Erlotinib Monotherapy in Patients with Advanced Non-small Cell Lung Cancer: An Effective Approach with Low Toxicity

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Abstract. *Background: Treatment of non-small cell lung cancer (NSCLC) with tyrosine kinase inhibitors (TKIs) of epidermal growth factor receptor (EGFR) and particularly erlotinib (Tarceva) has been a field of intense research. This retrospective study was conducted to assess the efficacy of erlotinib and its impact on survival. Patients and Methods: Patients with stage IIIB or IV, advanced or recurrent metastatic NSCLC were included in the study and were administered erlotinib 150 mg daily, at different lines of treatment. Results: Thirty-six patients were included in the study: 29 (81%) male, 7 (19%) female. At the time of analysis, all patients had progressed and died. Median progression-free survival (PFS) was 4 months ± 2.43 months (range 0-8 months), whereas median overall survival (OS) was 7 months ± 2.65 months (range 3-15 months). Patients with ECOG performance status of 0 or 1 had better OS and significantly higher PFS rates. Overall response rate was 16.7%, while the disease control rate was 81%. Conclusion: Erlotinib is effective and well tolerated in pretreated patients with advanced NSCLC and a good performance status.*

Non-small cell lung cancer (NSCLC) accounts for 75-80% of new lung cancer cases and the majority of patients present with advanced inoperable or metastatic disease (Stage IIIb or IV) (1).

Although surgery is crucial for localized disease, a large proportion of these patients will eventually recur, experiencing metastatic disease (2). The prognosis for such patients is poor, with 5-year survival rates of less than 10% (3). Median survival for patients with locally advanced or metastatic disease is 18 and 9 months, respectively (4).

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For first-line treatment of patients with unresectable advanced (Stage IIIb/IV) NSCLC, platinum-based doublets are the standard treatment (5, 6). The introduction of third generation cytotoxic agents (such as paclitaxel, docetaxel, gemcitabine, vinorelbine and irinotecan) achieved improvements in tumor response and tolerability, but only modest improvements in survival, and it may be that chemotherapy has reached its maximum potential (7-9).

A new modality for treatment of cancer is molecular-targeted therapy that blocks receptors stimulating cell proliferation and inhibiting apoptosis (10). Along this line, epidermal growth factor receptor (EGFR) inhibitors may be an effective treatment for selected subgroups of patients with NSCLC. Three EGFR inhibitors have been widely used and studied in clinical trials of patients with NSCLC and other cancer types: cetuximab, gefitinib and erlotinib (Tarceva, OSI-774; OSI/Genentech/Roche), the last two belonging to the group of tyrosine kinase inhibitors (TKIs).

NSCLC is among the epithelial types of cancer that are characterized by generally high expression levels of members of the EGFR family of ligands and receptors (11). Overexpression of EGFR has also been demonstrated in bronchial premalignant lesions, suggesting that the EGFR-mediated pathway might play an important role in lung carcinogenesis (12). EGFR has proven to be an important target in some patients with NSCLC. Although the EGFR is overexpressed in most cases of NSCLC, inhibition of this target results in responses in only 10% to 20% of patients (13, 14).

Early trials of TKIs in advanced NSCLC yielded promising results (15, 16); however, large, randomized trials failed to show any benefit when combining TKIs, either gefitinib or erlotinib, with standard chemotherapy as first-line treatment (17-20). Although all other controlled trials of biologically unselected patients given treatment with EGFR inhibitors showed limited impact on time-to-progression and overall survival, a recent controlled phase III study comparing erlotinib with placebo (the BR.21 study (21)) provided the first evidence of significant survival

Table I. *Baseline patient and disease characteristics.*

	No. of patients (n=36)	%
Gender		
Male	29	80.6
Female	7	19.4
Smoking status		
Non-smoker	5	13.9
Smoker	31	86.1
Histological classification		
Adenocarcinoma	15	41.7
Squamous cell	12	33.3
Undifferentiated	9	25.0
Initial brain metastases		
None	29	80.6
Present	7	19.4
Previous chemotherapy		
None	4	11.1
Non platinum	5	13.9
Platinum + nonplatinum	15	41.7
Platinum	12	33.3
Line of treatment		
1st	4	11.1
2nd	14	38.9
3rd	12	33.3
>3rd	6	16.7
ECOG† performance status		
0	11	30.6
1	12	33.3
2	11	30.6
3	2	5.6

†ECOG: Eastern Cooperative Oncology Group.

