Asian Journal of Current Research in Clinical Cancer
2021, Volume 1, Issue 1, Page No: 20-27

Available online at: www.galaxypub.co/page/journals

Galaxy Publication

The Predictive Role of Sarcopenia in Lung Adenocarcinoma Patients Treated with Erlotinib

Havva Yesil Cinkir[1]*, Tulay Kus[1], Gokmen Aktas[2], Umut Elboga[3]

[1]Departments of Medical Oncology, Faculty of Medicine, Gaziantep University, Gaziantep, Turkey.
[2]Department of Medical Oncology, Faculty of Medicine, Kahramanmaras Sutcu Imam University, Kahramanmaras, Turkey.
[3]Department of Nuclear Medicine, Faculty of Medicine, Gaziantep University, Gaziantep, Turkey.

***E-mail** ✉ drhavva1982@gmail.com

Received: 03 March 2021; **Revised:** 23 May 2021; **Accepted:** 29 May 2021

ABSTRACT

In advanced non-small cell lung cancer (NSCLC), factors such as susceptibility to epidermal growth factor receptor tyrosine kinase inhibitors with pathological subtype of adenocarcinoma, smoking history, and female gender are predictive. However, we need novel predictive markers as well as driver mutations for improved therapy choices. The present study aimed to investigate the prognostic significance of sarcopenia in lung adenocancer patients treated with erlotinib. Skeletal muscle index (SMI) was calculated using a single cross-sectional area of the muscle at the third lumber vertebra (L3, cm^2)/(height × height) (m^2), and this study was performed retrospectively. The median cut-off values of SMI for males (< 32.7 cm^2/m^2) and women (< 28.2 cm^2/m^2) were used to characterize sarcopenia. The cox-regression model was used to evaluate the predictive role of sarcopenia and other factors. The age range was 36 to 84 years, with a median of 56 years. The median progression-free survival (PFS) of the sarcopenic group was 38 weeks (95% CI = 21.3–54.6), while that of the non-sarcopenic group was 49 weeks (95% CI = 0–101.4; P = 0.053). Sarcopenia and the number of metastasis were the independent predictors of PFS in multivariate analysis, and there was no significant difference in disease control rate or overall survival between the sarcopenic and nonsarcopenic groups. We demonstrated that the presence of sarcopenia and the number of metastases are prognostic signs in NSCLC patients treated with erlotinib. Early detection of sarcopenia and appropriate patient management are crucial. We demonstrated that the existence of sarcopenia and multiple metastases is a prognostic sign in NSCLC patients treated with erlotinib. Early detection of sarcopenia and appropriate patient management are crucial.

Keywords: Erlotinib, Lung adenocancer, Sarcopenia, Skeletal muscle index

How to Cite This Article: Cinkir HY, Kus T, Aktas G, Elboga U. The Predictive Role of Sarcopenia in Lung Adenocarcinoma Patients Treated with Erlotinib. Asian J Curr Res Clin Cancer. 2021;1(1):20-7.

Introduction

The identification of active driver mutations paved the door to attaining higher survival rates with lesser toxicity compared to cytotoxic treatment in non-small cell lung cancer (NSCLC). The most prevalent driver mutation among them is in the epidermal growth factor receptor (EGFR), and we have extensive expertise with EGFR tyrosine kinase inhibitors (TKIs), which are molecularly targeted medications. In many instances, early tumor development is unavoidable, even though higher progression-free survival (PFS) with first/second-generation EGFR-TKIs has been shown in the presence of exon 19 q deletion and exon 21 L858R point mutation [1, 2]. The susceptibility to EGFR-TKIs in NSCLC has been recognized to be predicted by adenocancer pathologic subtype, smoking history, and female gender; nevertheless, new predictive markers and driver mutations are required for improved treatment choices [3, 4].

