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Prognostic factors affecting survival in third-line treatment of advanced non-small cell lung cancer: Retrospective cohort study

İleri evre küçük hücre dışı akciğer kanserinde üçüncü basamak tedavide sağ kalımı ekileyen prognostik faktörler: Retrospektif kohort çalışma

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Abstract

Aim: In patients who have reached third-line treatment, survival times are short and response to treatment is poor. However, in some patients, survival times and treatment responses are good despite advanced treatment lines. The present study investigates the prognostic factors that affect survival among patients who have undergone third-line treatment for non-small cell lung cancer (NSCLC).

Methods: Among the 1,150 patients who were treated for and followed-up with a diagnosis of NSCLC between January 2008 and December 2015, 102 (8%) who had received third-line treatment were included in this retrospective cohort study.

Results: The mean patient age was 56 years (SD: 10.1), and 70.6% were male. The third-line treatment provided a median PFS of 2.36 (range: 1.15–36.1) months and an OS of 4.2 (range: 1.28–38.1) months. Cox hazard-model analyses indicated significant associations between prolonged survival and gender, smoking, non-squamous histology, age below 45 years, the presence of EGFR mutations and the use of EGFR tyrosine kinase inhibitors.

Conclusion: The prognosis may be better for some patients who have reached third-line treatments, namely, young patients, females, non-smokers, and those with a non-squamous histology. In these patients, physicians should be alert in terms of driver mutations, such as EGFR mutation.

Keywords: Third-line treatment, Anti-EGFR, Treatment, Prognosis, Non-small cell lung cancer

Öz

Amaç: Üçüncü basamak tedaviye ulaşmış hastalarda sağkalım süreleri kısa ve tedaviye yanıtları kötüdür. Ancak bazı hastalarda sağkalım süreleri ve tedavi yanıtları ilerlemiş tedavi basamağına rağmen iyidir. Bu çalışmadaki amacımız, küçük hücreli dışı akciğer kanserinde (KHDAK) üçüncü basamak tedaviye ulaşmış olan hastaların sağkalımlarını etkileyen prognostik faktörleri saptamaktır.

Yöntemler: Ocak 2008-Aralık 2015 tarihleri arasında KHDAK tanısı ile tedavi edilen ve takip edilen 1.150 hastadan üçüncü basamak tedavi alan 102 (%8) hasta bu retrospektif kohort çalışmada değerlendirildi.

Bulgular: Hastaların ortalama yaşı 54 (Standard sapma: 10,1) ve %70,6 sı erkekti. Üçüncü basmakta ortanca progresyonsuz sağkalım süresi ortanca 2.36 (Aralık: 1,15-36,1) ve ortanca toplam sağkalım 4.2 (1,28-38,1) aydı. Cox hazard modeli analizinde uzun sağkalımı etkileyen temel faktörler; cinsiyet, sigara, skuamöz dışı histoloji, 45 yaş altında olmak, EGFR mutasyon durumu ve Anti-EGFR tedavi almış olmak olarak saptandı.

Sonuç: Kadın, sigara içmeyen, skuamöz dışı histolojisi olan, genç olan üçüncü basamak tedaviye ulaşmış hastalarda prognozun daha iyi olabileceği ve bu hastalarda EGFR mutasyonu gibi driver mutasyonları açısından hassas olunması gerektiği bilinmelidir.

Anahtar kelimeler: Üçüncü basamak tedavi, Anti-EGFR, Tedavi, Prognoz, Küçük hücre dışı akciğer kanseri

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Introduction

The five-year overall survival (OS) rate associated with all lung cancers was previously reported as 16.8% [1-3]. At the time of diagnosis, 57% of all patients present with metastatic disease and the five-year OS rate for metastatic disease was reported as 4.2% [3,4].

Epidermal growth factor receptor (EGFR) exon 19 deletion and exon 21 L858 mutations are valuable predictors of benefit from EGFR tyrosine kinase inhibitor (TKI) therapy, while rearrangements in the Anaplastic lymphoma kinase (ALK) gene predict benefit from ALK TKI agents [5,6]. The currently available second and third-line treatment options include targeted therapies for patients with driver mutations, and immunotherapies and chemotherapeutic agents for patients without mutations [7-12].

