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Second-line treatment of advanced NSCLC: Comparison of efficacy of erlotinib and chemotherapy

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Molecular targeted therapy based on tyrosine kinase inhibitors, directed at the epidermal growth factor receptor (*EGFR*) is one of novel options for management of NSCLC. Erlotinib is *EGFR* tyrosine kinase inhibitor used for treatment of the advanced NSCLC. This presented study is focused on comparison of erlotinib and chemotherapy efficacy in the second line treatment of the advanced NSCLC. DCR and PFS became the primary endpoints.

Total number of patients was 290. A group treated with chemotherapy in the second line consisted of 150 patients and a group treated with erlotinib in the second line consisted of 140 patients. Comparison of DCR was performed using Fisher's exact test, visualization of PFS was performed using Kaplan-Meier survival curves and differences were tested using the log-rank test. Genetic testing was performed using PCR direct sequencing.

In the group treated with chemotherapy 2 CR, 23 PR and 51 SD were achieved vs. 5 CR, 10 PR and 55 SD in the group treated with erlotinib in the second line. DCR in patients treated with chemotherapy was 54.0% vs. 51.3% in patients without *EGFR* mutation treated with erlotinib (p=0.707); in patients harboring *EGFR* mutation, treated with erlotinib (n=9) outstanding results were achieved: 4 CR, 2 PR and 3 SD (not tested). Median of PFS in patients treated with chemotherapy was 2.1 months vs. 1.9 months in patients without *EGFR* mutation (p=0.879) vs. 8.4 months in patients harboring *EGFR* mutation treated with erlotinib (p=0.017).

Results of analysis show that even patients without *EGFR* mutation are able to benefit from erlotinib treatment in the second line. The efficacy (DCR, PFS) of erlotinib in patients without *EGFR* mutation was comparable with chemotherapy. The treatment efficacy in a subgroup of patients harbouring *EGFR* mutation treated with erlotinib was significantly better than in patients without *EGFR* mutation.

Key words: EGFR-TKI, NSCLC, erlotinib, targeted treatment of NSCLC

Lung cancer is a leading cause of cancer related deaths worldwide and its incidence has been still increasing. Non-small cell lung cancer (NSCLC) accounts for approximately 80% of lung cancers. One of novel therapeutic modalities in thoracic oncology is a molecular targeted therapy using low-molecular tyrosine kinase inhibitors blocking activation of an epidermal growth factor receptor (*EGFR*) cascade. Erlotinib is an *EGFR* tyrosine kinase inhibitor, in clinical practice commonly used for treatment of advanced stage NSCLC. Clinical studies have shown high efficacy of erlotinib, particularly in patients harboring activating *EGFR* mutations [1-13]. Results of randomized phase III trials IPASS [14], OPTIMAL [15] and EURTAC [16] recently showed higher efficacy of first line treatment with *EGFR* tyrosine kinase inhibitors (gefitinib, erlotinib) in comparison with standard chemotherapy regimens in patients harboring *EGFR* mutation. These findings resulted to change of recommendations for treatment of advanced NSCLC. Treatment with *EGFR* tyrosine kinase inhibitors is now recommended for the first-line treatment of patients harboring *EGFR* mutation [17]. Clinical trials comparing efficacy and safety of erlotinib with standard chemotherapy regimens in the second line proved comparable efficacy and better toxicity profile of erlotinib [18-20]. It should be mentioned that these published results were irrespective of *EGFR* muta-

