Original Article

Decrease in estimated glomerular filtration rates in non-small cell lung cancer patients treated with crizotinib

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ABSTRACT

Introduction: Crizotinib is a tyrosine kinase inhibitor used in patients with non-small cell lung cancer, and there are uncertainties about its effect on kidney function. In this study, it was aimed to document the possible adverse effect of the drug on kidney functions.

Materials and Methods: The estimated glomerular filtration rates (eGFRs) of the patients were calculated by creatinine-based Chronic Kidney Disease Epidemiology Collaboration and compared by months using the paired samples *t*-test. Kaplan–Meier survival method was used for progression-free survival and overall survival (OS) analysis.

Results: Twenty-six patients who received crizotinib were included in the study, and the median progression-free survival time with crizotinib was 14.2 months and the median OS time was 27.4 months. There was a significant reduction of eGFR after the 1st month of crizotinib treatment when compared to the rate before treatment initiation ($P < 0.001$). The eGFR values at the end of the 1st month and the 2nd month of treatment and the 2nd and 3rd months of treatment were statistically similar ($P = 0.086$, $P = 0.663$; respectively). This decrease in eGFR values was reversible, and there was no difference detected between pretreatment and posttreatment discontinuation ($P = 0.100$).

Conclusion: A reversible decrease in renal functions was detected in patients using crizotinib. When the literature data are examined, it is thought that the reason for this decrease may be related to the increase in renal inflammation or a pseudo decrease due to the decrease in creatinine excretion. When evaluating renal functions in these patients, using noncreatine-based (iothalamate, etc.) calculations can give more accurate results.

KEY WORDS: Crizotinib, glomerular filtration rate, lung cancer

INTRODUCTION

Anaplastic lymphoma kinase (ALK) rearrangement is a series of chromosomal changes involving the *ALK* gene. It is observed in approximately 5% of lung adenocarcinomas and detected in the form of EML4-*ALK* fusion rearrangement, which is the most common chromosomal insertion.[1] As a result of ALK gene anomalies, it causes the expression of oncogenic fusion proteins and plays a role in lung cancer pathogenesis. Similar to ALK, ROS1 rearrangement occurs in approximately 1%–2% of non-small cell lung cancer (NSCLC) patients and results in the expression of ROS1 fusion kinases that support cellular transformation through activation of ROS1.[2]

Significant changes have occurred in the treatment of lung cancer in the last 10 years with the advancement of genetics. One of the most important of these changes is the detection of driver mutations and the development of targeted therapies for these mutations. Crizotinib, one of these therapies, is a tyrosine kinase inhibitor that inhibits ALK, hepatocyte growth factor receptor hepatocyte growth factor receptor (HGFR),

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receptor tyrosine kinase (ROS1), and Recepteur d'Origine Nantais. Crizotinib is an oral tyrosine kinase inhibitor approved by the Food and Drug Administration (FDA) (U. S. FDA) in patients with NSCLC with ALK or ROS1 rearrangement. The most common side effects reported in the efficacy and safety study of crizotinib are visual disturbances, diarrhea, edema, nausea, vomiting, and constipation.[3]

There are different studies in the literature investigating the renal side effects of targeted therapies. Vascular endothelial growth factor inhibitors (bevacizumab, etc.) trigger renal failure by causing damage and hypertrophy in glomerular endothelial cells due to decreased nephrin in renal cells.[4] Gefitinib, one of the estimated glomerular filtration rate (eGFR) inhibitors used in lung cancer, can cause nephrotic syndrome by increasing allergic and immune reactions.[5] Other eGFR inhibitors have been shown to cause renal insufficiency by causing renal inflammation and disease and by other different mechanisms.[6] There are limited studies in the literature investigating the renal effects of crizotinib use.

In this study, we aimed to investigate the renal side effects that develop in NSCLC patients using crizotinib and the clinical significance of these side effects.

MATERIALS AND METHODS

Patient selection

This study was planned as a multicenter study investigating drug side effects. Twenty-six NSCLC patients with ALK and ROS1 rearrangements in six oncology departments in Turkey and receiving crizotinib treatment were included in the study between 2 January 2016 and 30 December 2020. All data were collected retrospectively. Inclusion criteria were those who were over 18 years, had ALK or ROS1 rearrangement, had used crizotinib for at least 3 months, and had sufficient follow-up data.

