Crizotinib Extends Survival in ALK-Positive Advanced NSCLC: Single Center Experience

Crizotinib ALK-Pozitif İleri Evre KHDAK'lerinde Sağkalıma Etkisi: Tek Merkez Deneyimi

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ÖZET

GİRİŞ ve AMAÇ: Küçük hücre dışı akciğer kanseri (KHDAK) hastalarında, konvansiyonel, birinci basamak sitotoksik kemoterapi (platin çiftler veya platin olmayan çiftler) 7-8 ay ortanca sağkalım platosuna ulaşmıştır. Crizotinib tedavisi, PROFILE 1014 ve PROFILE 1007 çalışmalarında standart birinci ve ikinci sıra kemoterapilere kıyasla daha yüksek yanıt oranları ve progresyonsuz sağkalım elde etmiş ve dünya çapında ALK-pozitif ileri KHDAK tedavisi için kabul görmüştür.

YÖNTEM ve GEREÇLER: Bu çalışmada, crizotinib tedavisi alan, klinik olarak ileri evre ALK-pozitif olan 11 hasta (6 erkek ve 5 kadın; ortalama yaş: 50,29 ± 12,72 yıl; yaş aralığı 30-66 yıl) retrospektif olarak değerlendirildi.

BULGULAR: Çalışmaya toplam 11 hasta alındı. Ortalama yaş 50,29 ± 12,72 (dağılım: 30-66 yıl) idi. Hastaların tamamı tanı anında Evre 4'te idi. Tüm hastalar daha önce platin rejimleri almıştı. Crizotinib tedavisi altında toplam 3 hastada, beyin metastazı, sürrenal metastaz ve primer kitle progresyonu olmak üzere progresyonu gözlendi. Crizotinib tedavisinin 6. ayında surrenal metastaz ile progresyonu olan bir hasta öldü. Progresyonsuz sağkalım 25,46 ± 6,56 ay (%95 CI: 12,59-38,33 ay) idi ve genel sağ kalım 104,17 ± 13,72 aydı (%95 CI: 77,23-131,04 ay).

TARTIŞMA ve SONUÇ: Hastalarımızın Crizotinib tedavisini iyi tolere ettiği ve ALK-pozitif ileri evre KHDAK olan hastalarda ümit verici etkinlik gösterdiği gözlendi.

Anahtar Kelimeler: Crizotinib, Sağkalım, tolerans

ABSTRACT

INTRODUCTION: Conventional, first-line cytotoxic chemotherapy (platinum doublets or nonplatinum doublets) has reached a plateau of a median survival of 7- 8 months in NSCLC patients. Crizotinib treatment achieve higher response rates and progression free survival compared to standard first-line and second-line chemotherapy in PROFILE 1014 and PROFILE 1007 studies and now accepted worldwide for treating ALK-positive advanced NSCLC.

METHODS: A total of 11 patients (6 males and 5 females; mean age: 50.29 ± 12.72 years; age range 30–66 years) with ALK-positive clinically advanced NSCLC who received crizotinib treatment were retrospectively evaluated in the study.

RESULTS: A total of 11 patients were enrolled in the study. Characteristics of patients are given in Table 1. Mean age was 50.29 ± 12.72 (range: 30–66 years). All patients were at stage 4 at the time of diagnosis and had previously received platin doublet regimens. A total of 3 patients had disease progression under crizotinib treatment, including brain metastasis, surrenal metastasis and primary mass progression. One patient who progressed with surrenal metastasis was died at the 6th month of crizotinib treatment. Progression free survival was 25.46±6.56 months (95% CI: 12.59-38.33 months) and overall survival was 104.17 ± 13.72 months (95% CI: 77.23-131.04 months).

DISCUSSION AND CONCLUSION: Crizotinib was well tolerated and showed promising efficacy in patients with ALK-positive, advanced NSCLC.

Keywords: Crizotinib, survival, tolerance

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INTRODUCTION

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related death worldwide[1]. NSCLCaccounts for the majority (approximately 85 percent) of lung cancers with the remainder as mostly small cell lung cancer. Despite new chemotherapeutic, immunomodulating and molecularly targeted agents, patients with locally advanced or metastatic disease still have a poor prognosis, with the median survival in this population less than a year. Only 16% of patients diagnosed with lung cancer are expected to live 5 years[2].

NSCLC is divided into the following three major histological subtypes from most to less frequent: adenocarcinoma, squamous cell carcinoma and large cell carcinoma. Conventional, first-line cytotoxic chemotherapy (platinum doublets or nonplatinum doublets) has reached a plateau of a median survival of 7- 8months.

The treatment of advanced NSCLC has undergone a paradigm shift since the early 2000s.The identification of molecular subtypes of the disease, based on oncogenic drivers, has led to the development of personalized medicine and the ability to deliver molecularly targeted therapies to patients.