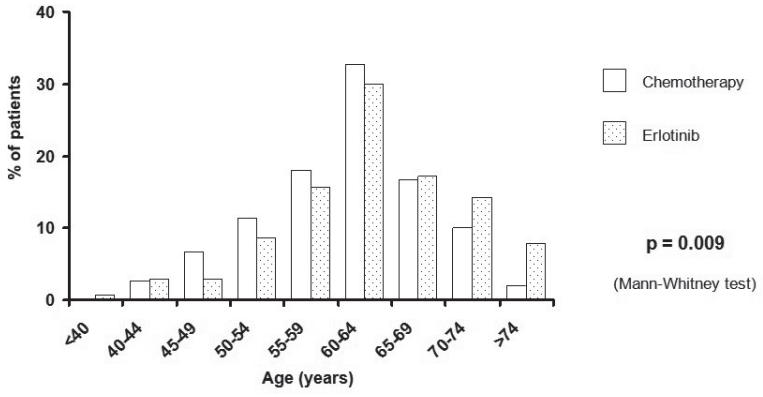


Figure 1. Age of patients at the time of diagnosis

tion status. Erlotinib is usually well tolerated, treatment is not burdened with risk of serious side effects and clinical studies showed that it is effective in patients with poor performance status and patients of higher age categories [21-23]. The oral administration is another advantage. Skin toxicity, which is usually well controlled with local treatment, represents the main and most common adverse effect; in serious cases it is possible to reduce dose of erlotinib [24,25]. We conducted this retrospective study based on a clinical experience to compare the efficacy of erlotinib and chemotherapy in the second-line treatment of advanced NSCLC.

Patients and methods

Study design. We analysed data of patients with cytologically or histologically confirmed advanced stage (IIIB, IV) NSCLC enrolled in the Tarceva clinical registry. Patients were diagnosed and treated at Department of Tuberculosis and Respiratory Diseases at the University Hospital in Pilsen between 2008 and 2011. Treatment was prospectively monitored and clinical course of patients was continuously assessed at time points. Oral erlotinib (Tarceva®) was administered once daily at a standard dose 150 mg until unacceptable toxicity, disease progression or death. Dose interruption or reduction was permitted in the event of treatment-related toxicity. The total number of patients was 290. We compared outcome of two groups of patients. The first group involved patients treated in the second line with chemotherapy; all these patients were treated with erlotinib in the third line, 37 patients were treated with pemetrexed, 70 patients were treated with docetaxel and 43 were treated with other chemotherapy regimen. The second group involved patients treated with erlotinib in the second line. The outcome of patients treated with erlotinib in the second line was analysed with regard to *EGFR* mutation status. The analysis was primarily focused on comparison of the disease control rate (DCR) and progression-free survival (PFS).

Clinical assessments and statistical methodology. Tumor response was assessed using Response Evaluation Criteria in Solid Tumors (RECIST) [26]. Comparison of DCR was performed using Pearson's Chi-square test. Visualization of PFS as well as the estimation of survival probabilities was performed using Kaplan-Meier survival curves; all point estimates were accompanied with 95% confidence intervals. The differences in survival were tested using the log-rank test. As a level of statistical significance α=0.05 was used. Patients´ groups were compared according to age using Mann-Whitney test. Pearson's Chi-square test was used for comparison according to sex, smoking history, histological type and Estern Cooperative Oncology Group (ECOG) performance status (PS). As a level of statistical significance α=0.05 was used. Since the patients' data originate from the Tarceva clinical registry therefore all the patients receiving chemotherapy in the second line were treated with erlotinib in the third line comparison of the overall survival could not have been performed.

Patients. The group treated with chemotherapy in the second line consisted of 150 patients, 40 women and 110 men, 79 patients with squamous-cell carcinoma (SCC), 59 patients with adenocarcinoma (ADC), 10 patients with poorly differentiated NSCLC and 2 patients with not otherwise specified NSCLC (NOS), 81 smokers, 57 former smokers and 12 never-smokers. The group treated with erlotinib in the second line consisted of 140 patients, 43 women and 97 men, 67 patients with SCC, 61 patients with ADC, 8 patients with poorly differentiated NSCLC and 4 patients with NOS NSCLC, 56 smokers, 51 former smokers and 33 never-smokers. Both groups differed significantly with regard to patients' age at diagnosis (Figure 1) and performance status (ECOG PS) evaluated at the time of diagnosis (Figure 2) and smoking history (Figure 3). The group treated with chemotherapy in second line involved more patients in younger age categories (61 years vs. 63 years, p=0.009) and patients with better ECOG PS at the time of diagnosis (PS 0: 27.3% vs. 17.1%, PS 1: 64.7% vs. 66.4%, PS 2: 7.3% vs. 16.4%, PS 3: 0.7% vs. 0.0%, p=0.022) and vice versa in the group treated with erlotinib. The group treated with erlotinib in second line involved more never-smokers (8.0% vs. 23.6%, p=0.001). The groups did not

