in the patients who did not receive any treatment (P = .004). In other words, alectinib worked well in patients who developed crizotinib resistance. Then, we may wonder if it would be more logical to save alectinib for the second-line treatment for patients who develop resistance to crizotinib. However, we think that we should not forget the 9 patients who were not given any treatment due to performance impairment. Alex clinical research investigator Peters et al's study found that the rate of 12-month progression-free disease was 68.4% with alectinib and 48.7% with crizotinib, which supported our results.[6] In ALUR study[19], patients who progressed with crizotinib were received alectinib or chemotherapy in the second line of treatment. The alectinib group provided statistically significantly better PFS in both intracranial metastases extracranial metastases compared to the chemotherapy group.

The limitations of our study are that it is retrospective, there are imbalances between the groups in terms of basal characteristics, the number of patients is low, and until recently, only chemotherapy could be used in the progression after alectinib treatment in our country.

In conclusion, in light of all these data, we saw that in patients with ALK-positive NSCLC, alectinib was superior to crizotinib in patients with poor prognostic features in first-line treatment, with or without brain metastasis. In the future, this study will be even more meaningful as the number of patients increases, and the real data of the patients who received alectinib have emerged.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital (Approval No: 2021-15-28).

Informed Consent: An informed consent form is not required due to the fact that it is a retrospective study.

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