This study investigates the prognostic factors that affect survival among patients who received third-line treatment for non-small cell lung cancer (NSCLC).

Materials and methods

The study sample was formed after reviewing the medical files of 1,150 patients who were treated for and followed-up with a diagnosis of stage IV NSCLC at two separate centers between January 2008 and December 2015. Of those patients, 980 (85%) were screened in the Health Sciences University Dr Abdurrahman Yurtaslan Ankara Oncology Hospital, and 170 (15.6%) were screened at the Health Sciences University Ankara Atatürk Chest Diseases Hospital.

Patients aged 18 years and above, with a pathologically confirmed diagnosis of stage IV metastatic non-small cell lung cancer and a history of receiving at least one cycle of third-line treatment, were evaluated in this study. Of all the screened patients, 102 (8%) had received third-line treatment for metastatic disease. Patients were stratified based on gender, smoking status, age below or above 45 years, the presence of EGFR mutations, use of anti-EGFR treatment and histology. Data on the response evaluations were collected from the medical records of the patients.

Statistical analysis

The SPSS 17.0 program was used to estimate survival rate, and descriptive data were calculated through the use of the same program. Kaplan-Meier curves and a Long-rank test were used to analyze the survival data, and a Cox Regression analysis was performed to identify factors that affect survival. *P*-values of <0.05 were considered statistically significant.

Results

The mean age of 102 evaluated patients was 54 years (SD 10.1), 72 (70.6%) patients were male and 70 (68.1%) were smokers. Histopathological examinations confirmed non-squamous histology in 68 (66.6%) patients, and EGFR mutations were detected in 24 (23.5%) patients, of whom 21 (20.5%) were female, 23(22.5%) had non-squamous histology, and 21 (20.5%) had no history of smoking (Table 1).

All patients underwent platinum-doublet chemotherapy as the first-line treatment. The median number of first-line treatment cycles was five, and the disease control rate was 68%. The most commonly preferred agents for second-line treatment were docetaxel 40 patients (39.2%), a platinum-doublet regimen 27 patients (26.4%) and pemetrexed 16 patients (15.7%). The median number of first-line treatment cycles was four, and the disease control rate was 58.6%. The most frequently used third-line treatments were vinorelbine in 26 patients (28.3%), docetaxel in 19 patients (18.6%), gemcitabine in 17 patients (16.7%) and erlotinib in 14 patients (13.7%). The median number of cycles was three and the disease control rate was 40.8% (Table 2).

Table 1: Patient demographics and clinical characteristics

Characteristics	n	%
	102	100
Age-year mean (SD)	54 (10.1)	
Age, years	n	%
≥45	84	82.4
<45	18	17.6
Sex		
Female	30	29.4
Male	72	70.6
Smoking status		
Yes	70	70.6
No	32	29.4
Histology		
SCC	34	33.3
Adenocarcinoma	60	58.8
Large cell	4	3.9
Others	4	3.9
EGFR mutation		
Male	3	2.9
Female	21	20.5
Squamous	1	0.9
Non squamous	23	20.5
Smoker	3	2.9
Non smokers	21	20.5
ALK rearrangement	4	3.9
Died	102	100

EGFR: Epidermal growth factor receptor, ALK: Anaplastic lymphoma kinase, SCC: Squamous cell carcinoma

Table 2: Treatment characteristics

	First-line		Second-line		Third-line	
	n	%	n	%	n	%
Treatment						
Doublet platin based	102	100	27	26.4	6	5.8
Docetaxel	-		40	39.2	19	18.6
Gemcitabin	-		7	6.9	17	16.7
Pemetrexed	-		16	15.7	10	9.8
Vinorelbine	-		2	2	26	28.3
Erlotinib	-		8	7.8	14	13.7
Crizotinib	-		2	2	2	2
Others	-			-	5	4.9
Treatment Response						
Complete response	1	1	-	-	-	-
Partial response	33	32.4	18	17.4	11	10.4
Stabil disease	35	34.3	42	41.2	31	30.4
Progression	33	32.4	42	41.2	60	58.8
Number of cycle(Median)	5		4		3	
Number of drug						
Single agent	-	-	75	73.5	96	94.1
Doublet	102	100	27	26.5	6	5.9
Overall Survival Month	25		12.8		4.2	
Median (Range)	(9-63.7)		(4.5-46.1)		(1.28-38.1)	
Progression free survival-Month						
Median (range)	7.2		5.25		2.36	
	(2.63-24.25)		(1.4-34.79)		(1.15-36.1)	

