Original Article

Sarcopenia is a Predictive Marker for Response to Erlotinib in Patients with Lung Adenocancer

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Abstract

Background: Adenocancer pathologic subtype, smoking history, and women gender have been known to predict the parameters such as the sensitivity to epidermal growth factor receptor tyrosine kinase inhibitors in advanced non-small cell lung cancer (NSCLC); however, we need new predictive markers as well as driver mutations for better treatment options. The aim of this study is to investigate the predictive role of sarcopenia in lung adenocancer patients treated with erlotinib. **Materials and Methods:** This study was designed as retrospectively. Skeletal muscle index (SMI) was measured with a single cross-sectional area of the muscle at the third lumber vertebra (L3, cm^2)/(height × height)(m^2). Sarcopenia was defined by median cutoff values of SMI of women (<28.2 cm^2/m^2) and men (<32.7 cm^2/m^2). The predictive role of sarcopenia and other parameters was assessed by the cox-regression model. **Results:** The median age was 56 years (range, 36–84). Median progression-free survival (PFS) was 38 (95% confidence interval [CI]: 21.3–54.6) weeks in the sarcopenic group and 49 (95% CI: 0–101.4) weeks in the nonsarcopenic group (P = 0.053). In multivariate analysis, the presence of sarcopenia and number of metastatis were the independent predictive factors for PFS. Disease control rate and overall survival were not significantly different between sarcopenic and nonsarcopenic groups. **Conclusion:** We found that the presence of sarcopenia and number of metastasis were a predictive marker in NSCLC patients treated with erlotinib. It is important to recognize sarcopenia early and manage patients accordingly.

Keywords: *Erlotinib, lung adenocancer, sarcopenia, skeletal muscle index*

Introduction

The discovery of active driver mutations paved the way to achieve longer survival rates with lower toxicity compared to cytotoxic chemotherapy in non-small cell lung cancer (NSCLC). Among them, the epidermal growth factor receptor (EGFR) is the most common driver mutation and we have had long experience in molecular-targeted drugs of EGFR tyrosine kinase inhibitors (TKIs). Although better progression-free survival (PFS) with the first/second-generation EGFR-TKIs has been demonstrated in the precence of exon 19 q deletion and exon 21 L858R point mutation, early tumor progression is inevitable in some cases.[1,2] Adenocancer pathologic subtype, smoking history, and women gender have been known to predict parameters the sensitivity to EGFR-TKIs in NSCLC; however, we need new predictive markers as well as driver mutations for better treatment options.[3,4]

Sarcopenia is an emerging biomarker considered a major component of cancer cachexia syndrome, which predicts poor outcomes in many types of cancer.[5-9] Although the prognostic value of sarcopenia in NSCLC patients treated with conventional chemotherapy has been demonstrated, the predictive value in lung adenocancer treated with EGFR-TKI in first, and latter line was uncertain. Sarcopenia is defined as the generalized and progressive loss of skeletal muscle mass and strength and low physical performance with a consequent risk of adverse outcomes according to the European Society for Clinical Nutrition and Metabolism (ESPEN) guideline.[10] Although muscle mass can be estimated by handgrip strength method, dual X-ray absorptiometry or bio-electric impedance analysis, the calculation of skeletal muscle area at the third vertebra level with computed tomography (CT) scanning has recently become a standard approach and that is easier to use.[10]

Sarcopenia is an important prognostic marker for the early and advanced stage

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of cancer. Since some patients experience rapid clinical deterioration with EGFR-TKIs without candidates for further treatment options, we need better predictive markers in this field. We aimed to clarify the predictive value of sarcopenia in lung adenocancer patients treated with erlotinib in the first and latter lines therapy.

