RESEARCH ARTICLE

Clinical Outcomes and Prognostic Factors Associated with the Response to Erlotinib in Non-Small-Cell Lung Cancer Patients with Unknown EGFR Mutational Status

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Abstract

Background: The efficacy of erlotinib is controversial in patients with unknown EGFR mutational status. The aim of this study was to identify the clinicopathological factors that are predictive of erlotinob treatment outcomes for NSCLC patients with unknown EGFR mutational status. Materials and Methods: A retrospective analysis of 109 patients with advanced NSCLC who had previously failed at least one line of chemotherapy and received subsequent treatment with erlotinib (150 mg/day orally) was performed. A Cox proportional hazard model for univariate and multivariate analyses was used to identify the baseline clinical parameters correlating with treatment outcome, expressed in terms of hazard ratios (HRs) and 95% confidence intervals. Results: The median treatment duration was 15 weeks (range, 4-184). The disease control rate was 55%, including disease stability for ≥3 months for 40% of the patients. Median progression-free survival and median overall survival (OS) were 4.2 and 8.5 months, respectively. The Cox model indicated that an Eastern Cooperative Oncology Group performance status (ECOG PS) ≥2 (HR 3.82; p<0.001), presence of intra-abdominal metastasis (HR 3.42; p=0.002), 2 or more prior chemotherapy regimens (HR 2.29; p=0.021), and weight loss >5% (HR 2.05; p=0.034) were independent adverse prognostic factors for OS in NSCLC patients treated with erlotinib. Conclusions: This study suggests that NSCLC patients should be enrolled in erlotinib treatment after a first round of unsuccessful chemotherapy to improve treatment success, during which they should be monitored for intra-abdominal metastasis and weight loss.

Keywords: Non-small-cell lung cancer - erlotinib - prognostic factors - second-line - EGFR

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Introduction

Lung cancer is the most common cause of cancer-related mortality worldwide, accounting for 32% and 25% of all cancer-related deaths in males and females, respectively (Parkin et al., 2005). Patients with advanced non-small-cell lung cancer (NSCLC) have poor prognoses and 5-year survival rates<5-10%. Most patients with advanced disease status eventually show tumour progression after standard first-line platinum-based combination chemotherapy. Current data suggest that chemotherapy has reached a therapeutic plateau, indicating a continuing need for new and more effective treatment strategies (Mazzoni et al., 2011).

Recently, several key molecules involved in signal transduction pathways and angiogenesis have been identified as therapeutic targets. Overexpression of the epidermal growth factor receptor (EGFR) is reported in 40 to 80% of NSCLC cases (84% of squamous cell carcinomas and 65% of adenocarcinomas) (Veale et al., 1993). The EGFR is a cell surface receptor expressed on airway epithelial cells and activated through tyrosine kinase-dependent oligomerisation. Dysregulation of receptor function due to mutation, overexpression or gene amplification can promote cell proliferation, tumour progression, invasion, and metastasis (Schlessinger, 2000; Ciardiello et al., 2008).

Currently, erlotinib (Tarceva®) is the only EGFR inhibitor approved by the Food and Drug Administration for the treatment of patients with NSCLC. Erlotinid is a reversible tyrosine kinase inhibitor (TKI) specifically designed to prevent the activation of EGFR. The National Cancer Institute of the Canada Clinical Trials Group (NCICCTG; BR.21 trial) (Shepherd et al., 2005) demonstrated the treatment efficacy of erlotinib monotherapy compared to placebo for patients with advanced NSCLC who had relapsed or recurred after chemotherapy and were not eligible for further chemotherapy. This treatment significantly improved overall survival (OS). Moreover, a better response to tyrosine TKI therapy appears to be associated with certain molecular and clinical characteristics, such as an