Table II. *Response to erlotinib and adverse events.*

	No. of patients	%
Response (WHO criteria)		
Progressive disease	7	19.4
Stable disease	23	63.9
Partial response	6	16.7
Adverse events		
None	9	25.0
Diarrhea	12	33.3
Rash	15	41.7

prolongation by an EGFR inhibitor in chemotherapy-refractory/-resistant NSCLC (10, 21).

In an effort to evaluate the effectiveness of erlotinib in the treatment of patients with locally advanced or metastatic NSCLC and its impact on survival, we conducted this retrospective study.

Patients and Methods

Records of patients treated with erlotinib in our clinic during the past 2 years were reviewed. Safety as well as efficacy data were collected. A retrospective analysis of the data was performed.

The study population included 29 male and 7 female patients, 46 to 84 years of age. The main inclusion criteria for therapy with Tarceva were documented stage IIIB or IV, advanced or recurrent metastatic NSCLC. Baseline assessment included detailed history and physical examination, standard laboratory studies, ECG, computed tomography (CT) of the chest and abdomen, head CT or magnetic resonance imaging (MRI), and assessment of performance status according to ECOG (22). Lung cancer histology was classified using the 1999 WHO classification system (23).

Patients received erlotinib at an initial dose of 150 mg in a tablet formulation that was self-administered orally, once daily on a continuous basis.

Tumor characteristics were evaluated according to local current practice every 8 or 12 weeks, with radiographic imaging studies (X-ray, CT and/or MRI scans) in order to assess response to treatment. Responses were determined by the investigators according to WHO criteria (24).

The primary endpoints of the study were median overall (OS) and progression-free survival (PFS). Secondary endpoints included clinical response rate, toxicity and correlation of various patients characteristics with clinical outcomes. OS and PFS were estimated with the Kaplan-Meier method (25), while univariate comparisons were performed with the log-rank test (26). Analysis was performed on the following variables: performance status (0 *vs.* 1 *vs.* 2 *vs.* 3), line of treatment (1st *vs.* 2nd, *vs.* 3rd *vs.* >3rd), histological type (adenocarcinoma *vs.* squamous *vs.* undifferentiated) and smoking status (smoker *vs.* non-smoker) (27). A p-value less than 0.05 was considered statistically significant, while all analyses were performed using SPSS statistical package v15.0 for Windows (Statistical Package for the Social Sciences, SPSS Inc., Chicago, IL, USA).

Results

Thirty-six patients were included in the analysis. Their median age was 64.5 years (range 46-84 years), 7 (19%) were female and 31 (86%) were smokers (Table I).

Fifteen of the patients (42%) had adenocarcinoma, 12 (33%) squamous and 9 (25%) undifferentiated histological type (Table I).

Twenty-nine patients (81%) achieved disease control (Table II). Median follow-up was 8 months (range 2-16 months). At the time of analysis, all patients had progressed and died. Median PFS was 4±2.43 months [range 0-8, 95% confidence interval (CI) 3-5 months] whereas the median OS was 7±2.65 months (range 3-15, 95% CI 6-8 months) (Table III, IV; Figures 1, 2).

Results of univariate analysis for PFS are shown in Table III. No statistically significant variables were found, with the exception of PS: patients with PS >1 had a statistically significant shorter PFS ($p<0.007$) compared to patients with a lower PS score.