A new biomarker called sarcopenia is thought to be a key element of cancer cachexia syndrome, which is a precursor to inadequate prognoses for a variety of cancer kinds [5-9]. While the predictive significance of sarcopenia in patients with non-small cell lung cancer treated with conventional chemotherapy has been

established, it remained unclear in the first and second lines of treatment for lung adenocancer treated with EGFR-TKI. The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines describe sarcopenia as a widespread and gradual loss of skeletal muscle mass and strength, accompanied by poor physical performance and a corresponding risk of negative consequences [10]. The computation of skeletal muscle area at the third vertebra level using computed tomography (CT) scanning has recently become a standard method and is more user-friendly, even though muscle mass can be estimated using the handgrip strength method, dual X-ray absorptiometry, or bio-electric impedance analysis [10].

Sarcopenia is a significant indicator of prognosis for both early and late cancer stages. We need stronger prognostic indicators in this area since some patients with EGFR-TKIs exhibit fast clinical deterioration without the potential for additional therapy choices. Our goal was to elucidate the prognostic significance of sarcopenia in patients with lung adenocancer receiving erlotinib as a first- and second-line treatment.

Materials and Methods

Study design and patient selection

One Turkish center served as the retroactive site for this investigation. Our medical records were the source of all clinical data. The Gaziantep University Oncology Hospital examined patients with histopathologically proven lung adenocancer treated with erlotinib in the first or later lines at the metastatic stage between 2011 and 2019. The investigation was carried out in compliance with the Helsinki Declaration and authorized by Gaziantep University's Independent Ethics Committee (decision no: 2019/456, date: 04.12.2019). 35 patients with EGFR-sensitizing mutations who had CT scans and accessible clinical data within a month of the start of EGFR-TKIs were included in the study. Patients with anaplastic lymphoma-kinase or ROS-1 rearrangement, exon 20 mutation, initial T790M, and those who had received immunotherapy in the past were not included.

Clinical-pathological factors were noted, such as age, sex, smoking status, EGFR-sensitizing mutation, treatment line, central nervous system (CNS) metastases, and number of metastatic lesions. Starting at 150 mg/day, taken orally one hour before or two hours after meals, erlotinib was progressively lowered to 100 mg/day if toxicity occurred beyond grade 2. Therapy was continued until the illness progressed or the toxicity became intolerable. A CT scan was performed on each patient every three months or as soon as indications of clinical progression appeared, following the response assessment criteria for solid tumors (RECIST 1.1).

Computed tomography image analysis

As part of standard clinical practice, muscle mass was determined by examining electronically captured CT scans before the start of erlotinib medication. The usual marker was thought to be the third lumbar vertebra (L3). At the L3 (cm^2)/(height × height) (m^2), a single cross-sectional area of the muscle was used to calculate the skeletal muscle index (SMI). Sarcopenia was defined as median cutoff values for men's and women's SMIs (< 32.7 cm^2/m^2 and < 28.2 cm^2/m^2, respectively).

Statistical analysis

Descriptive and frequency statistics were used to examine clinical and demographic features. The categorical variables were assessed using the Chi-squared or Fisher's exact test. The median SMI was reassessed by gender after being established as the threshold point. The Kaplan-Meier technique was used to provide survival data, and the log-rank test was used to analyze group differences. PFS, which was expressed in weeks, was defined as the interval between the first day of erlotinib medication and the advancement of the illness or its death. When expressed as months, overall survival (OS) was defined as the interval from the commencement of erlotinib medication to the date of the last control or death. To investigate the prognostic importance of the sarcopenia group, EGFR status, age, smoking habit, number of metastases, presence of CNS metastases, gender, and treatment line with PFS and OS, a univariate analysis was employed. Based on the univariate analysis, the multivariate analysis looked at prognostic variables with $P < 0.1$. Using the 95% CI, the hazard ratio (HR) was used. One was considered statistically significant if $P < 0.05$. Windows version 22.0 of the Statistical Package for the Social Sciences (SPSS) software (SPSS, Inc., Chicago, IL, USA) was used to conduct all of the statistical analyses.

