original article

Non-small-cell lung cancer (NSCLC) harboring driver mutation (EGFR mutation or ALK translocations) with clinical characteristics and management in a real-life setting: a retrospective observational multicenter case series study

EGFR mutasyonu veya ALK translokasyonu olan küçük hücreli dışı akciğer kanseri (KHDAK) tanılı hastaların klinik özelliklerinin ve yönetiminin incelenmesi: retrospektif gözlemsel çok merkezli vaka serisi çalışması

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Abstract

Aim: Lung cancer is a leading cause of cancer-related mortality. The most common type of lung cancer is Non-small-cell lung cancer (NSCLC). Molecular targeting drugs are used in the treatment of patients with metastatic NSCLC who have a driver mutation. In this study, we aimed to investigate the relationship between the selected treatment modality in the first line setting, patients characteristics and outcomes on NSCLC patients who had driver mutations.

Material and Method: We designed this retrospective study to analyze the effect of the treatment line of tyrosine kinase inhibitors on survival parameters and disease prognosis in NSCLC patients. We enrolled 62 patients with NSCLC who had driver mutations from three cancer centers; Şanlıurfa Research and Training Hospital, Başkent University, and Acıbadem Mehmet Ali Aydınlar University medical oncology departments.

Results: Median age was 62 years old (range 30-81). There were 45 (71.4%) and 18 (28.6%) patients with EGFR mutation and EML4-ALK fusion gene rearrangement, respectively. Out of 45 EGFR mutant patients, 22 (34.9%) patients had exon 19 deletion and other 16 (25.4%) patients had exon 21 mutation. Median overall survival (OS) and progression free survival (PFS) was 31 and 9 (95% CI, 5.4-12.6) months, respectively. Univariate statistical analysis failed to show significant difference between EGFR mutation positive and FISH-ALK positive patients regarding OS and PFS (p:0.33). Among patients with EGFR mutation, survival times for patients with exon 19 deletions were statistically significantly higher than those with exon 21 mutations (p:0.02). The overall survival time of oligometastatic patients was statistically significantly higher than the other patients (p:0.001). The PFS of patients who received tyrosine kinase inhibitor in first-line treatment was statistically significantly higher than patients using chemotherapy in first line setting. (14 months vs 5 months) (p:0.01)

Conclusion: This study showed that treatment preference in favor of tyrosine kinase inhibitors in first line setting produce fairly good outcomes in metastatic NSCLC patients who had driver mutations.

Keywords: Driver mutation, TKI, NSCLC

Öz

Amaç: Akciğer kanseri, kansere bağlı ölümlerin önde gelen nedenlerinden biridir. Akciğer kanserinin en yaygın tipi Küçük hücreli dışı akciğer kanseri (KHDAK) 'dir. Moleküler hedefli ilaçlar, sürücü mutasyon içeren metastatik KHDAK'lı hastaların tedavisinde kullanılır. Bu çalışmada, sürücü mutasyonu bulunan KHDAK hastalarında birinci basamakta seçilen tedavi şekli, hasta özellikleri ve sonuçları arasındaki ilişkiyi araştırmayı amaçladık.

Gereç ve Yöntem: Bu retrospektif çalışmayı, KHDAK hastalarında tirozin kinaz inhibitörlerinin kullanıldığı tedavi basamağının sağkalım parametreleri ve hastalık prognozu üzerine etkisini analiz etmek için tasarladık. Üç kanser merkezinden (Şanlıurfa Araştırma ve Eğitim Hastanesi, Başkent Üniversitesi ve Acıbadem Mehmet Ali Aydınlar Üniversitesi medikal onkoloji) sürücü mutasyonları bulunan 62 KHDAK hastasını kayıt ettik