Results of univariate analysis for OS are summarized in Table IV. No statistically significant variables were found

Table III. *Progression-free survival (months) according to smoking status, histological type, line of treatment and performance status.*

Variable	N	Median (range)	Median 95% CI	*p*-value
Total	36	4 (0-8)	6-8	
Smoking status				0.34
Non-smoker	5	5 (3-7)	3-7	
Smoker	31	4 (0-8)	3-5	
Histological type				0.75
Adenocarcinoma	15	4 (0-8)	2-6	
Squamous	12	4 (0-7)	3-5	
Undifferentiated	9	4 (0-6)	3-5	
Line of treatment				0.60
1-2	18	4 (0-7)	3-5	
≥3	18	4 (0-8)	3-5	
ECOG performance status†				**0.007**
0-1	23	5 (0-8)	3-7	
2-3	13	3 (0-6)	1-7	

†ECOG: Eastern Cooperative Oncology Group.

Table IV. *Overall survival (months) according to smoking status, histological type, line of treatment and performance status.*

Variable	N	Median (range)	Median 95% CI	*p*-value
Total	36	7 (3-15)	6-8	
Smoking status				0.41
Non-smoker	5	7 (4-11)	3-11	
Smoker	31	7 (3-15)	6-8	
Histological type				0.45
Adenocarcinoma	15	7 (3-15)	6-8	
Squamous	12	6 (4-11)	5-7	
Undifferentiated	9	7 (3-9)	4-10	
Line of treatment				0.33
1-2	18	7 (3-15)	4-10	
≥3	18	6 (4-11)	5-7	
ECOG performance status†				**0.004**
0-1	23	8 (4-1)	7-9	
2-3	13	5 (3-9)	3-7	

†ECOG: Eastern Cooperative Oncology Group.

with exception of PS: OS was shorter for patients with PS>1 ($p<0.004$) compared to those with a lower PS.

Erlotinib was generally well tolerated and toxicities were mild and easily managed. Adverse events occurred in 27 (75%) patients: 12 (33%) with diarrhea and 15 (42%) with skin rash (Table II). Four patients (11%) discontinued erlotinib as a result of an adverse event. The response to erlotinib according to gender, smoking habits, histological type and line of treatment can be seen in Table V but as with survival, statistical significance among different subgroups was not apparent.

Table V. *Response to erlotinib of patients with NSCLC according to gender, smoking habit, histological type, line of treatment and performance status.*

	No. of patients	No. of patients with objective response (%)	*p*-value
Gender			
Male	29	3 (10.3%)	0.073†
Female	7	3 (42.9%)	
Smoking status			
Non-smoker	5	2 (40%)	0.186†
Smoker	31	4 (12.9%)	
Histological type			
Adenocarcinoma	15	2 (13.3%)	0.852‡
Squamous	12	2 (16.7%)	
Undifferentiated	9	2 (22.2%)	
Line of treatment			
1st	4	0 (0%)	0.465†
2nd, 3rd, 3rd+	32	6 (18.8%)	
ECOG performance status			
≤2	34	6 (17.6%)	0.690†
>2	2	0 (0%)	

†Fisher's exact test; ‡Pearson Chi-Square.

Discussion

In this study, we evaluated the efficacy of erlotinib in patients with advanced NSCLC. It was shown that the OS for all patients receiving erlotinib was 7 months, while the PFS was 4 months (median values). Patients with a PS of 0 or 1 had better OS and significantly higher PFS rates. Overall response rate was 16.7%. The treatment with erlotinib was well tolerated and 75% of patients presented adverse events which were easily managed. Eleven percent of patients discontinued the treatment due to toxicity.

In the literature, erlotinib, pemetrexed, or docetaxel monotherapy after failure of one prior chemotherapy regimen have demonstrated an approximate OS and PFS of 7 and 3 months, respectively (21, 28, 29-33). Additionally, in another study (the BR. 21), the response rate of erlotinib in patients with stage IIIB or IV NSCLC, with PS 0-3, who had received one or two chemotherapy regimens, was 8.9% while the OS and PFS were 6.7 and 2.2 months, correspondingly (21). The objective response rate was higher in women (14% *versus* 6%), in patients with adenocarcinoma as compared with other histologies (14% *versus* 4.1%) and in patients without smoking history (25% *versus* 4%); all these findings are consistent with those of the literature (21).