Results and Discussion

Patients' characteristics

A total of 35 NSCLC patients who were treated with erlotinib and had an adenocarcinoma histological subtype were examined. Patients were mostly under 65 years old (85.7%), with a median age of 56 years (range: 36–84 years). Male patients made up the remaining group, with female patients making up 54.3%. In 57.1% of the patients, an EGFR-sensitizing mutation was found; in 25.7% of the patients, it was not found; and 17.1% of the patients had an unknown mutation status. Exon 19 deletion (15 individuals, 83.3%) was the most prevalent EGFR-sensitizing mutation. 62 patients (9%) had never smoked. **Table 1** summarizes patient and tumor characteristics. The median SMI value was used to split the patients into two groups: < 28.2 cm^2/m^2 for women and < 32.7 cm^2/m^2 for males. When comparing sarcopenia groups to age, gender, smoking status, EGFR mutation status, treatment line, and CNS metastases, we did not discover any significant differences **(Table 1)**.

Table 1. Patients' and tumor characteristics according to sarcopenic and nonsarcopenic groups

Characteristics	All patients (n = 35)	Sarcopenic (n = 18; 51.4%)	Nonsarcopenic (n = 17; 48.6%)	P-value
Age (years), median (range)	56 (36-84)	55 (36-75)	58 (39-84)	0.310
Age group (years)				
< 65	30	15 (83.3%)	15 (88.2%)	0.679
≥ 65	5	3 (16.7%)	2 (11.8%)	
Gender				
Female	19	10 (55.6%)	9 (52.9%)	0.877
Men	16	8 (44.4%)	8 (47.1%)	
Smoking history				
Yes	13	6 (33.3%)	7 (41.2%)	0.631
No	22	12 (66.7%)	10 (58.8%)	
CNS metastasis				
Present	14	8 (47.1%)	6 (33.3%)	0.407
Absent	21	9 (52.9%)	12 (66.7%)	
Number of metastasis				
1	8	5 (27.8%)	3 (17.6%)	0.747
2	18	9 (50.0%)	9 (52.9%)	
≥ 3	9	4 (22.2%)	5 (29.4%)	
EGFR mutation				
Positive	20	11 (61.1%)	9 (52.9%)	0.868
Negative	9	4 (22.2%)	5 (29.4%)	
Unknown	6	3 (16.7%)	3 (17.6%)	
Treatment line				
1st	10	6 (33.3%)	4 (23.5%)	0.680
2nd	20	9 (50.0%)	11 (64.7%)	
≥ 3 line	5	3 (16.7%)	2 (11.8%)	
Best response				
CR	-	-	-	0.359
PR	10	7 (38.9%)	3 (17.6%)	
SD	19	8 (44.4%)	11 (64.7%)	
PD	6	3 (16.7%)	3 (17.6%)	
Disease control rate				
CR + PR + SD	29	15 (83.3%)	14 (82.4%)	0.939
PD	6	3 (16.7%)	3 (17.6%)	

CNS: Central nerve system, CR: Complete response, PR: Partial response, SD: Stabil disease, PD: Progression disease, EGFR: Epidermal growth factor receptor

Survival analysis according to clinicopathological parameters and sarcopenia

94.3% of patients (n = 33) passed away due to the course of their condition, and the median follow-up period was 25.6 (6.1–68.6) months. 44 (33.4–54.6) weeks was the median PFS for the entire cohort. For both the sarcopenic and nonsarcopenic groups, the median PFS was 38 (95% CI = 21.3–54.6) weeks and 49 (95% CI = 0–101.4) weeks, respectively (P = 0.053). While PFS was not affected by EGFR-sensitizing mutation or CNS metastases, it was shortened by male gender, younger age, smoking, erlotinib usage after first-line therapy, number of metastases, and sarcopenia. The independent prognostic indicators for PFS in the multivariate analysis were the number of metastases and the presence of sarcopenia (HR = 2.605; 95% CI = 1.115–6.087, P = 0.027) **(Table 2)**. **Figure 1** displays the Cox regression analysis for PFS based on the existence of sarcopenia.