Sonuçlar: Ortanca yaş 62 idi (aralık 30-81). EGFR mutasyonu ve EML4-ALK füzyon geni bulunan sırasıyla 45 (% 71.4) ve 18 (% 28.6) hasta vardı. EGFR mutant 45 hastanın 22'sinde (% 34.9) ekson 19 delesyon vardı ve diğer 16 hastada (% 25.4) ekson 21 mutasyonu vardı. Ortanca genel sağkalım (OS) ve progresyonsuz sağkalım (PFS) sırasıyla 31 ve 9 (% 95 CL, 5.4-12.6) ay idi. Tek değişkenli istatistiksel analiz, EGFR mutasyonu pozitif ve FISH-ALK pozitif hastalar arasında OS ve PFS açısından anlamlı farklılık göstermedi (p: 0.33). EGFR mutasyonu bulunan hastalar arasında, ekson 19 delesyonu olan hastalarda sağkalım süresi, ekson 21 mutasyonları olanlara göre istatistiksel olarak anlamlı derecede yüksekti (p: 0.02). Oligometastatik hastaların genel sağkalım süresi diğer hastalardan istatistiksel olarak anlamlı derecede yüksekti (p: 0.001). Birinci basamak tedavide tirozin kinaz inhibitörü alan hastaların PFS'si birinci basamakta kemoterapiyi kullanan hastalardan istatistiksel olarak anlamlı derecede yüksekti. (14 ay vs 5 ay) (p: 0.01).

Tartışma: Bu çalışma, birinci basamak tedavide tirozin kinaz inhibitörleri lehine tedavi tercihinin, sürücü mutasyonları olan metastatik KHDAK hastalarında oldukça iyi sonuçlar verdiğini göstermiştir

Anahtar Kelimeler: Sürücü mutasyon, TKI, KHDAK

Introduction

Non-small-cell lung cancer (NSCLC) remains the most common type of lung cancer (85% to 90% of lung cancer) and the leading cause of cancer-related deaths worldwide [1,2]. Clinically, most NSCLC patients are initially diagnosed with advanced stages. The treatment options for patients with non-small cell lung cancer (NSCLC) depend on the stage of disease, disease histology, epidermal growth factor receptor (EGFR) mutation status, performance status, comorbidities and patient preferences Rapid advances in understanding the molecular pathogenesis of NSCLC have demonstrated that NSCLC is a heterogeneous group of diseases. After the discovery of driver mutations as EGFR, ALK and ROS, molecular targeted drugs have begun to be used therapeutically. EGFR mutation varies between 15% and 50% for different ethnic groups in NSCLC patients [3]. Rearrangements of the anaplastic lymphoma kinase (ALK) gene are present in 3 to 5% of non–small-cell lung cancers (NSCLCs) [4,5]. The current recommended standard of care for EGFR-mutant NSCLC in the advanced stage is epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) monotherapy. ALK inhibitor crizotinib is recommended for first line treatment in patients with previously untreated advanced ALK-positive NSCLC [6]. In the absence of significant toxicity, treatment with these drugs are continued until there is evidence of progression.

In this study, we aimed to investigate the relationship between the selected treatment modality in the first line setting, patients characteristics and outcomes on NSCLC patients who had driver mutations.

Material and Method

We designed current observational study to explore main clinicopathological characteristics and clinical outcomes of patients harboring driver mutations. We included 65 patients from three cancer centers (Şanıiurfa Research and Training Hospital, Başkent University Department of Medical Oncology and Acıbadem Mehmet Ali Aydınlar University Department of Medical Oncology) between the years of 2011 and 2016. All patients were above 18 years-old, had pathological diagnosis of NSCLC either detected EGFR mutation with PCR or EML-4-ALK translocation by FISH, and treated with erlotinib or crizotinib at any line.

Statistics

All results were presented as the rate for categorical values or mean and median for continuous variables. Overall survival (OS) and Progression free survival (PFS) were defined time from diagnosis to death or last control time and progression, death or last control time, respectively. Survival curves were estimated according to the Kaplan-Meier method, and log-rank tests were used for univariate statistical comparisons. Cox-regression analysis was used for multi-variate analysis. Adjusted Hazard Ratio (HR) and 95% confidence interval (95% CIs) were used for estimation. All statistical data were analyzed using the SPSS version 17.0, and a p value of <0.05 was considered statistically significant.