Our study was retrospective and the number of patients included was relatively small. In addition, there was no control group. However, it becomes apparent from the results that erlotinib represents a promising treatment modality in advanced NSCLC, where 81% of patients achieved disease

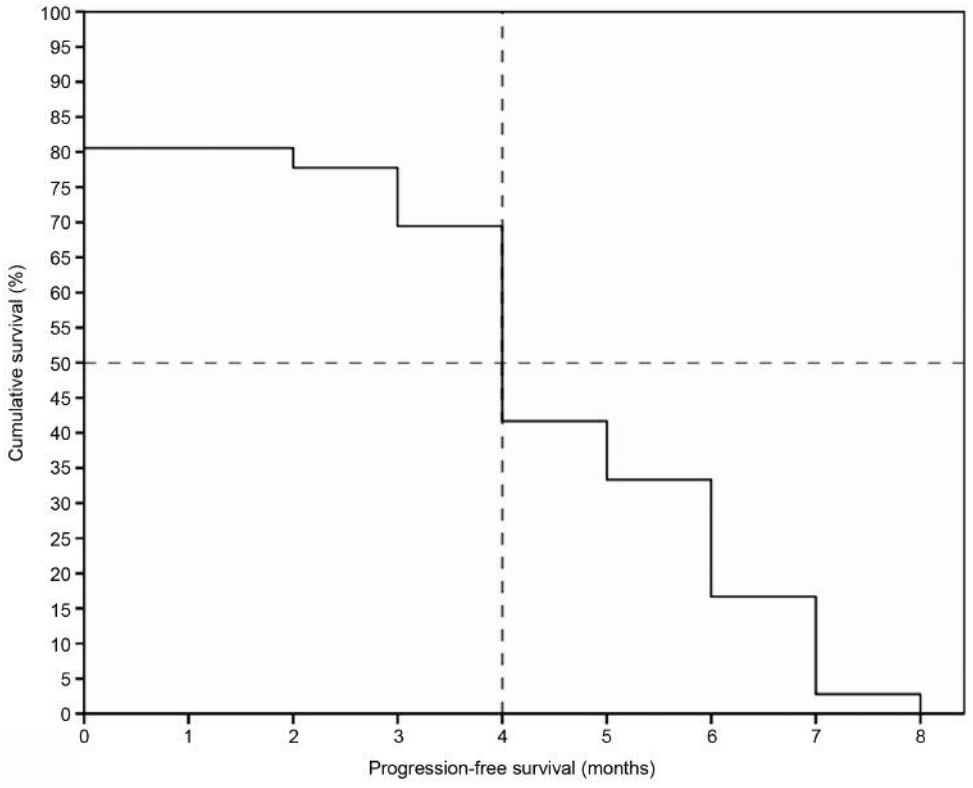