Materials and Methods

Study design and patient selection

This study was conducted as retrospectively at a single center in Turkey. All clinical data were obtained from our medical records. Between 2011 and 2019, patients with histopathologically confirmed lung adenocancer treated with erlotinib in the first or latter lines at metastatic stage in Gaziantep University Oncology Hospital were screened. The study was approved by the Independent Ethics Committee of the Gaziantep University (decision no: 2019/456, date: 04.12.2019) and was conducted in accordance with the Helsinki declaration. In total, 35 patients with EGFR-sensitizing mutations who have available clinical data and CT scans within 1 month from the onset of EGFR-TKIs were included. Patients with exon 20 mutation and initial T790M, anaplastic lymphoma-kinase or ROS-1 rearrangement, and patients previously treated with immunotherapy were excluded.

Clinicopathological variables, including, age, gender, smoking habit, presence of EGFR-sensitizing mutation, treatment line, presence of central nervous system (CNS) metastasis, and number of metastatis were recorded. Erlotinib was started at a 150 mg/day dosage, orally, 1 h before or 2 h after meals, and gradually reduced to 100 mg/day if any toxicity develops over grad 2. The therapy was continued until disease progression or unacceptable toxicity. All patients were followed-up by CT scan according to response evaluation criteria in solid tumors (RECIST 1.1) every 3 months or immediately after the symptoms of clinical progression developed.

Computed tomography image analysis

Muscle mass was calculated by analyzing electronically recorded CT images before the onset of erlotinib treatment during the routine clinical practice. The third lumbar vertebra (L3) was considered the standard landmark. Skeletal muscle index (SMI) was measured with a single cross-sectional area of the muscle at the L3 (cm^2)/(height × height)(m^2). Sarcopenia was described as median cutoff values of SMI of women (<28.2 cm^2/m^2) and men (<32.7 cm^2/m^2).

Statistical analysis

Demographic and clinical characteristics were analyzed by the descriptive and frequency statistics. The Fisher's exact or Chi-square test was applied to evaluate the categorical variables. Median SMI was determined as the cutoff value, and then re-assessed according to gender. Survival analysis was obtained using the Kaplan–Meier method, and differences between the groups were compared with the log-rank test. PFS was determined as the time between the 1st day of erlotinib therapy to disease progression or death and presented as weeks. Overall survival (OS) was defined as the time between the date of starting erlotinib therapy to the date of last control or death and presented as months. A univariate analysis was used to examine the prognostic significance of gender, age, smoking habit, presence of CNS metastasis, number of metastasis, sarcopenia group, EGFR status, and treatment line with PFS and OS. According to the univariate analysis, prognostic factors with $P < 0.1$ were examined in the multivariate analysis. Hazards ratio (HR) with its 95% confidence interval (CI) was applied. $P < 0.05$ was defined as statistically significant. All of the statistical analyses were performed by the Statistical Package for the Social Sciences (SPSS) software version 22.0 for Windows (SPSS, Inc. Chicago, IL, USA).

Results

Patients' characteristics

Thirty-five NSCLC patients with histological subtype of adenocarcinoma treated with erlotinib were analyzed. The median age was 56 years (range, 36–84), and the majority of patients (85.7%) were under the age of 65 years. 54.3% of the patients were female, and the remaining was male. EGFR-sensitizing mutation was detected in 57.1% of the patients, EGFR-sensitizing mutation was not detected in 25.7% of the patients, and mutation status was not known in 17.1% of the patients. The most common EGFR-sensitizing mutation was exon 19 deletion (15 patients, 83.3%). Most of the patients were never smokers (62.9%). Patients and tumor characteristics are summarized in Table 1.

The patients were divided into two groups as <28.2 cm^2/m^2 for women <32.7 cm^2/m^2 for men according the median SMI value. We did not find a significant difference between sarcopenia groups and age, gender, smoking status, EGFR mutation status, treatment line, and CNS metastasis [Table 1].