Results

Study Patients

Patient and tumor characteristics are summarized in Table 1. Median age was 62 years old (range 30-81). There were 34 (54 %) male patients. 28 of the 63 (44.4%) patients had active smoking history. Histopathological diagnosis of adenocarcinoma and adeno-squamous carcinoma were found in 62 (98.4%) and 1 (1.6%) patients, respectively. There were 45 (71.4%) and 18 (28.6%) patients with EGFR mutation and EML4-ALK fusion gene rearrangement, respectively. Out of 45 EGFR mutant patients, 22 (34.9%), 16 (25.4%), and 7 (11%) had exon 19 deletion, exon 21 insertion, and unknown, respectively. Significant percent (n=32, 50.8%), of driver mutation positive patients had less than 5 metastases and could be included into oligometastatic definition. But there is no statistically significant difference between EGFR mutation (20 of 45 patients, 44.4%) and ALK positive (12 of 18 patients, 66.6%) patients with regard to oligometastatic presentation. The most common site of metastases were lymph nodes, bone, and brain metastasis with a rate of 77.8 % (n=49), 60.3% (n=38), 28.6% (n=18), respectively. Although, numerically higher rate of cranial metastases (28.8% vs 27.7%) and bone metastases (62.2% vs 55.5%) were found in EGFR mutant compared to ALK positive patients, statistical analysis failed to show significant difference.

Table 1. Patient and tumor characteristics

Characteristics	n (%)
Median age	62 (30-81) years old
Gender	
Male	34 (54)
Female	29 (46)
Smoking	
Yes	28 (44.4)
No	27 (42.9)
Histological diagnosis	
Adenocarcinoma	62 (98.4)
Adenosquamos carcinoma	1 (1.6)
Mutation type	
EGFR mutation	45 (71,4)
EML4-ALK fusion	18 (28.6)
EGFR mutation type	
Exon 19 deletion	22 (34.9)
Exon 21 mutation	16 (25.4)
Unknown	7 (11.1)
Number of metastases	
<3	14 (22.2)
3-5	18 (28.6)
>5	31 (49.2)
Step of TKIs	
First Line	25 (39.7)
Second Line	28 (44.4)
Third Line	5 (7.9)
Not used	5 (7.9)

Treatment and outcomes

After a median follow-up of 20 (range: 1-52) months, 24 (35.3%) patients were death. The probability of 1-year survival was 79% in whole group. Median overall survival (OS) and progression free survival (PFS) was 31 months and 9 months (5.4-12.6, 95%CI), respectively (Figure-1 and Figure-2). There was no statistically significant correlation between overall survival and occurring EGFR or ALK mutation (p:0.33). Among patients with EGFR mutation, survival times for patients with exon 19 deletions were statistically significantly higher than those with exon 2t1 mutations (p:0.02) (Figure-3). The overall survival time of oligometastatic patients was statistically significantly higher than the other patients (p: 0.001) (Figure-4). There was no significant relationship between the selected treatment modality in the first line setting

and overall survival time (p:0.60). Cox-regression multivariate analysis showed that significant effect of number of metastatic sites that had clinical potential effect on survival parameters (Table 2).