Figure 1. *Progression-free survival of all patients treated with erlotinib.*

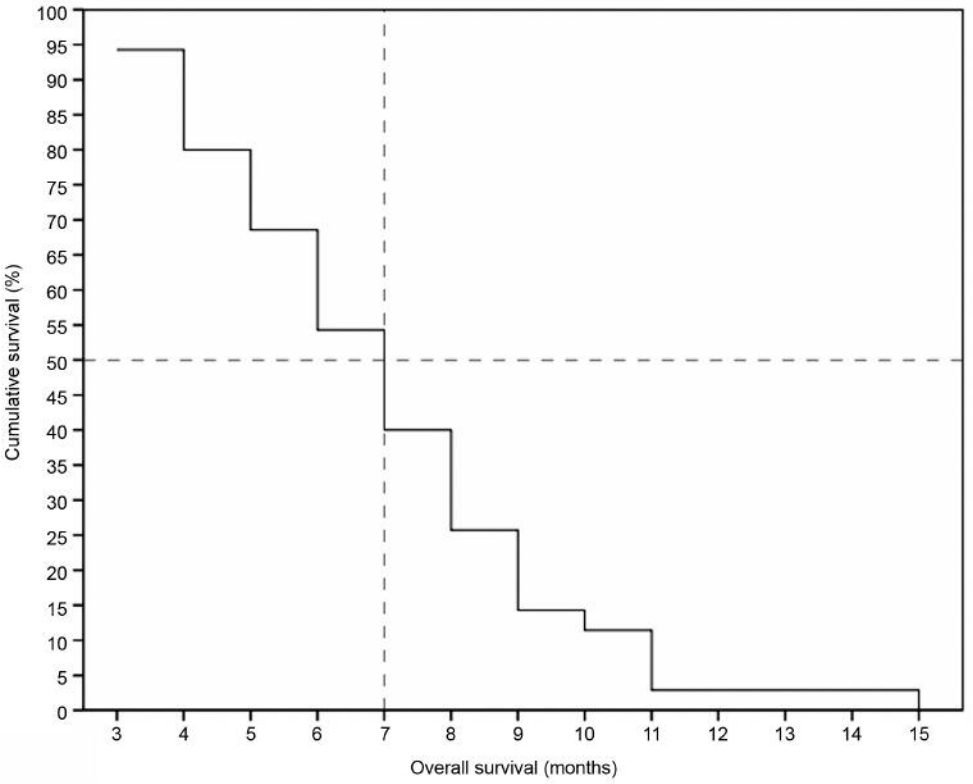

Figure 2. *Survival of all patients treated with erlotinib.*

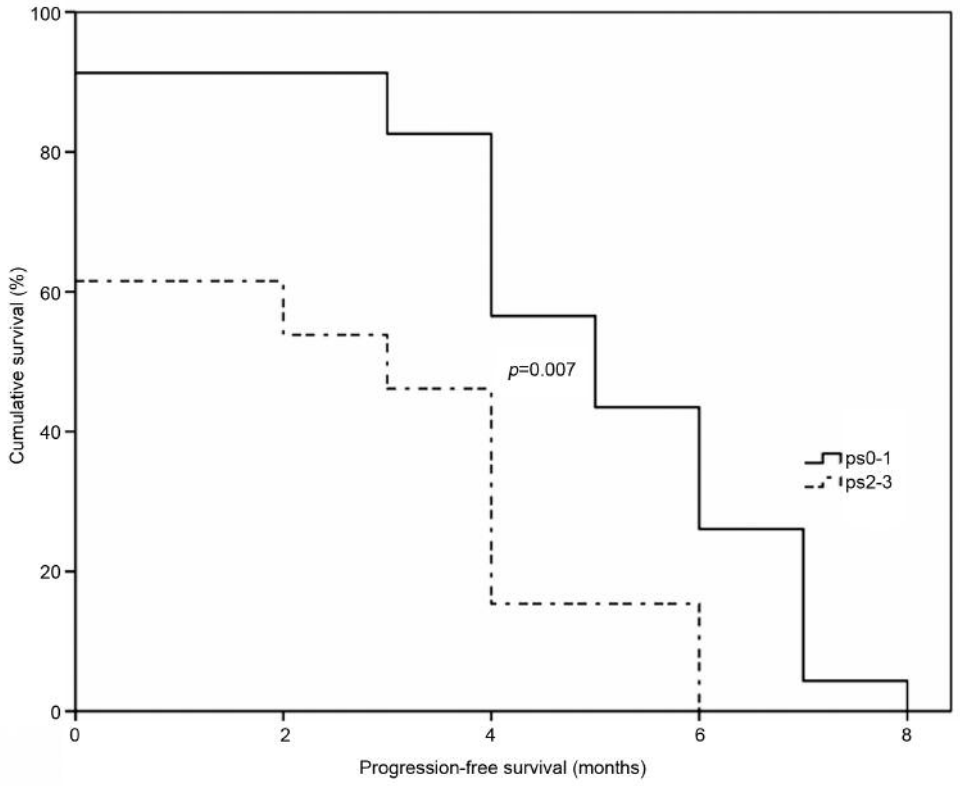

Figure 3. *Progression-free survival according to ECOG performance status*.