Table 2. Progression-free survival after erlotinib onset according to the clinicopathological factors by cox-regression analysis

Factor	Univariate analysis		Multivariate analysis	
	HR (95% CI)	**P-value**	**HR (95% Cl)**	**P-value**
Age (years)				
< 65	2.975 (1.006-8.767)	***0.049***	2.005 (0.872-10.29)	0.81
≥ 65	1 (reference)			
Gender				
Female	1 (reference)	***0.030***	1.505 (0.379-5.972)	0.56
Male	2.174 (1.068-4.426)			
Smoking history				
Nonsmoker	1 (reference)	***0.021***	1.760 (0.406-7.626)	0.45
Smoker	2.228 (1.136-4.811)			
CNS metastasis				
Present	1 (reference)	0.660	-	
Absent	1.181 (0.564-2.471)			
Number of metastasis				
1	1 (reference)	0.83	1 (ref)	***0.014***
2	1.325 (0.565-3.106)		3.449 (1.178-10.10)	
≥ 3	3.145 (1.085-9.114)		6.059 (1.756-20.90)	
EGFR mutation				
Positive	1 (reference)	0.770	-	
Negative	1.331 (0.593-2.987)			
Unknown	0.988 (0.388-2.514)			
Treatment line				
1st	1 (reference)	***0.002***	-	0.074
2nd	1.257 (0.554-2.854)		0.841 (0.319-2.217)	
≥ 3rd line	7.893 (2.318-26.87)		4.271 (0.957-19.05)	
Sarcopenia status				
Nonsarcopenic	1 (reference)	***0.060***	2.605 (1.115-6.087)	***0.027***
Sarcopenic	2.062 (0.968-4.394)			

Bold italic: P < 0.1. HR: Hazard ratio, CI: Confidence intervals, CNS: Central nervous system, EGFR: Epidermal growth factor receptor

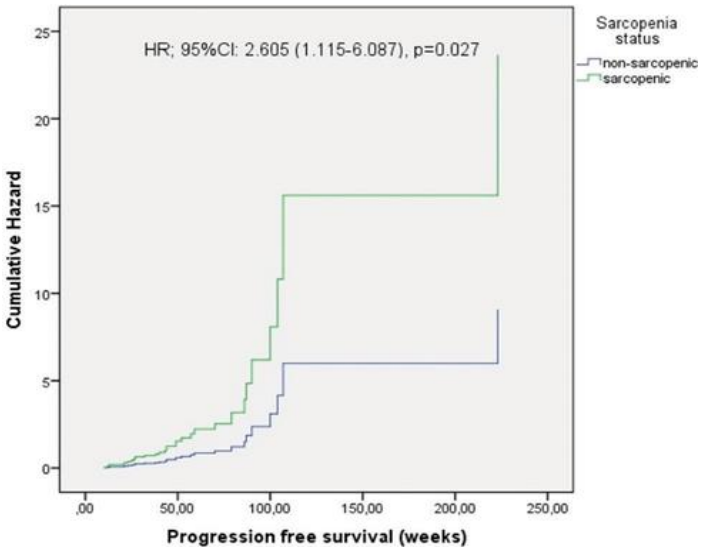

Figure 1. Cox regression analysis according to the presence of sarcopenia for progression-free survival.

Additionally, the OS did not differ between the nonsarcopenic (24.4 months, 95% CI = 11.7–37.1) and sarcopenic (15.7 months, 95% CI = 5.9–25.4) groups (HR = 1.826; 95% CI = 0.859–3.884, P = 0.138). Conversely, in univariate analysis, poor OS was linked to male gender (P = 0.012), smoking habit (P = 0.006), and erlotinib usage after the first line (P = 0.016) **(Table 3)**.