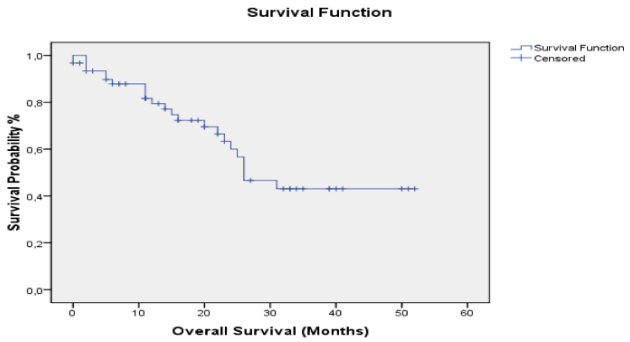

Figure 1. Kaplan-Meier Overall survival of patients, 31 months

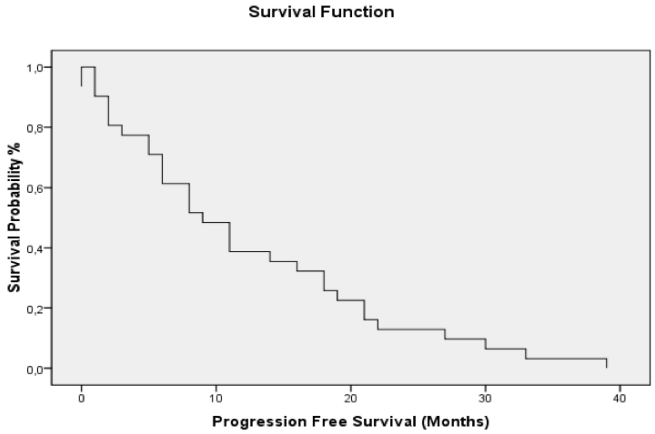

Figure 2. Kaplan-Meier Progression-free survival of patients, 9 months

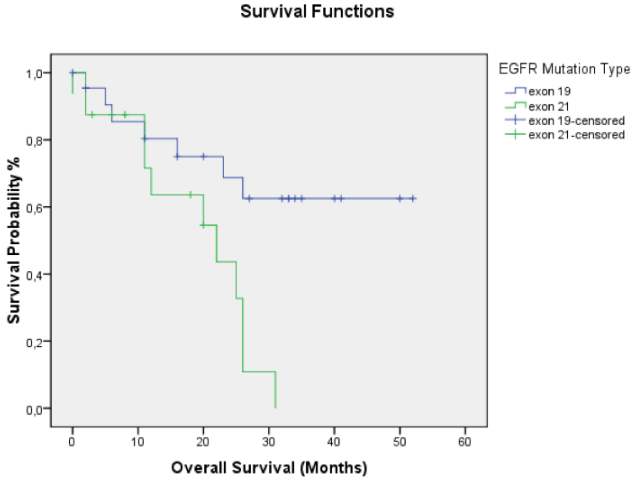

Figure 3. Among patients with EGFR mutation, survival times for patients with exon 19 deletions were statistically significantly higher than those with exon 2t1 mutations (p:0.02)

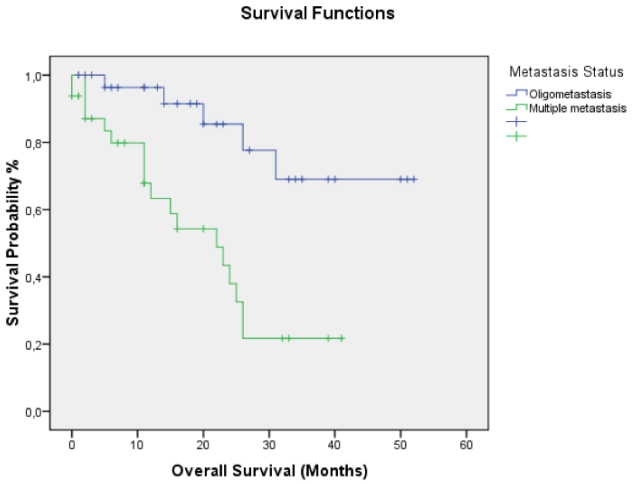

Figure 4. The overall survival time of oligometastatic patients was statistically significantly higher than the other patients (p: 0.001)

Table 2. Multivariate Analyses of Overall Survival

Variables		Multivariate analysis	
	P	HR	95%CI
Sex	0.37	0.56	0.15 to 2.03
Age	0.44	1.01	0.97 to 1.06
Presence of EGFR mutation	0.93	1.05	0.30 to 3.67
Smoking	0.69	0.80	0.25 to 2.46
Presence of cranium metastases	0.93	0.94	0.27 to 3.29
Presence of bone metastases	0.49	1.44	0.50 to 4.15
First line treatment option b	0.69	1.27	0.37 to 4.32
Number of metastatic foci c	0.01 a	0.24	0.08 to 0.73

a Statistically significant
b Tyrosine kinase inhibitor or chemotherapy
c Oligometastatic or not
Abbreviations: HR, Hazad ratio, CL=Confidence limits