The local institutional review board approved the project. Moreover, this study conformed to the provisions of the 1995 Declaration of Helsinki. All patients provided informed consent, and the Local Ethics Committee gave formal approval to this multicenter retrospective study (approval no: 2020.213.08.22 on April 27, 2021).

Methods used in estimated glomerular filtration rate calculation

eGFR was calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatine-based formula.[7] eGFR was calculated separately for each patient by CKD-EPI using creatinine measurements before treatment, at 1 month, 2 months, and 3 months, and after treatment discontinuation. CKD was defined as irreversible eGFR below 60 mL/min/1.73 m^2 for 3 months or more regardless of the cause.[8] CKD staging was divided into six as G1, G2, G3a, G3b, G4, and G5 according to KDIGO (Kidney Disease: Improving Global Outcomes).[9]

For all patients, all medicines and conditions, including nonsteroidal anti-inflammatory drug, angiotensin-converting-enzyme inhibitor, and angiotensin receptor blocker (ARB) that can affect eGFR, contrast-enhanced computed tomography, prior use of cisplatin, and medicines that may be nephrotoxic were noted and evaluated for use in the analysis. According to the Common Terminology Criteria for Adverse Events, patients with vomiting–diarrhea side effects with Grade 1 and above were not included in the analysis because it directly affects the creatine results.

Progression-free survival was calculated from the starting date of crizotinib treatment as the date when progression was detected according to response evaluation criteria in solid tumors, and the date of last visit in patients without progression. For the overall survival (OS) time, the period from the date of diagnosis of the disease to the date that the data were obtained from the e-Pulse (online health system provided by the Turkish Ministry of Health and providing instant survival information) was used.

Statistical procedures

Statistical analysis was performed using SPSS Statistic software version 24 (SPSS Inc., Chicago, III, USA). The variables were investigated using Kolmogorov–Smirnov test to determine whether or not they are normally distributed. Paired samples *t*-test was used to compare pretreatment eGFRs and posttreatment eGFRs of the patients. Kaplan–Meier analysis was used to show progression-free survival and OS. The significance level was accepted as $P < 0.05$.

RESULTS

In this study, the data of 26 (female = 10, male = 16) NSCLC patients treated with crizotinib between 2016 and 2020 in six oncology centers were analyzed. The median age of the patients was 53 (minimum: 40, maximum: 74), the mean age was 55.2 ± 10.1. Brain metastasis was present in 38.5% of the patients at the time of diagnosis, 23.1% of them had adrenal metastasis, and 46.2% of them had bone metastasis.

About 42.3% of the patients had used cisplatin before crizotinib. Along with the treatment, four patients (15.4%) were using metformin or ARB regularly. During the 3-month follow-up, there was no patient using contrast nephrotoxic drugs. Grade 1 most common side effects were fatigue (11.5%) and anemia (11.5%), while Grade 2 most common side effects were aspartate aminotransferase–alanine aminotransferase (ALT elevation, 7.7%) and fatigue (7.7%) [Table 1].

The median progression-free survival with crizotinib was 14.2 months (95% confidence interval [CI] 1.5–26.8 months) and the median OS time was 27.4 months (95% CI: 10.7–44.1 months) with crizotinib as assessed by the Kaplan–Meier survival analysis of the patients [Figures 1 and 2].

Table 1: Basic characteristics of patients taking crizotinib

Characteristics	*n* (%)
Gender	
Female	10 (38.5)
Male	16 (61.5)
Age	
Median (minimum-maximum)	53 (40-74)
Nephrotoxic drug use N	
No	22 (84.6)
Yes	4 (15.4)
Contrast-enhanced CT during treatment	
No	0
Yes	26 (100)
Cisplatin usage history	
No	15 (57.7)
Yes	11 (42.3)
Brain metastasis	
No	16 (61.5)
Yes	10 (38.5)
Surrenal metastasis	
No	20 (76.9)
Yes	6 (23.1)
Bone metastasis	
No	14 (53.8)
Yes	12 (46.2)
Best response after crizotinib	
CR	6 (23.1)
PR	10 (38.5)
SD	4 (15.4)
PD	6 (23.1)
Did progression happen	
No	12 (46.2)
Yes	14 (53.8)
CKD when treatment is started	
No	24 (92.3)
Yes	2 (7.7)
CKD when treatment is discontinued	
No	22 (84.6)
Yes	4 (15.4)
Grade 1 side effects	
Fatigue	3 (11.5)
Anemia	3 (11.5)
Edema	2 (7.7)
Other	5 (19.2)
Grade 2 side effects	
AST-ALT elevation	2 (7.7)
Fatigue	2 (7.7)
Other	4 (15.4)
Last status	
Survived	13 (50.0)
Exitus	13 (50.0)