Irrespective of the agent used, the median PFS with first-line treatment was 7.2 months (range: 2.6–24.2), and the median OS was 25 months (range: 9–63.7). The median PFS and OS with second-line treatment were 5.25 (range: 1.4–34.79) and 12.8 (range: 4.5–46.1) months, respectively. The median PFS and OS with third-line treatment were 2.36 (range: 1.15–36.1) and 4.2 (range: 1.28–38.1) months, respectively (Table 2).

In a univariate analysis of the sub-groups of patients receiving third-line treatment, overall survival was found to be better among women, non-smokers, patients with non-squamous histology, patients younger than 45 years, EGFR mutant patients and those treated with anti-EGFR agents. Multivariate analyses indicated that non-squamous histology, the presence of EGFR

mutations and the use of anti-EGFR treatments were associated with better survival (Table 3).

Table 3: Univariate and multivariate analysis of prognostic factors-associated overall survival

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95 % CI	*P*-value	HR	95% CI	*P*-value
Histology						
Non-squamous	0.46	0.3-0.72	0.001	0.62	0.3–0.98	0.041
Squamous						
Sex						
Female	0.36	0.22-0.59	<0.001			
Male						
Smoking status						
Non-smokers	0.34	0.21-0.57	<0.001			
Smokers						
EGFR mutation						
Mutant	0.26	0.15-0.45	<0.001	0.48	0.25-0.93	0.032
Wild						
Anti- EGFR treatment						
Yes	0.20	0.09–0.44	0.001	0.35	0.14–0.87	0.025
No						
Age						
<45 years	0.51	0.3–0.86	0.013			
>45 years						

HR: Hazard ratio, EGFR: Epidermal growth factor receptor

Among the EGFR-mutant patients, PFS was 12.45 months [95%CI, 9.06 to 15.83] in patients who received anti-EGFR, and 2.33 months [95%CI, 2.15 to 2.5] in patients who received conventional therapies as third-line treatment (P=0.001). The OS in these patient groups was 21.02 months [95%CI, 12.8 to 29.16] and 3.64 months [95%CI, 2.85 to 4.4], respectively (P<0.001) (Figure 1). PFS and OS did not significantly differ with anti-EGFR treatment as a second- or third-line treatment (Figure 2).

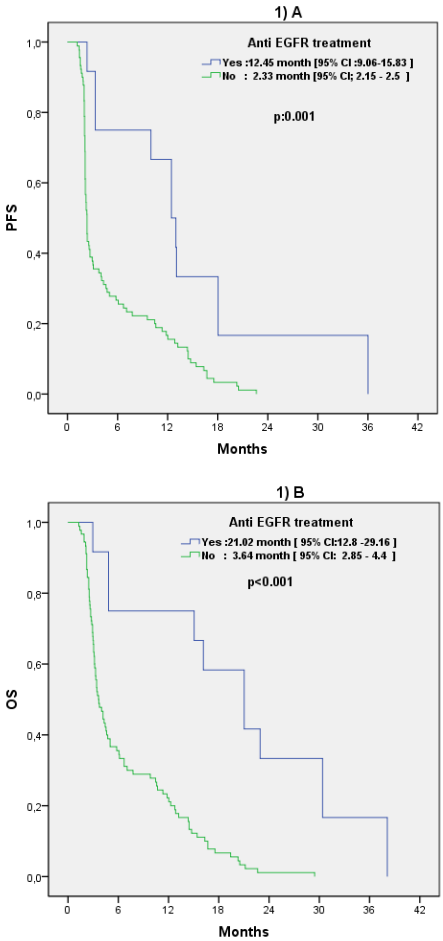

Figure 1: A) Comparison of progression free survival (PFS) rate of Anti-EGFR treatment status B) Comparison of overall survival (OS) rate of Anti-EGFR treatment status