The PFS of patients who received tyrosine kinase inhibitor in first-line treatment was statistically significantly higher than patients using chemotherapy in first line setting (14 months vs 5 months) (p:0.01) (Figure-5). PFS of patients with EGFR mutation was statistically significantly higher than patients with ALK mutation (11 months vs 2 months) (p:0.007) (Figure-6). Patients with exon 19 deletions had numerically but not statistically significant higher PFS than patients with exon 21 mutations (17 months vs 8 months) (p:0.197). There was no significant relationship between PFS and metastatic regions (bone or cranium). Treatment was changed in 25 of 34 patients who developed progression with first line treatment. Cox-regression multivariate analysis failed to show that significant effect of any parameter on PFS (Table 3).

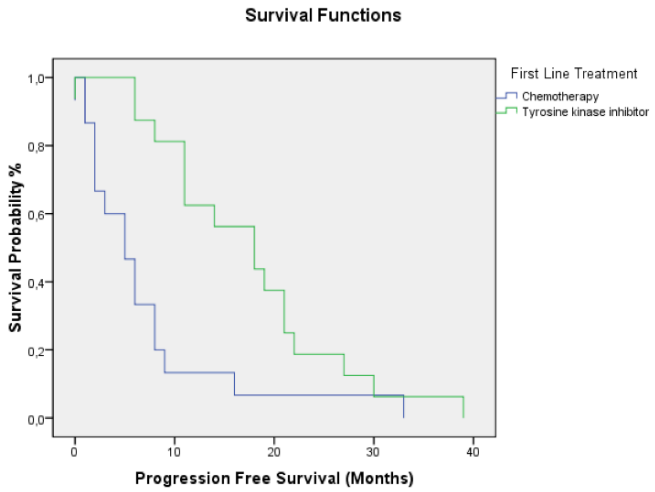

Figure 5. The PFS of patients who received tyrosine kinase inhibitor in first-line treatment was statistically significantly higher than patients using chemotherapy in first line setting.(14 months vs 5 months) (p:0.01)

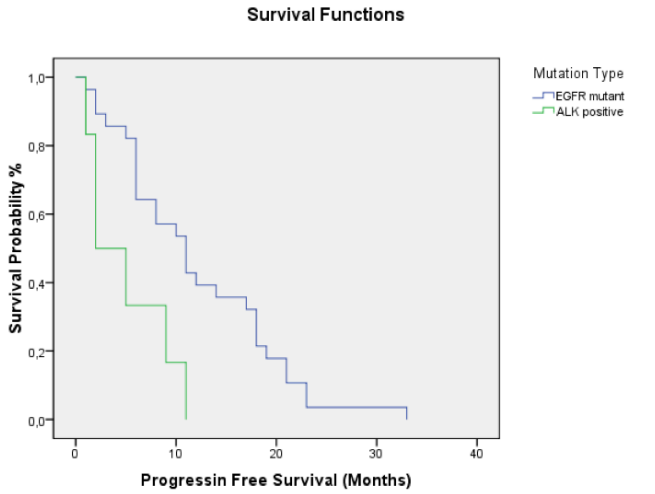

Figure 6. PFS of patients with EGFR mutation was statistically significantly higher than patients with ALK mutation (11 months vs 2 months) (p:0.007)

Table 3. Multivariate analyses of progression-free survival

		Multivariate analysis	
Variables	P	HR	95%CI
Sex	0.29	0.44	0.09 to 2.04
Age	0.78	1.00	0.96 to 1.05
Presence of EGFR mutation	0.06	0.24	0.05 to 1.06
Smoking	0.60	0.76	0.27 to 2.12
Presence of cranium metastases	0.77	0.86	0.30 to 2.43
Presence of bone metastases	0.24	1.75	0.68 to 4.54
First line treatment option a	0.09	3.53	0.79 to 15.6
Number of metastatic foci b	0.69	0.78	0.23 to 2.62

a Tyrosine kinase inhibitor or chemotherapy
b Oligometastatic or not
Abbreviations: HR, Hazad ratio, CL=Confidence limits