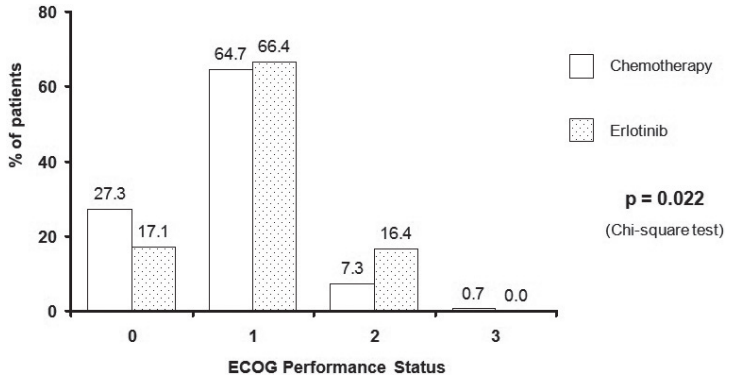


Figure 2. ECOG Performance Status at the time of diagnosis

significantly differ in histological type (p=0.516) nor in sex representation (p=0.448).

***EGFR* mutation analysis.** In the group treated with erlotinib 83 % of the patients with ADC and 40 % of patients with SCC were successfully genetically tested. The tumor specimens acquired during an initial bronschoscopy examination were evaluated by a senior cytologist using a regular giemsa staining. In a few cases a tumor biopsy was processed into formalin-fixed paraffin embedded (FFPE) histology sections. The cytology slides or, eventually, the FFPE sections, were submitted for molecular genetic test being included detection of somatic mutations in *EGFR* genes. If it was necessary, tumour cells were carefully selected and removed from samples by laser microdissection using P.A.L.M. microlaser instrument [Carl Zeiss MicroImaging GmbH, Germany]. The microdissected cells were collected directly into the PCR buffer and processed without a special DNA extraction step. In all other cases the DNA was extracted from tissue cells by a standard spin column procedure using JetQuick Tissue DNA Issolation Kit [GENOMED GmbH, Loehne, Germany]. The mutations in exons 19 and 21 of *EGFR* gene Genoscan *EGFR* kits [Genomac International, Prague, Czech Republic] utilizing a denaturing capillary electrophoresis (DCE) technique on ABI PRISM 3100 16-capillary genetic analyzer. Detected mutations were identified by regular DNA sequencing using a BigDye v 3.0 chemistry (Applied Biosystems, Foster City, CA). In rare cases, where the overall fraction of mutated DNA was below the 20% minimum required for DNA sequencing, mutation was identified indirectly after forming only a homoduplex fragment with a given known mutation reference standard.

Results

In patients treated with chemotherapy in the second line (n=137) complete response (CR) was achieved in 2 (1.3%), partial response (PR) in 23 (15.2%), stable disease (SD) in 50 (36.5%), for an overall disease control rate (DCR) of 54.0%; in patients without *EGFR* mutation (including not tested patients) treated with erlotinib in the second line

	CR+PR+SD	PD	Total
Chemotherapy	74 (54.0%)	63 (46.0%)	**137 (100.0%)**
Erlotinib	61 (51.3%)	58 (48.7%)	**119 (100.0%)**

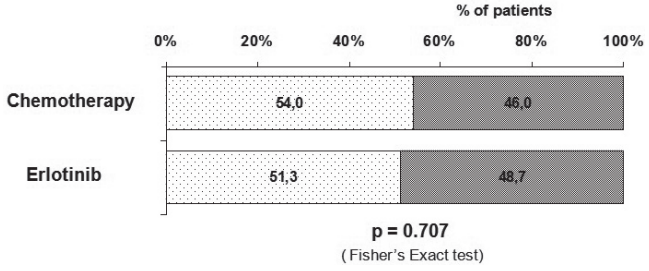


Figure 3. Comparison of disease control rate (DCR) in patients without *EGFR* mutation treated with erlotinib and patients treated with chemotherapy in the second line