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adenocarcinoma histotype, Asian ethnic origin, female gender, skin toxicity and non-smoking status (Shepherd et al., 2005). EGFR mutation is the most relevant predictor of response to treatment (Tsao et al., 2005; De Maio et al., 2010). Still, the role of erlotinib is controversial in patients with unknown EGFR mutational status (Karam et al., 2012). Other than the BR.21 trial, other studies have established erlotinib as a standard, even in patients without mutational analysis (Shepherd et al., 2005; Cappuzzo et al., 2010; Ciuleanu et al., 2012). On the other hand, little attention has been given to the prognostic factors for patients with NSCLC in this era of molecular-targeted therapy. This retrospective study describes the outcome of a patient population with advanced NSCLC and a mixed wild-type/mutant EGFR status treated with erlotinib after chemotherapy and proposes a prognosis model based on their clinicopathological features

Materials and Methods

Eligibility criteria

We retrospectively reviewed the records of 147 metastatic or relapsed NSCLC patients who had been treated with erlotinib as a salvage therapy at the Institute of Oncology, Istanbul University, Istanbul, between July 2006 and September 2010. Of these patients, 38 were not available for evaluation because of the short duration of treatment (<4 weeks), loss to follow-up, or absence of a measurable tumour. Clinical data with complete information were available for 109 patients. Staging was performed according to the TNM classification, 7th version (Goldstraw et al., 2007). Patients were considered candidates to receive erlotinib if they had histologically or cytologically confirmed NSCLC and met the following criteria: unresectable stage IIIB or IV disease; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-3; adequate haematologic, renal and hepatic function; previous failure of at least one line of chemotherapy; and no prior treatment with anti-EGFR agents. Patients with stable or controlled brain metastases who received whole-brain radiotherapy or stereotactic radiosurgery were included in this study. No patient received concurrent chemotherapy or other experimental agents during erlotinib treatment. Patients with squamous cell subtypes were not included. As per institutional policy, all patients signed a written informed consent before treatment. The Institutional Review Board at our university approved the study protocol before the clinical records were accessed.

Treatment regimen and toxicity

Oral erlotinib was administered at a dose of 150 mg/day and continued until disease progression, unacceptable toxicity or patient refusal or death. Erlotinib treatment was discontinued when there was no improvement of a grade 3 non-haematologic toxicity after a 4-week interruption or in cases of grade 4 non-haematologic toxicity or grade 2 pneumonia. Laboratory results, adverse events, and other symptoms were graded using the National Cancer Institute Common Toxicity Criteria (version 3.0) (Trotti et al., 2003).

Baseline clinicopathological features before erlotinib treatment

Data were collected pertaining to patient demographics, smoking status, ECOG PS, histological type and grade, initial stage at diagnosis, number of prior regimens, nature of prior regimens (platinum vs. non-platinum), sites of metastatic spread, time interval from diagnosis to erlotinib, duration of response to erlotinib, and response to erlotinib. The metastatic sites were divided into 5 regions, as follows: i) the central nervous system (CNS) including the brain, spinal cord, and leptomeninges; ii) lung to lung, including metastasis to the contralateral lung or a different lobe of the ipsilateral lung; iii) intra-abdomen, including the liver, spleen, adrenal gland, intra-abdominal lymph nodes, and peritoneum; iv) bone; and v) skin/soft tissues. Smoking status was defined as never-smoker (<10 pack-years in life), current smoker (>10 pack-years and continuing smoking during the last year) and former smoker (>10 pack-years in life but quit more than 1 year prior).

Determination of EGFR mutations

In the available NSCLC patients (n=65), EGFR exon 19 deletion mutations and EGFR L858R point mutations were analysed using pyrosequencing real-time polymerase chain reaction (PCR)-based methods from paraffin blocks of tissue obtained before treatment. The PCR conditions have been described previously (Paez et al., 2004).

Erlotinib treatment outcome parameters

The treatment outcomes were response rate, disease control rate, OS, and progression-free survival (PFS). To assess tumour response, we considered the best response obtained during erlotinib treatment. OS was defined as the time elapsed from the date of erlotinib treatment initiation to the date of death. PFS was defined as the time from the date of erlotinib treatment initiation to the date of disease progression or death from any cause. Radiological assessments of the tumour were performed at erlotinib treatment onset and repeated every 6 to 8 weeks until disease progression. Tumour response was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 criteria (Therasse et al., 2000). A complete response (CR) was defined as the total disappearance of the tumour mass, and a partial response (PR) was defined as a ≥30% decrease in the sum of the longest diameter of the target lesions. A CR or PR had to be confirmed at least 4 weeks after its initial documentation. Progressive disease (PD) was defined as a ≥20% increase in the sum of the longest diameter of the target lesions or the appearance of new lesions. Tumour responses that did not meet either the PR or PD criteria were defined as stable disease (SD), and SD required disease control for at least 6 weeks.