There was no discernible difference in the illness control rate between the sarcopenic and nonsarcopenic groups (P = 0.939).

Table 3. Overall survival after erlotinib onset according to the clinicopathological factors by Cox regression analysis

Factor	**Univariate analysis**	
	HR (95% CI)	***P***
	Age group (years)	
< 65	2.211 (0.757-6.458)	0.147
≥ 65	1 (reference)	
	Gender	
Female	1 (reference)	***0.012***
Male	2.682 (1.242-5.792)	
	Smoking history	
Nonsmoker	1 (reference)	***0.006***
Smoker	2.976 (1.358-6.519)	
	CNS metastasis	
Present	1 (reference)	0.46
Absent	1.338 (0.622-2.875)	
	Number of metastasis	
1	1 (reference)	0.171
2	1.284 (0.548-3.005)	
≥ 3	2.509 (0.913-6.896)	
	EGFR mutation	
Positive	1 (reference)	0.74
Negative	1.156 (0.517-2.587)	
Unknown	1.454 (0.555-3.813)	
	Treatment line	
1st	1 (reference)	***0.016***

2nd	1.012 (0.454-2.258)	
≥ 3rd	4.709 (1.421-15.59)	
	Sarcopenia status	
Nonsarcopenic	1 (reference)	***0.118***
Sarcopenic	1.826 (0.859-3.884)	

Bold italic: P<0.1. HR: Hazard ratio, CI: Confidence interval, CNS: Central nervous system, EGFR: Epidermal growth factor receptor

The current study examined the predictive usefulness of sarcopenia in patients with non-small cell lung cancer (NSCLC) responding to EGFR-TKIs, whether or not they had EGFR-sensitizing mutations in the first or second line. In univariate analysis, EGFR-sensitizing mutation and CNS metastasis did not influence PFS, whereas male gender, younger age, smoking, erlotinib usage beyond first-line, number of metastatic sites, and sarcopenia were linked to shorter PFS. Furthermore, it was discovered that the only prognostic indication in this regard, together with the number of metastases, was the presence of sarcopenia.

Despite being the most significant predictor of response to EGFR-TKIs, EGFR-sensitizing mutations are less common in the final line of treatment. In this regard, further prognostic clinicopathological indicators are required to comprehend the advantages of using EGFR-TKIs in the later line. Sarcopenia has been shown to have a bad prognostic impact both at the start of treatment and during chemotherapy in newly diagnosed patients with advanced non-small cell lung cancer [8]. Chemotherapy, however, had a far greater effect on muscle loss following treatment than EGFR-TKIs [9]. Researchers have long examined the impact of sarcopenia on the prognosis of patients receiving first-line EGFR-TKI treatment. While Rossi *et al*. found that sarcopenia was an independent unfavorable prognostic factor for OS (12.6 vs. 23.5 months, P = 0.035), they did not find that patients on gefitinib had a different PFS in terms of sarcopenia (11 vs. 14 months, P = 0.26) [11]. Another research study looked at the connection between survival and the psoas muscle index (PMI) in patients with first- and second-generation EGFR-TKIs [12]. There was no discernible change in either OS (P = 0.37) or PFS (P = 0.18). Although the prognostic significance of sarcopenia has been variable, it has been demonstrated that it has no predictive value in patients with EGFR-sensitizing mutations who react to EGFR-TKIs at the first line [10, 12]. According to the current study and our understanding of this subject, EGFR-sensitizing mutation is the primary factor influencing response to EGFR-TKIs in first-line treatment; nevertheless, sarcopenia may be a contributing factor for subsequent lines, independent of EGFR-sensitizing mutation.

Although EGFR-sensitizing mutations are the primary predictors of clinical outcome with EGFR-TKI therapy in progressive non-small cell lung cancer, the DELTA trial, which evaluated the effectiveness of erlotinib following first-line treatment in patients with EGFR-mutant and wild-type tumors, revealed that PFS was comparable and statistically insignificant with a duration of 9.3 versus 7 months in the erlotinib arm and docetaxel arm, respectively (HR = 0.96; 95% CI = 0.51–1.79; P = 0.91) [13].