	CR	PR	SD	PD	NA	Total
***EGFR* mutation**	4 (44.4%)	2 (22.2%)	3 (33.3%)	0 (0.0%)	0 (0.0%)	**9 (100.0%)**
Without *EGFR* mutation	1 (0.8%)	8 (6.1%)	52 (39.7%)	58 (44.3%)	12 (9.2%)	**131 (100.0%)**

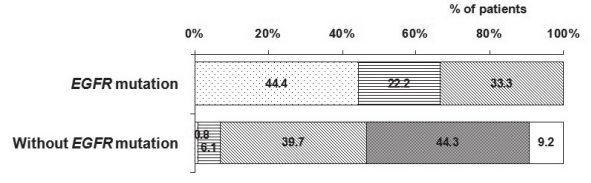
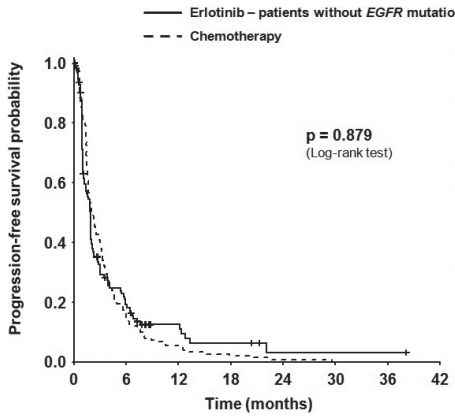


Figure 4. Comparison of objective response rate (ORR) according to the presence of *EGFR* mutations in patients treated with erlotinib in the second line

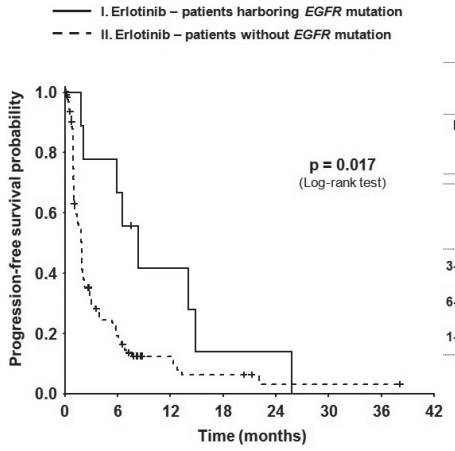
(n=119), CR was achieved in 1 (0.8%), PR in 8 (6.7%), SD in 52 (43.7%), for an overall DCR of 51.3% (Figure 4). The difference between these two compared groups in DCR was



	PFS	
	Erlotinib	CHT
Number of patients	129	150
Median (95% IS)	1.9 months (1.6; 2.1)	2.1 months (1.7; 2.6)

	PFS probability (%; 95% IS)	
	Erlotinib	CHT
3-month survival	30.0 (21.7; 38.2)	38.7 (30.9; 46.5)
6-month survival	19.1 (11.9; 26.3)	14.7 (9.0; 20.3)
1-year survival	12.4 (6.3; 18.6)	5.3 (1.7; 8.9)

Figure 5. Comparison of progression-free survival (PFS) in patients without *EGFR* mutation treated with erlotinib and patients treated with chemotherapy in the second line



	PFS	
	I.	II.
Number of patients	9	129
Median (95% IS)	8.4 months (4.0; 12.7)	1.9 months (1.6; 2.1)

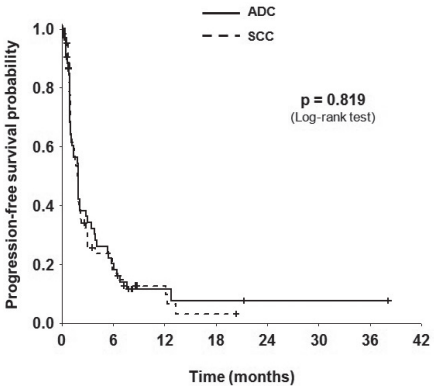
	PFS probability (%; 95% IS)	
	I.	II.
3-month survival	77.8 (50.6; 104.9)	30.0 (21.7; 38.2)
6-month survival	66.7 (35.9; 97.5)	19.1 (11.9; 26.3)
1-year survival	41.7 (7.8; 75.6)	12.4 (6.3; 18.6)