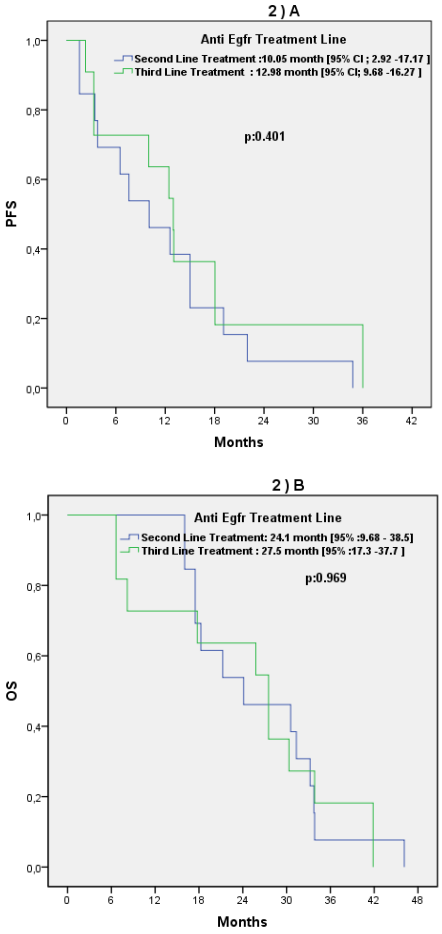

Figure 2: A) Comparison of progression free survival (PFS) rate of Anti-EGFR treatment line B) Comparison of overall survival (OS) rate of Anti-EGFR treatment line

Discussion

The use of EGFR-TKIs such as erlotinib, gefitinib, afatinib in first-line treatment in EGFR mutant patients has been shown in many studies [13-18]. In recent years, Osimertinib has proven to be more effective than other Anti EGFR-TKİs in first-line treatment in EGFR mutant patients, taking its place in the guidelines [18]. In the progression after EGFR-TKI, in the second-line treatment, the efficacy of osimertinib was proven if the T790M mutation was shown in the new biopsy [20].

Patients who were evaluated retrospectively were selected between 2008 and 2015. In the present study, we retrospectively evaluated the data of 102 patients who had received third-line treatment in two different centers.

In the years shown, chemotherapy agents were recommended as monotherapy in second and third-line therapy. EGFR-TKIs allowed national healthcare institutions to be given in second-line and third-line in our country. Although we have limitations in this retrospective study, the main issue we try to emphasize is to address factors that may be prognostic in patients who come to third-line treatment. The results of the present study showed that the female gender, being a non-smoker, younger than 45 years of age, the presence of EGFR mutations and the use of EGFR-TKIs were significant prognostic factors for third-line treatment.

While 8% of the patients screened in this study received third-line treatment for NSCLC, 172 patients (14%) received third-line treatment following a previously reported Austrian study [21]. In both the present and Australian studies, monotherapy was more commonly preferred as the second and

third-line treatments for metastatic NSCLC due to its low toxicity and the better tolerability profile seen with monotherapy regimens [21].

In a retrospective analysis performed by Kaira et al. [22] on 124 patients with metastatic NSCLC, patients who survived for more than five years were found to have adenocarcinoma histology and a good PS. In the present study, analyses of patients according to pathologic sub-types indicated that non-squamous histology was a prognostic factor that was associated with better survival. In a previous study, Kawaguchi et al. [23] reported that PS (Performance status) and smoking were independent prognostic factors, while non-smoking was found to be a prognostic factor in the present study. Zhen et al. [24] previously reported that non-smoking, adenocarcinoma histology, good PS and use of EGFR-TKIs were associated with a better OS in the third-line treatment of metastatic NSCLC.

A DELTA study that evaluated second and third-line regimens in an EGFR-wild patient group compared erlotinib with docetaxel and reported superior response rates and PFS with docetaxel than with erlotinib [25]. In a study that evaluated 503 Asian patients, female gender, the presence of EGFR mutations, use of EGFR-TKIs, adenocarcinoma histology, non-smoking and PS 0–1 were associated with statistically significant survival benefits [26].

Limitations

The limitations of the present study include its retrospective design, in addition to the limited number of patients and study centers.

Conclusion

EGFR mutations were found to be more common in non-smokers, younger population, the female gender and non-squamous histology in the present study. The use of EGFR-TKIs for the third-line treatment of NSCLC in EGFR-mutant patients provided better survival outcomes when compared to conventional chemotherapy regimens.

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