*CRD=Chronic renal disease. CR=Complete response, PR=Partial response, SD=Stable, PD=Progressive, CT=Computed tomography, CKD=Chronic kidney disease, ALT=Alanine aminotransferase, AST=Aspartate aminotransferase

Assessment of nephrotoxic side effects

When the patients were compared with pretreatment state, there was a decrease in eGFR in the 1st month of crizotinib treatment ($P < 0.001$). In the 2nd month after treatment compared to the 1st month, although there was a decrease in eGFR, it was not statistically significant ($P = 0.086$). In the 3rd month, eGFR was similar compared to the previous month ($P = 0.663$) [Table 2].

When eGFR changes during treatment were evaluated, 80.8% of patients had a decrease in eGFR from baseline values in the

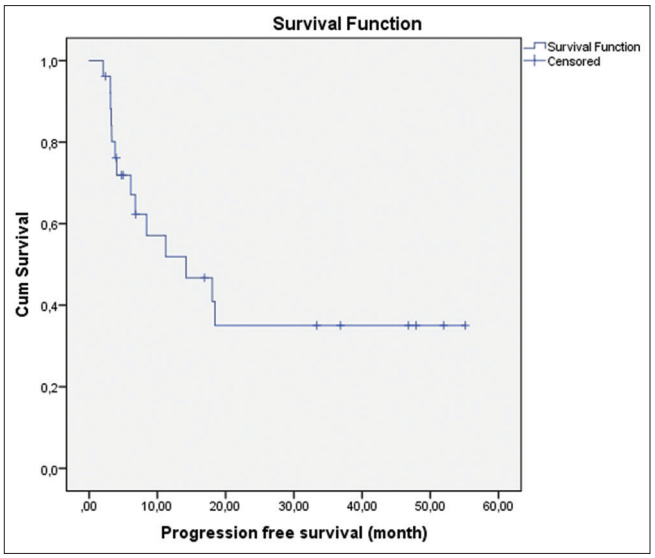

Figure 1: Progression-free survival with crizotinib treatment

1st month of treatment, 61.5% had a decrease in eGFR in the 2nd month compared to the 1st month, while 73.1% of patients had either unchanged or elevated eGFR in the 3rd month compared to the previous month [Figure 3].

When the first eGFR values measured after the discontinuation of crizotinib were compared with the baseline eGFR values before starting the crizotinib treatment, the results were statistically similar ($P = 0.100$). After the crizotinib treatment of the patients was discontinued due to progression, 6.714 ml/min/1.73 m^2 increase compared to the 1st month of the treatment ($P = 0.013$), 7.929 ml/min/1.73 m^2 increase compared to the 2nd month of the treatment ($P = 0.015$), and 7.714 ml/min/1.73 m^2 increase compared to the 3rd month of the treatment ($P = 0.018$) were detected in eGFR values. Patients who discontinued crizotinib due to disease progression had 7 ml/min/1.73 m^2 mean increase in eGFR values ($P = 0.023$) [Table 3].

PATIENT-BASED RESULTS

When treatment was initiated, two patients had Stage 3a CKD. During the treatment period, a Stage 3 CKD developed in one patient, and as a result, eGFR was between 45 and 60 ml/min/1.73 m^2 for 3 months in a total of four patients. Due to the increase in creatine and ALT in patient number three, the daily dose was decreased from 500 mg to 250 mg, and when creatine recovered, it was returned to the old dose. Clinically important creatine and ALT elevations did not recur in this patient. There was no patient whose treatment was discontinued due to high creatine levels.