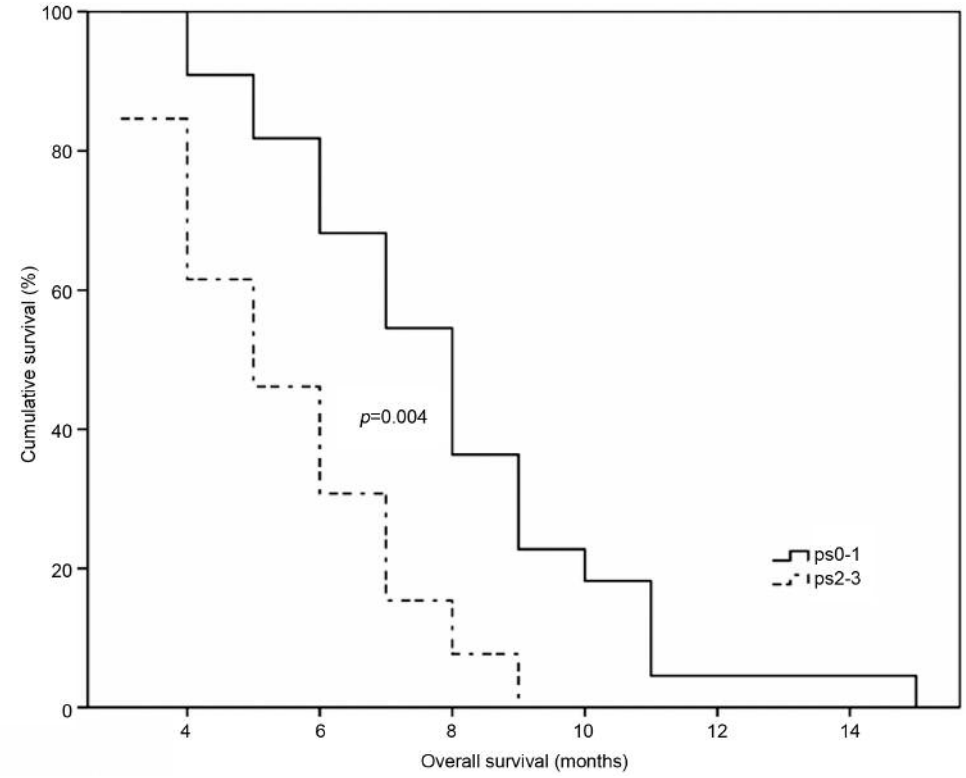

Figure 4. *Survival according to ECOG performance status*.

control, a rate which exceeds the rates previously reported in other studies (21). Nevertheless, it was shown that patients with a PS≤1 had a longer OS and a statistically significant longer PFS compared to those with PS>1 (p<0.004 and 0.007 respectively) (Tables III, IV).

The results of this study are consistent with the data of global literature. There are a few studies that confirm survival benefit all patients subgroups treated with erlotinib (33). There are several clinical and biological features associated with EGFR TKI sensitivity, with some factors being predictors of response and others being predictive for survival and therefore further investigation in this direction could shed a light on such a complex field as is the case of NSCLC therapy. Molecular assays have shown promise in prospectively identifying patients who are most likely to respond to EGFR TKI therapy and thus derive clinical benefit. It is hoped that several prospective ongoing studies, such as SATURN (erlotinib as first-line maintenance) and TITAN (erlotinib *vs*. docetaxel or pemetrexed) will add important information about the value of clinical and molecular markers for predictive the efficacy of EGFR TKIs (28).

In conclusion, erlotinib prolonged survival and has shown activity as monotherapy following the failure of one or two chemotherapy regimens in an unselected population of patients with a PS of 0 or 1. Despite the retrospective design and the small number of patients included, this study reflects a 'real-life' clinical setting and indicates the importance of good performance status and timely therapy initiation and their effect on clinical and treatment outcomes.

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