Statistical analyses

The quantitative data are presented as the mean, standard error, median, minimum and maximum, whereas the qualitative analyses are presented as the frequency and percentage. Time-to-event analyses were performed using the Kaplan-Meier method, and the curves were compared using the log-rank test. A Cox proportional

hazards regression model was used for both univariate and multivariate analyses to identify the prognostic factors for patient survival. The significant prognostic variables in the univariate analysis were included in the multivariate analyses as follows: ECOG PS (ECOG 0-1 vs. 2-3), weight loss before erlotinib treatment (<5 vs. ≥5%), smoking status (ever smokers vs. never smokers), number of prior regimens (1 vs. ≥2), and intra-abdominal metastasis (yes vs. no). All p values represent 2-sided tests of statistical significance, and p values<0.05 were considered significant. SPSS version 16.0 (SPSS Inc., Chicago, IL) was used for the statistical analyses.

Results

Baseline patient characteristics

The clinical characteristics of the 109 patients are listed in Table 1. The median patient age was 57 years (range, 24–80 years), and the sample comprised 68 males (62%) and 41 females (38%). There were 59 (54.1%) smokers (>10 pack-year smoking history). The tumour histology types included adenocarcinoma (n=80) and large cell (n=2), bronchioloalveolar (n=9) and poorly differentiated (n=18) tumours. Among the 65 patients available, only 11 (17%) presented EFGR mutations: 8 patients with exon 19 deletions and 3 patients with the exon 21 L858R point mutation. The median duration of treatment was 15 weeks (range, 4–184 weeks).

Response rate and survival

At the time of analysis, the median follow-up time was 17.1 months (range, 1.4-68.5), and there were 60 deaths. The median OS and PFS times were 8.5 months (95% confidence interval (CI), 2.58-14.37) and 4.2 months (95%CI, 2.61-5.87), respectively. Based on the RECIST criteria, the erlotinib treatment resulted in a 55% disease control rate (including CR, PR and SD), with 40 patients stabilised for ≥3 months, 2 cases of CR and 13 cases of PR (Table 2). Response data were available for 100 (92%) patients; 4 patients were lost to follow-up, and 5 patients discontinued erlotinib due to adverse effects prior to response assessment.

Adverse effects of the erlotinib treatment

The most frequent adverse event was skin toxicity, including papulopustular rash, acne, itching, and dry skin, which were observed in 65 (60%) patients (grade 2 or more: 34 patients; 31%). Acne was mainly localised to the face, while the rashes were equally distributed on the face and upper trunk. Other grade 2 or higher adverse events were fatigue in 20 patients (18%), nausea in 10 patients (9%), anorexia in 8 patients (7%), diarrhoea in 7 patients (6%) and mucositis in 3 patients (3%). No significant grade 3 or higher haematological toxicities were noted. Six per cent of patients (n=9) discontinued erlotinib because of toxic effects. Interstitial lung disease was observed in one patient. There was no treatment-related death.

Treatment regimen withdrawals and adjustments

The main reason for treatment withdrawal was disease progression (63 patients, 87.5%), followed by toxicity (9 patients, 12.5%). The median duration of treatment interruption was 2 weeks. Based on the evaluation of the treating physician, no attempts were made to lower the dose in patients who were intolerant of 150 mg; these patients were referred to supportive care due to PS decline.

Relationships between baseline characteristics and clinical outcome

The efficiency of erlotinib may be influenced by a number of factors aside from the EGFR mutations, such as disease severity, the overall health status of the patients, and the number of prior chemotherapy regimens.