Figure 6. Comparison of progression-free survival (PFS) in patients harbouring *EGFR* mutation and patients without *EGFR* mutation treated with erlotinib in the second line

not statistically significant (p=0.707). In the subgroup of patients treated with erlotinib in the second line harboring *EGFR* mutation (n=9) outstanding results were achieved: CR was achieved in 4 patients, PR in 2 and SD in 3 patients (Figure 5). The difference from the patients without *EGFR* mutation was not statistically tested due to a low number of patients. Median of PFS in patients treated with chemotherapy in the second line was 2.1 months vs. 1.9 months in patients without *EGFR* mutation (including not tested patients) treated with erlotinib in the second line; the difference between compared groups was not statistically significant (p=0.879) (Figure 5). In the subgroup of patients harboring *EGFR* mutation, treated with erlotinib in the second line, the median PFS was 8.4 months; the difference from patients without *EGFR* mutation treated with erlotinib in the second line was statistically significant (p=0.017) (Figure 6). Median PFS in patients with ADC (n=53) or SCC (n=67) treated with erlotinib, was equal 1.9 months; the difference in PFS between the two most common histological types of NSCLC in patients treated with erlotinib, without *EGFR* mutation (including not tested patients) was not statistically significant (p=0.819) (Figure 7).

Discussion

The study results proved, no statistically significant difference in DCR between patients treated in the second line with chemotherapy and the subgroup of patients treated with erlotinib without *EGFR* mutation (54.0% vs. 51.3%, p=0.707); in the subgroup of patients harboring *EGFR* mutation treated with erlotinib in the second line (n=9), outstanding results were achieved (4 CR, 2 PR, 3 SD). Comparing PFS, no statistically significant difference between patients without *EGFR* mutation treated in the second line with erlotinib and patients treated with chemotherapy was found (2.1 months vs. 1.9 months, p=0.879); in patients harbouring *EGFR* mutation,



	PFS	
	ADC	SCC
Number of patients	53	67
Median (95% IS)	1.9 months (1.4; 2.5)	1.9 months (1.4; 2.3)

	PFS probability (%; 95% IS)	
	ADC	SCC
3-month survival	34.2 (21.0; 47.3)	27.2 (16.0; 38.3)
6-month survival	20.1 (9.0; 31.2)	18.2 (8.3; 28.0)
1-year survival	11.5 (2.4; 20.6)	12.7 (4.1; 21.4)

Figure 7. Comparison of progression-free survival (PFS) in patients without *EGFR* mutation treated with erlotinib in the second line according to histological type of NSCLC

treated with erlotinib longer PFS compared to both previous groups (8.4 months vs. 2.1 months; 1.9 months, p=0.017).

Evaluating DCR and PFS, it is necessary to mention the fact that the group treated with chemotherapy involved more patients in younger age categories (p=0.009) and patients with better performance status (p=0.022) and vice versa in the group treated with erlotinib (Table 1,2). The probability of misinterpretation of the results due to activating *EGFR* mutations occurrence in not tested patients, especially in those with squamous-cell NSCLC is very low, particularly given the fact that in these patiens, the incidence of *EGFR* mutations is extremely low (less than 3.4 %) [27]. Genetic testing of patients with squamous-cell NSCLC enrolled in the study was performed preferentially in females and non-smokers. Furthermore there are studies questioning the predictive role of *EGFR* mutations in NSCLC of squamous-cell histology [28]. A limitation of the study is the impossibility of a real comparison of patients groups in terms of overall survival. Overall survival comparison could be misleading due to the fact that both groups significantly differed in performance status, age and subsequent treatment (63/150, approx. 45 % of the patients treated in the second line with erlotinib were treated with chemotherapy after the treatment failure vs. 100 % of the patients treated in the second line with chemotherapy were subsequently treated with erlotinib).

Conclusion

Results of conducted study showed comparable efficacy of erlotinib in patients without *EGFR* mutation and chemotherapy in the second-line treatment of advanced stage NSCLC. Patients of higher age groups and patients with poor performance status also benefit from erlotinib treatment. Study results confirmed high efficacy of erlotinib in patients harboring *EGFR* mutation. Genetic testing of *EGFR* mutations in patients with advanced stage NSCLC should be now a standard part of diagnostic procedure, however, an ongoing search for other potential predictors of molecular targeted therapies is essential.

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