Survival analysis according to clinicopathological parameters and sarcopenia

Median follow-up time was 25.6 (6.1–68.6) months and 94.3% of patients (n = 33) died as a result of the disease progression. In the whole cohort, median PFS was 44 (33.4–54.6) weeks. Median PFS was 38 (95% CI: 21.3–54.6) weeks in sarcopenic group and 49 (95% CI: 0–101.4) weeks in nonsarcopenic group (P = 0.053). While male gender, younger age, smoking habit, erlotinib use after first-line, number of metastasis, and the presence of sarcopenia were associated with shorter PFS, EGFR-sensitizing-mutation, and CNS metastasis had not effect on PFS. In the multivariate analysis, the presence of sarcopenia (HR: 2.605; 95% CI: 1.115–6.087, P = 0.027) and number of metastasis were the

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*
Age (years), median (range)	56 (36-84)	55 (36-75)	58 (39-84)	0.310
Age group				
<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

independent predictive factors for PFS [Table 2]. The cox regression anlaysis according to the presence of sarcopenia for PFS is shown in Figure 1.

Furthermore, there was no difference in OS between sarcopenic (15.7 months, 95% CI: 5.9–25.4) and nonsarcopenic (24.4 months, 95% CI: 11.7–37.1) groups (HR: 1.826; 95% CI: 0.859–3.884, P = 0.138). Contrarily, male gender (P = 0.012), smoking habit (P = 0.006), and erlotinib use after first line (P = 0.016) were associated with poor OS in univariate analysis [Table 3].

The disease control rate was not significantly different between sarcopenic and nonsarcopenic groups (P = 0.939).

Discussion

The predictive value of sarcopenia in NSCLC patients responding to EGFR-TKIs with or without EGFR-sensitizing mutations in the first or latter line

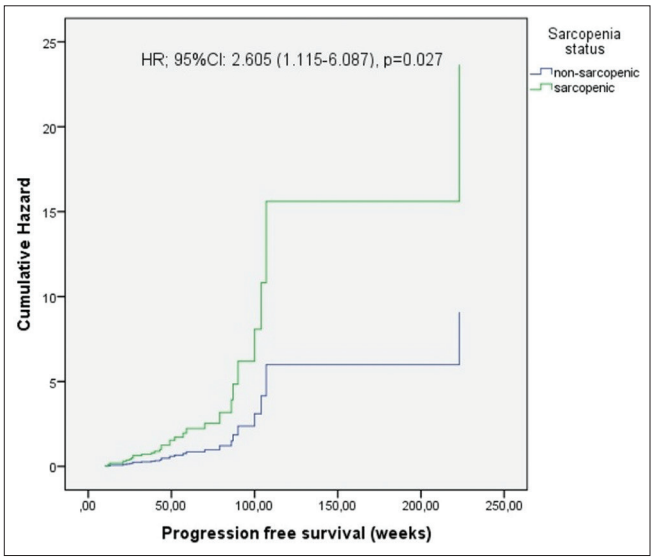

Figure 1: Cox regression anlaysis according to the presence of sarcopenia for progression free survival

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*	HR (95%CI)	*P*
Age				
<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

were studied in the present study. While male gender, younger age, smoking habit, erlotinib use after first-line, number of metastatic site, and the presence of sarcopenia were associated with shorter PFS in univariate analysis, EGFR-sensitizing-mutation and CNS metastasis were not effect on PFS. Moreover, the presence of sarcopenia was found to be sole predictive marker together with the number of metastasis in such use.

Although EGFR-sensitizing mutation the most important predictive tool for response to EGFR-TKIs, its overweight decreases in the latter line use. In this respect, we need further predictive clinicopathological parameters to understand the benefit of EGFR-TKIs use in the latter line. In newly diagnosed patients with advanced NSCLC treated with chemotherapy, the poor prognostic impact of sarcopenia at the beginning of treatment and during chemotherapy has been demonstrated.[8] However, the impact of chemotherapy on muscle loss during treatment was much higher than EGFR-TKIs.[9] In this regard, the effect of sarcopenia on the prognosis of patients treated with first-line EGFR-TKIs has been investigated over time. Rossi *et al*. reported that sarcopenia was an independent poor prognostic factor for OS (12.6 vs. 23.5 months, $P = 0.035$); however, they did not detect any difference in PFS in terms of sarcopenia in patients taking gefitinib (11 vs. 14 months, $P = 0.26$).[11] In another study, the relationship between psoas muscle index (PMI) and survival was investigated in patients receiving the first and second generation EGFR-TKIs.[12] No significant difference was found in neither PFS ($P = 0.18$) nor OS ($P = 0.37$) with PMI. Despite inconsistent results about the prognostic value of sarcopenia, it was shown that it does not have a predictive value in patients with EGFR-sensitizing mutation responding to EGFR-TKIs at the first line.[11,12] In light of the present study and our knowledge about of this topic, we can claim that EGFR-sensitizing mutation is the main determinant for response to EGFR-TKIs in first-line treatment; however, sarcopenia may be leading factor for subsequent lines, regardless of EGFR-sensitizing mutation.