Table 1. Patient Demographics and Baseline Clinical Characteristics

Characteristic			n (%)
Age (years), median (min-max)			57 (24-80)
Gender	Male		68 (62.4)
	Female		41 (37.6)
Smoking status	Present or former smoker		59 (54.1)
	Never smoked		43 (39.4)
	Unknown		7 (6.5)
Histopathological findings			
	Adenocarcinoma		80 (73.4)
	Large-cell carcinoma		2 (1.8)
	Bronchoalveolar carcinoma		9 (8.3)
	Poorly differentiated carcinoma		18 (16.5)
ECOG performance status		0-1	58 (58.6)
		2	36 (36.4)
		3	5 (5.0)
No. of disease sites		0	19 (17.6)
		1	52 (48.1)
		2	27 (25.0)
		≥3	10 (9.3)
Disease stage at initial diagnosis		IIIB	19 (17.4)
		IV	90 (82.6)
Prior systemic chemotherapy			
	One regimen		61 (56.0)
	Two or more regimens		48 (44.0)
	Prior radiotherapy		67 (70.5)
Prior surgery	No		88 (80.7)
	Lobectomy		15 (13.8)
	Pneumonectomy		4 (3.7)
	Wedge Resection		2 (1.8)
Response to first-line chemotherapy			
	PR		31 (28.4)
	CR		2 (2.8)
	SD		37 (33.9)
	PD		28 (25.7)
	Not evaluable		10 (9.2)
Time from diagnosis/surgery to erlotinib initiation			
	<12 months		68 (64.2)
	≥12 months		38 (35.8)

*ECOG:Eastern Cooperative Oncology Group; PR: partial response; CR: complete response; SD: stable disease; PD: progressive disease

Table 2. Objective Responses, Clinical Benefits and Disease Control Rates

	n (%)
Objective response	15 (00.0)
Complete response	2 (02.0)
Partial response	13 (13.0)
Stable disease for ≥3 months	40 (40.0)
Disease control rate	55 (55.0)

Therefore, we conducted univariate and multivariate analyses between the baseline parameters measured before the onset of erlotinib treatment and the clinical outcome parameters for patients without EGFR mutations. The univariate analyses revealed that a decreased OS was significantly associated with the following variables: ECOG PS ≥2, 2 or more prior regimens, ever- or current smoking, weight loss ≥5%, and the presence of intra-abdominal metastasis. Gender, age, response to first-line chemotherapy, number of metastatic sites, metastases to the lung, bone or CNS and the presence or absence of skin rash did not appear to affect OS (Table 3). In our analysis of 65 patients with a known EGFR mutation status, the patients with an EGFR mutation showed a trend toward a favourable OS (p=0.06) compared with patients with the wild-type EGFR gene.

Multivariate analyses revealed that ECOG PS ≥2 (HR 3.82; 95%CI 1.97-7.44%), the presence of intra-abdominal metastasis (HR 3.42; 95%CI 1.56-7.52%), a number of prior regimens ≥2 (HR 2.29; 95%CI 1.13-4.65%) and weight loss ≥5% (HR 2.05; 95%CI 1.05-3.98%) were independent prognostic factors for decreased OS (Table 4).

Development of a prognostic model for erlotinib

The parameters identified by the univariate and multivariate analyses were used to develop a new prognosis model for the treatment of lung cancer with erlotinib. Patients who screened positive for EGFR mutations were excluded to unmask the contribution of other parameters, and the remaining patients were classified into three categories based on each adverse factor. OS decreased significantly as the number of adverse predictive factors increased. Risk scoring in the prognostic model was in accordance with the number of significant risk factors in the multivariate analysis for OS. According to the prognostic model, the patients were categorised into the following 3 prognosis groups based on each adverse prognostic factor: 0 (favourable prognosis group), 1

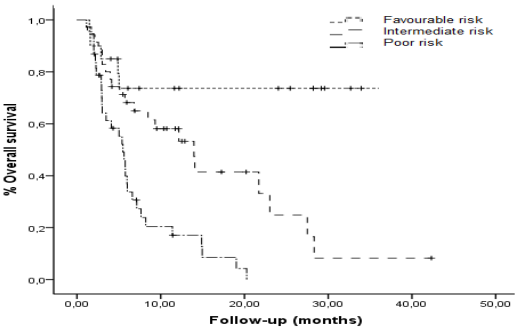

Figure 1. Kaplan-Meier Curves for Overall Survival in Patients who were Treated with Erlotinib in the Indicated Risk Groups (Favourable, Intermediate and Poor), According to the Prognostic Model