Therefore, simply having an EGFR-sensitizing mutation is not a reliable indicator of how patients may respond to EGFR-TKI treatment following first-line therapy. Following first/second-line chemotherapy and maintenance medication, erlotinib gave patients with EGFR mutations and wild-type malignancies a survival benefit [14, 15]. The existence of EGFR-sensitizing mutations is not the sole factor that determines the survival benefit of erlotinib; other molecular processes and pathogenetic variables likely also contribute to its therapeutic impact [16]. In a phase III, placebo-controlled study evaluating the impact of gefitinib on survival following first-line therapy in patients with progressive non-small cell lung cancer (NSCLC) whose EGFR status was unknown, the gefitinib group outperformed the placebo group in terms of survival in both Asian patients (median OS 9.5 vs. 5.5 months, P = 0.01) and non-smokers (median OS 8.9 vs. 6.1 months, P = 0.012) [17]. However, the TAILOR trial showed that responsiveness is not predicted by smoking behavior [18]. Accordingly, new markers are needed to forecast the reaction to EGFR-TKIs, which are often employed in first-line and additional treatments. Prior research in this area developed a novel prognostic marker based on the maximum standardized uptake value (SUVmax) on fluorine-18 fluorodeoxyglucose positron emission tomography/CT [19]. In patients with SUVmax values more than 11, erlotinib has performed poorly, despite the predictive usefulness of the EGFR-sensitizing mutation. Furthermore, there was no evidence of erlotinib efficiency in patients with SUVmax values > 11 in the wild-type and EGFR-unknown groups. However there was no prognostic relevance, we showed in the present investigation that sarcopenia had an independent predictive value for response to EGFR-TKI in patients with or without EGFR sensitizing mutation. First-line usage is a determinative predictive marker for response to EGFR-TKIs, while the

existence of an EGFR-sensitizing mutation was not a conclusive predictive sign. There was no correlation between sarcopenia and responsiveness in earlier research assessing the predictive importance of sarcopenia for response to EGFR-TKIs [11, 12]. This could have to do with the fact that the primary determining biomarker in this field is the evaluation of only first-line usage in patients with EGFR-sensitizing mutation. However, sarcopenia may also be a strong predictive biomarker following first-line treatment in patients who do not have an EGFR-sensitizing mutation, based on this current research.

Our study included several limitations. In terms of EGFR mutation status and erlotinib treatment line, the sample size was modest and diverse. Furthermore, the investigation was planned in hindsight. Nevertheless, a noteworthy relevance was discovered in all groups regarding the prognostic usefulness of sarcopenia for response to erlotinib, despite the small patient population and heterogeneous cohort. Thus, we believe that the results of this study should be taken into account to open the door to future research, including more patients.

Conclusion

In NSCLC patients receiving erlotinib, we discovered that the number of metastases and the presence of sarcopenia were predictive markers. Early detection of sarcopenia is crucial, and patients should be treated appropriately.