While EGFR-sensitizing mutations are the main predictive markers for clinical outcome with the therapy of EGFR-TKIs in progressive NSCLC, DELTA trial assessing the efficacy of erlotinib after first line treatment in patients with EGFR-mutant and wild-type tumor, showed that PFS was similar and statistically insignificant with a duration of 9.3 versus 7 months in erlotinib arm and docetaxel arm,

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		
<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)	0.460
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

respectively (HR 0.96; 95% CI: 0.51–1.79; $P = 0.91$).[13] Thus, the existence of the EGFR-sensitizing mutation is not a sole predictive marker for the outcome of patients treated with EGFR-TKIs after the first-line therapy. In patients with EGFR mutation as well as wild-type tumors, survival advantages with erlotinib were obtained after first/second-line chemotherapy and maintenance treatment.[14,15] The survival benefit of erlotinib does not only depend on the presence of EGFR-sensitizing mutations but additionally other molecular mechanisms and pathogenetic factors probably contribute to its therapeutic effect.[16] Phase III, placebo-controlled trial assessing the effect of gefitinib on survival as after first-line therapy in progressive NSCLC patients with unknown EGFR status revealed significantly better survival in the gefitinib group compared to the placebo group in no-smokers (median OS 8.9 vs. 6.1 months, $P = 0.012$) and Asian patients (median OS 9.5 vs. 5.5 months, $P = 0.01$).[17] On the other hand, TAILOR study showed that smoking habit is not predictive for response.[18] In this regard, new indicators are required to predict the response to EGFR-TKIs, which are widely used in first-line and other therapies**.** In a previous study, a new predictive marker based on maximum standardized uptake value (SUVmax) on fluorine-18 fluorodeoxyglucose positron emission tomography/CT has been introduced in this field.[19] Despite the predictive value of the EGFR-sensitizing mutation, erlotinib has worked at low efficiency in patients with SUVmax values >11. In addition, erlotinib efficiency in patients with SUVmax values >11 in wild-type and EGFR-unknown groups was not shown. In this study, we demonstrated the independent predictive value of sarcopenia for response to EGFR-TKI in patients with or without EGFR sensitizing mutation, although no prognostic significance was found. Whereas the presence of EGFR-sensitizing mutation was not a decisive predictive marker, first-line use is a determinative predictive marker for response to EGFR-TKIs. Previous studies evaluating the predictive impotance of sarcopenia for response to EGFR-TKIs did not showed the relationship between sarcopenia and response.[11,12] This may be related to the assessment of only first-line use in patients with EGFR-sensitizing mutation is the main determinant biomarker in this area. On the other hand, according to the present study, sarcopenia may also be a good predictor biomarker after first-line use in patients also without EGFR-sensitizing mutation.

There were several limitations of our study. The sample size was small and heterogeneous in terms of line of erlotinib therapy and EGFR mutation status. In addition, the study was designed retrospectively. However, despite the low number of patients and heterogen cohort, we found a remarkable significance in all groups in terms of predictive value of sarcopenia for response to erlotinib. Therefore, we think it is worth considering the findings of this study to pave the way of designing prospective studies with more patients.

Conclusion

We found that the presence of sarcopenia and number of metastasis were a predictive marker in NSCLC patients treated with erlotinib. It is important to recognize the sarcopenia early and manage the patients accordingly.

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Conflicts of interest

There are no conflicts of interest.

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