Conclusion

In our study, we reviewed the clinical features, treatment options and outcomes of patients with metastatic NSCLC who had a driver mutation. 45 (71.4) of the patients had EGFR mutation and 18 (28.6) had EML4-ALK fusion gene rearrangement. Median overall survival (OS) and progression free survival (PFS) was 31 months and 9 months (5.4-12.6, 95%CI), respectively. Patients using tyrosine kinase inhibitor in the first line had better outcomes but it is statistically significant for PFS only. Patients with exon 19 deletion and patients with oligometastatic disease had better survival parameters. PFS was numerically better in those with EGFR mutations and similarly it was numerically better in patients with exon 19 deletion. These results suggest that treatment preference in favor of tyrosine kinase inhibitors in first line setting produce fairly good survival rate with acceptable toxicity rate.

Currently, chemotherapy with a platinum-doublet is the gold standard for advanced NSCLC without a known driver mutation [7]. However, most patients ultimately progress and survived for less than 1 year [8]. Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) are gefitinib, erlotinib, and afatinib.EGFR-TKIs vs platinum-based chemotherapy as first-line treatment for EGFR-mutated NSCLC patients compared in several phase III randomized clinical trials and the results of these studies showed that EGFR-TKIs were better than standard platinum-chemotherapy for response rate (RR), progression free survival (PFS) and quality of life (QoL) [9-11]. Similarly, İt has been proved that the results of using crizotinib in first line was better for PFS in advanced stage ALK-positive patients [6]. In our study, PFS was better in patients using TKIs in first line consistent with the literature. But there was no significant relationship between the selected treatment modality in the first line setting and overall survival time in our study (p:0.24).

In our study, patients with exon 19 deletions had better OS and PFS than patients with exon 21 mutation. When the literature is examined, recent studies showed that the efficacy might differ in patients with same EGFR sensitive mutations [12]. Approximately, 85% of lung-cancer-specific EGFR-sensitive mutations comprise the in-frame deletions in exon 19 or a point mutation in exon 21. Studies showed that patients with 19del and 21L858R may exhibit different responses to EGFR-TKIs (A4,8,9,20-24). Riely

et al. [13] and Jackman et al. [14] discovered that patients with 19del had a significantly longer OS as compared to the patients with an L858R mutation. Several studies revealed that patients with 19del had significantly prolonged PFS as compared to patients with L858R mutation. However, Some Asian studies revealed that patients with 19del and 21L858R showed a similar survival benefit of EGFR-TKIs treatment [15,16]. Similarly, in IPASS trial, PFS of patients with 19 deletion were not statistically different as compared to those with exon 21 mutation [17].

Oligometastasis is relatively common in NSCLC, although the precise incidence is not clear. In retrospective studies, the survival of patients with oligometastatic NSCLC is more favorable than in those with more numerous metastases (>5), even without therapy specifically directed toward the metastases [18,19]. A comprehensive analysis of patients treated on consecutive Southwest Oncology Group protocols demonstrated that a single metastasis was significantly associated with improved survival compared with multiple metastases in a single organ or multiple organ involvement (8.7 versus 6.2 and 5.1 months, respectively) [20]. An analysis of 423 patients presenting with stage IV NSCLC from 2009 to 2012 found that the median survival was longer for patients with oligometastatic NSCLC (≤5 distant metastases) compared with patients with more extensive disease (17 versus 14 months hazard ratio [HR] 0.73, 95% CI 0.53-1.01) [19]. Our results provide compelling evidence with high PFS and OS in oligometastatic patients.

In conclusion, several factors are associated with the efficacy of TKIs in metastatic NSCLC patients with driver mutation. It is important to use of tyrosine kinase inhibitors in the first line in these patients. The prognosis of oligometastatic patients is better and more aggressive treatment approaches are needed in these patients.

Declaration of conflicting interests

The author declared no conflicts of interest with respect to the authorship and/or publication of this article.

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