In 2007, Soda et al.[3] first identified the EML4–ALK (echinoderm microtubule–associated protein 4) fusion oncogene in a patient with NSCLC[3]. A group of patients with NSCLC have tumors that contain an inversion in chromosome 2 that juxtaposes the 5' end of the echinoderm microtubule-associated protein-like 4 (EML4) gene with the 3' end of the anaplastic lymphoma kinase (ALK) gene, resulting in the novel fusion oncogene EML4-ALK [4]. Rearrangements of the anaplastic lymphoma kinase (ALK) gene are present in 3 to 5% of NSCLC [3, 5]. They define a distinct subgroup of NSCLC that typically occurs in younger patients who have never smoked or have a history of light smoking and that has adenocarcinoma histologic characteristics.

Crizotinib is an oral selective inhibitor of ALK and mesenchymal epithelial growth factor (c-Met)/hepatocyte growth factor receptor (HGFR) kinases[6]. In a randomized phase 3 trial involving patients with advanced ALK-positive NSCLC who had received previous platinum-based chemotherapy, crizotinib showed efficacy superior to that of single-agent second-line chemotherapy with either pemetrexed or docetaxel.

In this study, the efficacy and safety of crizotinib in treatment of patients with advanced ALK positive NSCLC was investigated.

MATERIALS and METHODS

A total of 11 patients (6 males and 5 females; mean age: 50.29 ± 12.72 years; age range 30–66 years) with ALK-positive NSCLC who received crizotinibat Department of Oncology, UludağUniversity Medical School, were retrospectively enrolled in the study. We reviewed each medical record and collected demographic and clinicopathologic characteristics including age, sex, degree of differentiation, distant metastasis and prior chemotherapy history.

Lesion staging was performed according to the eight edition of the American Joint Committee on Cancer (AJCC) staging manual for lung cancer.All patients were histologically diagnosed and staged as clinically advanced (stage IV) NSCLC.

Fluorescence in situ hybridization (FISH) were used for ALK detection. All the patients had adenocarcinoma that was negative for EGFR mutations.

Crizotinib treatment, response and Toxicity Assessment

All patients received oral crizotinib 250 mg twice daily in 28-day cycles.Toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria. Tumor response was graded according to the World Health Organization (WHO) criteria.

Statistical Method

Patients, who received at least two months of therapy, were considered assessable for response. Patients who received at one dose of therapy were assessable for toxicity. Time to progression was considered from the beginning of therapy to the date of disease progression. Overall survival was measured from the date of the first course of therapy to the date of death or last follow-up examination. Survival

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curves were plotted according to the Kaplan Meier method.

RESULTS

A total of 11 patients were enrolled in the study. Characteristics of patients are given in Table 1. Mean age was 50.29 ± 12.72 (range: 30–66 years).All patients were at stage 4 at the time of diagnosis. Cough, hemoptysis and shortness of breath are the main presenting symptoms and Eastern Cooperative Oncology Group (ECOG) Performance Score was 0 in six patients. Most of the patients had visceral metastases including brain, liver and lung involvement and 3 patients had multiple distant metastasis at the time of diagnosis.Radiological evaluation reveals upper lobe predilection (72.82%, Table 1).

Table 1: Characteristics of the Patients

Age of Dx	**50.29 ± 12.72 years**
Sex	
Male	6 (54.54%)
Female	5 (45.45%)
Stage at Dx	
Stage 4	11 (100%)
Symptoms	**Number of patients; n (%)**
Cough	2 (18.18%)
Hemoptysis	1 (9.09%)
SOB	1 (9.09%)
Weight loss	0 (0%)
Pain	0 (0%)
ECOG Score	**Number of patients; n (%)**
0	6 (54.54%)
1	5 (45.45%)
2	0 (0%)
3	0 (0%)
4	0 (0%)
Metastasis site at Dx	**Number of patients; n (%)**
Distant Lymphadenopathy	4 (36.36%)
Bone	3 (27.27%)
Brain	2 (18.18%)
Liver	1 (9.09%)
Lungs	1 (9.09%)
Adrenal	1 (9.09%)
Stomach	1 (9.09%)
Pleura	1 (9.09%)
Radiological evaluation of the tumors	
Tumor Diameter	**3.70 ± 0.95 cm**
Location	**Number of patients; n (%)**
Right upper lobe	5 (45.45%)
Left upper lobe	3 (27.27%)
Left lower lobe	2 (18.18%)
Right middle lobe	1 (9.09%)
Other specifications	**Number of patients; n (%)**
With Cavity	2 (18.18%)
With Effusion	2 (18.18%)

Dx= Diagnosis, SOB= Shortness of breath

All patients had previously received platin doublet regimens (Table 2) and had improvement in quality of life due to relief of lung cancer-related symptoms. These symptoms include dyspnea, cough, anorexia and fatigue. Most patients improved during the first cycle of treatment.While, 6 of 11 (54.5%) patients achieved a partial remission (PR) after the first cycle of treatment, no complete remissions (CR) were documented. A 54-year-old manmaintained a PR for 3 years and is still on treatment.