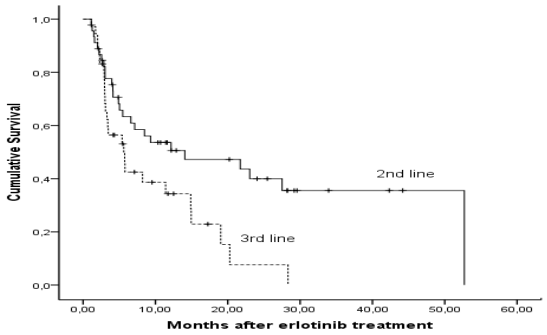

Figure 2. Overall Survival Rates for Erlotinib Based on Its Use as a Second- or Third-Line Therapy

Table 3. Univariate Analysis of the Factors Associated with Overall Survival

		n	Median OS	95%CI	p value
ECOG PS	0–1	51	28.3	17.1-39.1	<0.001
	≥2	39	4.9	2.4-7.4	
Gender	Male	68	6.8	4.5-9.1	0.73
	Female	41	11.4	2.9-19.9	
Time from diagnosis to erlotinib treatment					
	≤1 year	59	7.1	2.9-11.3	
	>1 year	29	14.8	2.3-27.5	0.62
Prior RT	Yes	58	8.5	0.0-17.1	
	No	27	25.0	2.1-22.2	0.68
No. of metastatic sites					
	≤2	61	9.3	0.8-17.9	
	>2	34	6.6	2.7-10.6	0.61
Lung metastasis					
	Yes	52	6.8	2.2-11.5	
	No	43	11.4	2.8-20.1	0.70
Intra-abdominal metastasis					
	Yes	22	5.4	4.1-06.9	
	No	63	13.9	7.5-20.5	0.046
Bone metastasis					
	Yes	22	14.8	4.3-25.4	
	No	61	5.9	2.9-09.1	0.37
CNS metastasis					
	Yes	17	11.4	0.0-25.2	
	No	70	6.8	2.9-10.7	0.61
Weight loss	<5%	37	5.9	4.2-07.8	
	≥5	56	13.9	0.0-30.2	0.025
No. of prior regimens					
	1	46	14.1	0.0-30.1	
	≥2	36	5.6	2.8-08.5	0.016
Prior platinum-based therapy					
	Yes	80	8.4	1.4-15.5	
	No	14	5.0	2.9-07.1	0.29
Response to first-line chemotherapy					
	CR+PR+SD	64	11.4	4.3-18.5	
	Progressive disease	26	6.0	0.0-13.5	0.28
Smoking status					
	Present or former smoker	56	5.6	03.8-07.4	
	Never smoked	32	20.6	10.1-30.4	0.039
Skin rash	Grade 0-1	66	6.8	3.4-10.2	
	Grade 2+	29	13.9	0.6-27.2	0.22

*OS: overall survival; CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group performance status; RT: radiotherapy; CR: complete response; PR: partial response; SD: stable disease

Table 4. Multivariate Analysis of the Factors Associated with Overall Survival

Parameter	Hazard Ratio	95%CI	p value
ECOG PS ≥2	3.82	1.97-7.44	<0.001
Presence of intra-abdominal metastases	3.42	1.56-7.52	0.002
Number of prior regimens ≥2	2.29	1.13-4.65	0.021
Presence of weight loss (>5%)	2.05	1.05-3.98	0.034