Acknowledgments: None

Conflict of Interest: None

Financial Support: None

Ethics Statement: None

References

1. Paz-Ares L, Soulières D, Melezínek I, Moecks J, Keil L, Mok T, et al. Clinical outcomes in non-small-cell lung cancer patients with EGFR mutations: pooled analysis. J Cell Mol Med. 2010;14(1-2):51-69.
2. Yang JC, Wu YL, Schuler M, Sebastian M, Popat S, Yamamoto N, et al. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. Lancet Oncol. 2015;16(2):141-51.
3. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol. 2011;12(5):489-95.
4. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. J Clin Oncol. 2013;31(12):1539-47.
5. Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff SC, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. Clin Nutr. 2017;36(1):49-64.
6. Miyake M, Morizawa Y, Hori S, Marugami N, Shimada K, Gotoh D, et al. Clinical impact of postoperative loss in psoas major muscle and nutrition index after radical cystectomy for patients with urothelial carcinoma of the bladder. BMC Cancer. 2017;17(1):237.
7. Villaseñor A, Ballard-Barbash R, Baumgartner K, Baumgartner R, Bernstein L, McTiernan A, et al. Prevalence and prognostic effect of sarcopenia in breast cancer survivors: the HEAL study. J Cancer Surviv. 2012;6(4):398-406.
8. Kim EY, Kim YS, Park I, Ahn HK, Cho EK, Jeong YM. Prognostic significance of CT-determined sarcopenia in patients with small-cell lung cancer. J Thorac Oncol. 2015;10(12):1795-9.
9. Kimura M, Naito T, Kenmotsu H, Taira T, Wakuda K, Oyakawa T, et al. Prognostic impact of cancer cachexia in patients with advanced non-small cell lung cancer. Support Care Cancer. 2015;23(6):1699-708.
10. Kakinuma K, Tsuruoka H, Morikawa K, Furuya N, Inoue T, Miyazawa T, et al. Differences in skeletal muscle loss caused by cytotoxic chemotherapy and molecular targeted therapy in patients with advanced non-small cell lung cancer. Thorac Cancer. 2018;9(1):99-104.

11. Rossi S, Di Noia V, Tonetti L, Strippoli A, Basso M, Schinzari G, et al. Does sarcopenia affect outcome in patients with non-small-cell lung cancer harboring EGFR mutations? Future Oncol. 2018;14(10):919-26.
12. Minami S, Ihara S, Nishimatsu K, Komuta K. Low body mass index is an ındependent prognostic factor in patients with non-small cell lung cancer treated with epidermal growth factor receptor tyrosine kinase ınhibitor. World J Oncol. 2019;10(6):187-98.
13. Kawaguchi T, Ando M, Asami K, Okano Y, Fukuda M, Nakagawa H, et al. Randomized phase III trial of erlotinib versus docetaxel as second- or third-line therapy in patients with advanced non-small-cell lung cancer: docetaxel and erlotinib lung cancer trial (DELTA). J Clin Oncol. 2014;32(18):1902-8.
14. Coudert B, Ciuleanu T, Park K, Wu YL, Giaccone G, Brugger W, et al. Survival benefit with erlotinib maintenance therapy in patients with advanced non-small-cell lung cancer (NSCLC) according to response to first-line chemotherapy. Ann Oncol. 2012;23(2):388-94.
15. Ciuleanu T, Stelmakh L, Cicenas S, Miliauskas S, Grigorescu AC, Hillenbach C, et al. Efficacy and safety of erlotinib versus chemotherapy in second-line treatment of patients with advanced, non-small-cell lung cancer with poor prognosis (TITAN): a randomised multicentre, open-label, phase 3 study. Lancet Oncol. 2012;13(3):300-8.
16. Lee JK, Shin JY, Kim S, Lee S, Park C, Kim JY, et al. Primary resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in patients with non-small-cell lung cancer harboring TKI-sensitive EGFR mutations: an exploratory study. Ann Oncol. 2013;24(8):2080-7.
17. Thatcher N, Chang A, Parikh P, Rodrigues Pereira J, Ciuleanu T, von Pawel J, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (iressa survival evaluation in lung cancer). Lancet. 2005;366(9496):1527-37.
18. Garassino MC, Martelli O, Broggini M, Farina G, Veronese S, Rulli E, et al. Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type EGFR tumours (TAILOR): a randomised controlled trial. Lancet Oncol. 2013;14(10):981-8.
19. Kus T, Aktas G, Sevinc A, Kalender ME, Yilmaz M, Kul S, et al. Prognostic impact of initial maximum standardized uptake value of (18) F-FDG PET/CT on treatment response in patients with metastatic lung adenocarcinoma treated with erlotinib. Onco Targets Ther. 2015;8:3749-56.