Table 2: Chemotherapy protocols received by the patients

Patient	**1. Line**	**2. Line**	**3. Line**	**4. Line**
1	Carbo+Pacl	Platin+Pemtxd	Docetaxel	***Crizotinib***
2	Platin+Pemtxd	***Crizotinib***		
3	Carbo+Pacl	Docetax+Gemsi	***Crizotinib***	
4	Carbo+Pacl	***Crizotinib***		
5	Carbo+Pacl	Pemetrexed	Docetaxel	***Crizotinib***
6	Carbo+Pacl	***Crizotinib***		
7	Platin+Pemtxd	***Crizotinib***		
8	Carbo+Pacl	Platin+Pemtxd	***Crizotinib***	
9	Pemetrexed	Capbo+Pacl	***Crizotinib***	
10	Carbo+Pacl	***Crizotinib***		
11	Platin+Pemtxd	Docetax+Gemsi	***Crizotinib***	

Carbo= Carboplatin, Pacl= Paclitaxel, Pemtxd= Pemetrexed, Gemsi=Gemcitabine,

Crizotinib treatment was well tolerated (Table 3). The most common adverse effects (AE) observed with crizotinib were fatigue, nausea, muscle cramps and vomiting.Elevated creatine (27.27%), peripheral edema (18.18%) and elevated liver transaminase levels (9.09%) observed during the crizotinib treatment. The most common Grade 3/4 AEs associated with crizotinib included elevated creatine (27.27%) and transaminase levels (9.09%). Two patients paused Crizotinib treatment until laboratory resultsreturn to normal levels.

A total of 3 patients had disease progression under crizotinib treatment, including a case with brain metastasis, a patient with surrenal metastasis and a patient with primary massprogression. One patient who progressed with surrenal metastasis was died at the 6th month of crizotinib treatment. Progression free survival was 25.46±6.56 months (95% CI: 12.59-38.33 months, figure

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1a) and overall survival was 104.17 ± 13.72 months (95% CI: 77.23-131.04 months, figure 1b).

Table 3: Signs and symptoms that seen during Crizotinib treatment

Symptoms	**Number of Patients; n (%)**
Nausea	3 (27.27%)
Vomiting	1 (9.09%)
Muscle Cramps	2 (18.18%)
Fatigue	3 (27.27%)
PE and Laboratory results	**Number of Patients; n (%)**
Transaminase elevation	1 (9.09%)
Creatinine elevation	3 (27.27%)
Hyperlipidemia	1 (9.09%)
Venous thrombosis	1 (9.09%)
New pleural effusion	1 (9.09%)
Peripheral edema	2 (18.18%)

PE= Physical examination

DISCUSSION

Crizotinib treatment achieve higher response rates and PFScompared to standard first-line and second-line chemotherapy in PROFILE 1014 and PROFILE 1007 studies[7, 8] and now accepted worldwide for treating *ALK*-positive advanced NSCLC[9].

The findings of this study suggest that crizotinib is well tolerated and has promising efficacy in ALK-positive, advanced NSCLCin our patients, with an objective response rate (ORR) of more than 50%.In the PROFILE 1007 study of previously treated patients with ALK-positive, advanced-stage NSCLC, crizotinib more than doubled the median PFS compared with standard chemotherapy[7]. In our study, all patients had received 2nd–3rdlines of chemotherapy, and 8 of them derived clinical benefit (PR or SD) from crizotinib treatment.The median PFS in our study population was over 2 years. Duruisseaux et al found median PFS as 6.8 months (95% CI: 5.6-8.3) in the evaluation of the 267 patients. Their ORR was similar (50.2% (95% CI: 44.2-56.2)) as in our results [9].Thepossible reason for higher PFS may be including the fact that our study was a single-center study with a relatively small sample size.

Crizotinib seemed to be well tolerated in our study, the adverse events observed in patients treated with crizotinib in this retrospective study were generally consistent with the drug's known adverse event (AE) profile. However, most adverse events were mild and transient. The most common Grade 3/4 AEs associated with crizotinib included elevated transaminases and elevated creatine.
In a study, conducted by Xing et al.[10] a total of 428 ALK-positive NSCLC patients were evaluated. The PFS was observed as 14.4 months for all participants and 15.5months for the first-line crizotinib therapy. OS was calculated as 53.4 months from the initiation of crizotinib treatment. Our study shows a single center, limited number of patients taking Crizotinib at any line except first-line.Our PFS (25.46±6.56 months) and OS (104.17 ± 13.72 months) was observed longer than the literature.Our small sample size may be considered as a limitation. Statistical analysis would be more reliable with larger sample size. In conclusion, crizotinib was well tolerated and showed promising efficacy in patients with ALK-positive, advanced NSCLC.

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