(intermediate prognosis group), and 2-4 (poor prognosis group). The median OS from the initiation of the salvage erlotinib treatment for the favourable (n=20) group was not calculated. For the intermediate (n=35) and poor prognosis (n=43) groups, the median OS times were 13.9 months (95%CI, 10.88-17.04) and 5.5 months (95%CI, 3.47-7.50), respectively (Figure 1; p <0.001). Likewise, the median PFS of the favourable group had not been achieved within 40 months after the onset of erlotinib treatment. For the intermediate and poor groups, the median PFS times were 7.9 months (95%CI, 0.00-16.28) and 2.9 months (95%CI, 2.48-3.37), respectively (p<0.001). In addition, there was a significant difference in OS after erlotinib treatment initiation when the patients were stratified by their use of erlotinib as a second- or third-line treatment (Figure 2; p=0.02). This model suggests that early erlotinib treatment improves the survival of lung cancer patients

Discussion

The highly variable response of patients with advanced NSCLC to the EGFR TKI erlotinib demands the development of prognostic predictive models. The current focus is on the predictive power of EGFR mutations, a high EGFR gene copy number, and k-ras mutations (Eberhard et al., 2005; Shepherd et al., 2005; Ahn et al., 2008). Unfortunately, standardised clinical tests for the molecular predictors of erlotinib treatment outcome are expensive and not readily accessible in most hospitals. Finally, the efficiency of erlotinib is unclear in patients without mutational analysis in the second line or in subsequent line settings. Our goal was to design a simple prognostic model of patient outcome based on readily available clinical variables to assist clinicians in selecting NSCLC patients mostly likely to benefit from EGFR TKI treatment. For this reason, we used a mixed population of NSCLC patients with wild-type and mutated EGFRs to develop a model representative of the general patient population. Based on the 4 prognostic factors of OS derived from multivariate analyses, the patients were categorised into 3 prognosis groups (good, intermediate and poor) with significantly different risks of disease progression and survival curves. This is the first study of this population in Turkish patients.

Erlotinib is generally considered a second- or third-line treatment option for NSCLC patients facing unsuccessful surgery and chemotherapy. The present study reported a positive treatment response in 55% of the patients. The drug stabilised the disease in 40% of the patients for ≥3 months, whereas CR and PR were reported in 2% and 13% of the patients, respectively. Additionally, the median PFS (4.2 months) and OS (8.5 months) of our patient cohort are comparable with the results of the previous, randomised BR.21 study (2.2 and 6.7 months, respectively) (Shepherd et al., 2005). Overall, these data demonstrate that the responsiveness of our patient groups was consistent with previous reports of randomly selected NSCLC patients with unknown EGFR mutational status.

Several cooperative groups have examined their databases to determine the prognostic factors for patients receiving systemic chemotherapy and to identify the most suitable lung cancer patients for treatment (O'Connell et al., 1986; Albain et al., 1991; Paesmans et al., 1995; Massarelli et al., 2003; Hoang et al., 2005). However, in general, these analyses included only patients receiving first-line chemotherapy and cytotoxic therapy (Massarelli et al., 2003). Few reports have studied the prognostic factors for patients with NSCLC receiving second- or even third-line targeted therapies (Massarelli et al., 2003; Hsu et al., 2012). Our scoring system includes clinical factors instead of molecular markers. Therefore, this system is more convenient for daily practice.

Florescu et al. (2008) proposed a clinical prognostic index for patients treated with erlotinib in the NCICCTG Study BR.21. Ten factors (smoking history, PS, weight loss, anaemia, lactic dehydrogenase, response to prior chemotherapy, time since diagnosis, number of prior regimens, EGFR copy number, and ethnicity) were predictive of OS in erlotinib-treated patients and used in a prognostic model. Of these prognostic factors, PS, weight loss, and the number of prior regimens played a significant prognostic role for OS in our study. In two recent retrospective studies, an ECOG PS of 2 or more, elevated serum LDH, and the absence of skin rash (Kim et al., 2010), as well as low BMI, stage IV disease, anaemia at diagnosis, and male gender (Hsu et al., 2012), were shown to be adverse prognostic factors for OS. Unlike these previous studies, the presence of an intra-abdominal metastasis was a negative prognostic factor for survival in patients with metastatic NSCLC treated with erlotinib in our study. Similarly, in another study, an intra-abdominal metastasis was an unfavourable prognostic factor for OS during gefitinib treatment (Park et al., 2009).