DISCUSSION

In this study, the data of patients with NSCLC who received crizotinib treatment were analyzed. There was a statistically

significant decrease in the eGFR of the patients before the start of treatment compared to the 1st month of treatment ($P < 0.001$). When the 1st and 2nd months of treatment were compared ($P = 0.086$) and the 2nd month and the 3rd month ($P = 0.663$) were compared, there was no statistical difference. Patients who discontinued crizotinib due to disease progression had 7 ml/min/1.73 m^2 mean increase in eGFR ($P = 0.023$). However, the eGFRs calculated prior to treatment and after discontinuation of treatment were similar ($P = 0.100$). With this study, we have shown that in patients who received crizotinib, a decrease in eGFR occurs in the 1st month of treatment and this decrease is reversible in the further course of treatment.

The primary clearance of crizotinib is by liver elimination/oxidative metabolism and its renal excretion is minimal at

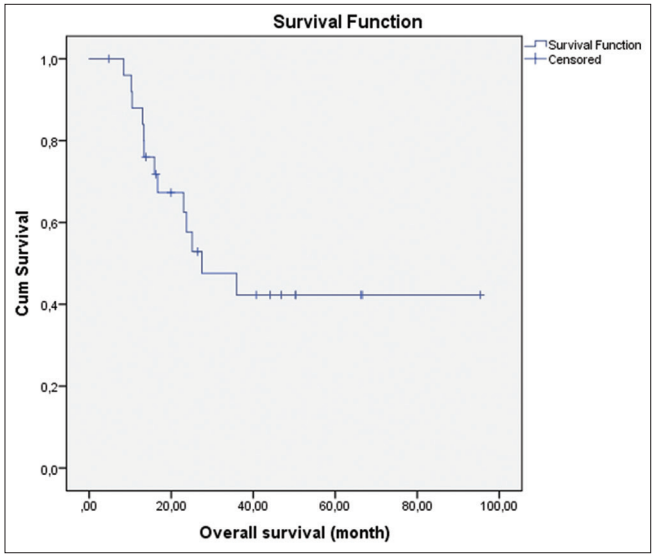

Figure 2: Overall survival with crizotinib treatment

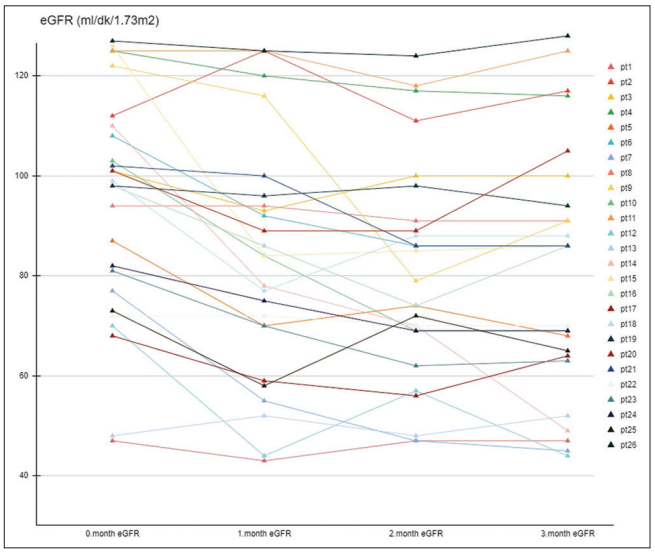

Figure 3: Change in creatinine-derived estimated glomerular filtration rate (eGFR) from baseline during first 3 months of crizotinib therapy (pt: patient)

Table 2: Paired samples *t*-test comparison of estimated glomerular filtration rates changes with respect to crizotinib start time

	Paired differences					*t*	*P**
	Mean	SD	SE	95% CI of the difference			
				Lower	Upper		
Pair 1							
eGFR 0th month-eGFR 1st month	10.538	11.921	2.338	5.724	15.353	4.508	**<0.001**
Pair 2							
eGFR 1st month-eGFR 2nd month	3.654	10.423	2.044	−0.556	7.864	1.788	0.086
Pair 3							
eGFR 2nd month-eGFR 3rd month	−0.654	7.568	1.484	−3.711	2.403	−0.441	0.663

*Statistically significant *P* values are marked in bold. SD=Standard deviation, SE=Standard error, CI=Confidence interval, eGFR=Estimated glomerular filtration rates

Table 3: Comparison of estimated glomerular filtration rates after crizotinib discontinuation and at starting months of treatment by paired samples *t*-test