Smoking history has been noted as a prognostic marker for survival in many clinical trials (Miller et al., 2004; Shepherd et al., 2005; Thatcher et al., 2005). However, in our study, smoking history was not significantly associated with OS. This finding is similar to the results of two recent Asian studies (Uhm et al., 2009; Kim et al., 2010). These studies reported that, on a multivariate level, smoking status did not retain significance for OS or time to progression in patients with advanced NSCLC who were treated with erlotinib as a salvage therapy.

Erlotinib, docetaxel, and pemetrexed are approved for the second-line treatment of NSCLC, although no direct data from large clinical trials are available. Recently, ınvestigators undertook the Tarceva in treatment of advanced NSCLC study to assess the efficacy and tolerability of second-line erlotinib versus chemotherapy in patients with refractory NSCLC (Ciuleanu et al., 2012). No significant differences in efficacy were noted between patients treated with erlotinib and patients treated with docetaxel or pemetrexed. The median OS was 5.3 months (95%CI, 4.0-6.0) with erlotinib and 5.5 months (95%CI, 4.4-7.1) with chemotherapy (hazard ratio [HR] 0.96; 95%CI, 0.78-1.19; log-rank p=0.73). In our study, undergoing 2 or more regimens before erlotinib treatment (HR 2.29; 95%CI, 1.13-4.65%; p=0.021) was an independent prognostic factor for a decreased OS. In contrast to our study, other retrospective studies have shown that OS after erlotinib use does not differ, regardless of its use as a second- or third-line therapy and whether

it is used in patients with recurrent, metastatic NSCLC (Ailawadhi et al., 2009; Aoki et al., 2012). Thus, taking into account the patient's preference and toxicity profile, especially in patients with comorbidities and marginal functional status, erlotinib use in second-line settings may be more convenient than chemotherapy.

More recently, the SATURN (Sequential Tarceva in Unresectable NSCLC) trial investigated the effect on PFS of erlotinib as maintenance therapy in patients with non-progressing disease after first-line platinum-doublet chemotherapy(Cappuzzo et al., 2010). That trial provided strong evidence that EGFR mutational testing should not be performed in settings after first-line chemotherapy. Compared with placebo, erlotinib resulted in significantly prolonged PFS in all analysable patients regardless of EGFR status (12.3 weeks vs. 11.1 weeks for placebo; HR: 0.71; 95%CI: 0.62 to 0.82; p<0.0001). A PFS benefit was observed in both EGFR mutation-positive (HR: 0.10; p<0.0001) and wild-type EGFR patients (HR: 0.78; p=0.0185). A greater benefit from erlotinib was noted in EGFR mutation-positive tumours, but both groups benefited. The secondary endpoint was OS, which was prolonged with erlotinib (median overall survival: 12.0 months vs. 11.0 months with placebo; HR: 0.81; 95%CI: 0.70 to 0.95; p=0.0088). Unlike this study, the superiority of docetaxal over erlotinib was demonstrated for EGFR mutation-negative, wild-type patients in second-line settings in the phase III TAILOR trial (at the ASCO 2012 meeting).

The current study has several limitations. First, the study sample was relatively small and derived from a single oncology centre in Turkey. Although we developed this prognostic model with readily available clinical parameters to make it easily applicable in clinical practice, this retrospective study is limited by selection, exclusion, and recall biases. In addition, the patients analysed in this study were Turkish. Given the ethnic differences in terms of erlotinib response and clinical benefit from EGFR TKIs, patient ethnicity must be considered a factor when applying this prognostic model. For these reasons, prospective investigations of clinical and molecular features in a large number of patients from other countries with NSCLC will be required.

In conclusion, this study suggests that NSCLC patients should be enrolled in erlotinib treatment after a first round of unsuccessful chemotherapy to improve treatment success, during which they should be monitored for intra-abdominal metastasis and weight loss. Our prognostic model, which is based on readily available variables, may be useful in identifying patients with unknown EGFR mutation status who might be responsive to erlotinib therapy and in making decisions in clinical practice. This prognostic model must be subjected to prospective validation to confirm its prognostic and predictive utility. Erlotinib may be more effective in a second-line setting than in third-line or subsequent settings.

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