	Paired differences					*t*	*P**
	Mean	SD	SE	95% CI of the difference			
				Lower	Upper		
Pair 1							
eGFR 0th month-eGFR after treatment is discontinued	5.500	11.607	3.102	−1.202	12.202	1.773	0.100
Pair 2							
eGFR 1st month-eGFR after treatment is discontinued	−6.714	8.766	2.343	−11.775	−1.653	−2.866	**0.013**
Pair 3							
eGFR 2nd month-eGFR after treatment is discontinued	−7.929	10.594	2.831	−14.045	−1.812	−2.800	**0.015**
Pair 4							
eGFR 3rd month-eGFR after treatment is discontinued	−7.714	10.615	2.837	−13.843	−1.585	−2.719	**0.018**
Pair 5							
eGFR before treatment is discontinued-eGFR after treatment is discontinued	−7.071	10.307	2.755	−13.022	−1.121	−2.567	**0.023**

SD=Standard deviation, SE=Standard error, eGFR=Estimated glomerular filtration rates, CI=Confidence interval, *Statistically significant *P* values are marked in bold

2.3%.[10] Although there is no renal excretion of crizotinib, there are studies showing that it may have an effect on renal functions. In the study by Brosnan *et al*., a decrease of upto 23.9% in eGFR was found in ALK-positive NSCLC patients who received crizotinib, and this decrease was significant in the 1st week of treatment initiation.[11] Camidge *et al*. have obtained similar results in their study. There was a decrease in the eGFR of the patients who started the crizotinib treatment and it started to become evident in the 2nd week.[12] Both studies showed improvement in eGFR after the cessation of treatment, and they concluded that the reduction in eGFR was reversible, not cumulative. In our study, there was a significant decrease in the eGFR of the patients in the 1st month of the treatment initiation. However, in the following process, we observed that this decrease in eGFR did not continue. One of the striking results in our analysis was that patients experienced an increase in their eGFRs in the period after treatment was discontinued due to progression. Thus, the patients' eGFRs returned to their pretreatment levels. In only one patient, the treatment dose was reduced due to renal toxicity, and when the target dose was returned, toxicity was not encountered again.

The effects by which crizotinib causes a decrease in eGFR and acute kidney injury and CKD in patients are unknown. In renal biopsy of a patient who developed crizotinib-associated renal failure by Gastaud *et al*., interstitial mononuclear cell infiltration and scattered interstitial eosinophils were detected with acute tubular necrosis.[13] In the case reported by Izzedine *et al*., they identified two types of lesions, including "acute tubular injury without interstitial cell infiltration" and "renal arteriolar myocyte vacuolization."[14] Animal models generated in the laboratory support the hypothesis that it triggers inflammation in the kidney.[15] Furthermore, in studies conducted in animal models, an increase of interleukin-6 and (HGF-6) in plasma and tumor necrosis factor-alpha in kidney tissue was detected together with crizotinib.[16] These results lead to the conclusion that crizotinib causes a temporary decrease in eGFR by activating inflammatory pathways and increasing renal inflammation rather than its direct nephrotoxic effect on the kidney.

The two cases reported by Camidge *et al*. took the discussion in a different direction. They demonstrated that crizotinib displayed a false decrease of eGFR by only reducing creatinine secretion from the kidney without impairing renal function. For this reason, creatinine-based eGFR calculations were causing incorrect results. While creatinine elevation due to crizotinib made the diagnosis of renal failure in calculations such as CKD-EPI, iothalamate reflected renal functions better in these patients.[17] In patients who are considered to be discontinued from crizotinib, noncreatine-based renal function tests such as iothalamate should be preferred in making a treatment decision.

There are some limitations regarding this study. The retrospective design of the study, calculation of eGFR based on serum creatinine, and the small number of patients are important limitations regarding the study. Although new generation ALK inhibitors have replaced crizotinib in many countries, crizotinib is still the first-line treatment for ROS1-positive NSCLC patients, as well as a treatment that may be effective in MET-14 mutations and after the development of secondary resistance to new generation ALK inhibitors.[18-22]

CONCLUSION

In this study, we were able to show that there is a transient decrease in eGFR in NSCLC patients receiving crizotinib; however, this decrease is generally reversible and that the drug should not be stopped immediately when there is an increase in serum creatinine values. Stabilization of renal functions is expected in most of the patients during the treatment.

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Conflicts of interest
There are no conflicts of interest.

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