Original article

The evaluation of the efficacy and toxicity of targeted treatment in non-small cell lung cancer patients – single centre experience

Joanna Kardas, MD, Agnieszka Buraczewska, MD, Paweł Chrom, MD, Anna Waśko-Grabowska, MD, PhD, Beata Młot, MD, Cezary Szczylik, MD, PhD, prof.

Department of Oncology, Military Institute of Medicine, Warsaw, Poland

Head of Department: Cezary Szczylik, MD, PhD, prof.

ABSTRACT

Introduction: Tyrosine kinase inhibitors (TKI) are the standard of treatment in patients with advanced non-small cell lung cancer (NSCLC) with EGFR (endothelial growth factor receptor) gene activating mutation.

Objective: The evaluation of the efficacy and toxicity of TKI drugs in NSCLC patients treated in single centre.

Material and methods: NSCLC patients treated with TKI (gefitinib, erlotynib, afatinib) between 2012–2016 were retrospectively analysed. We evaluated: overall response rate (ORR) which is the sum of complete responses (CR) and partial remissions (PR), progression free survival (PFS), overall survival (OS) and adverse events (AE) according to CTCAE (Common Terminology Criteria for Adverse Events) scale.

Results: The study group were 16 patients ORR was 50% (CR: 1, PR: 7). Median PFS and OS was 8,7 and 22,9 months respectively. Adverse events observed mainly in stage 1 and 2 were related to hyponatraemia, hyperbilirubinemia, skin toxicity and mucositis. There was one death reported due to infectious complications.

Conclusion: The efficacy and toxicity of TKI in study group were found to be similar to those described in the literature.

Key words: tyrosine kinase inhibitor, endothelial growth factor receptor, non-small cell lung cancer

Correspondence:
Joanna Kardas, MD
Department of Oncology,
Military Institute of Medicine
04-141 Warszawa,
ul. Szaserów 128
e-mail: jkardas@wim.mil.pl

Received:
23.04.2017.
Accepted:
31.05.2017.

DOI: 10.24292/01.OR.300617.7

INTRODUCTION

Lung cancer is the malignant neoplasm with a very poor prognosis. Among malignant tumors is the most common cause of death [1]. Histologically, we distinguish two subgroups of lung cancer: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) – here predominate adenocarcinoma and squamous cell carcinoma. The primary treatment for NSCLC is surgery and later radiotherapy and radiochemotherapy. Unfortunately these methods can be applied only in 30% of patients with NSCLC in lower stages. In most cases the disease is more advanced: locally advanced (30%) or metastatic (40%) [2]. Then only palliative systemic treatment can be applied – standard chemotherapy or in selected patients molecular targeted therapy. The aim of palliative treatment is to prolong survival and improve the quality of life.

Standard chemotherapy has specific side effects manifested by destroying fast-dividing cells (myelotoxicity and mucositis). So in our patients we can observe haematological and gastrointestinal complications as well as nephro- and hepatotoxicity. Therefore patients for such toxic treatment should be carefully selected by clinician.

Over a decade ago molecular targeted drugs became another option for NSCLC patients and for selected groups there was the only option for effective treatment. Despite an obvious therapeutic gain new side effects of targeted treatment appeared which we learned to deal with. The toxicity of molecular targeted drugs depends on its therapeutic target. In NSCLC patients small molecule tyrosine kinase inhibitors (TKIs) are in clinical use. These are epidermal growth factor receptor (EGFR) inhibitors. Physiologically EGFR is expressed in keratinocytes, eccrine and sebaceous glands, hair follicle and vascular endothelial cells [3]. Receptor activation transmits signal inside the cell which lead to biological response – regulation of proliferation, differentiation, cell cycle, migration and survival of cells. Inhibition of EGFR disturbs these processes. There are two kinds of EGFR inhibitors [4]:

- small molecule TKI work inside the cell and inhibit receptor phosphorylation
- monoclonal antibodies (mAbs) bind to external receptor domain.

In everyday practice only TKIs are applied in lung cancer treatment. It has been shown that only patients with NSCLC harboring activating *EGFR* mutations could respond to anti-EGFR TKIs. Other patients have a chance to respond to chemotherapy [5–8]. Sensitivity to EGFR inhibitors is closely related with presence of activating mutations on exon 18–21 of *EGFR* gene. Predominantly it is deletion on exon 19 (g.729_761del) or L858R point mutation on exon 21 (c.2573T>G). Unfortunately these mutations are present in only 10–15% of Caucasian NSCLC patients with adenocarcinoma histology [9]. The advantage of small molecule TKIs over chemotherapy in NSCLC patients harboring activating *EGFR* mutation is associated with improve on overall response rate (ORR), progression free survival (PFS) and quality of life (QL) [5–7]. Indirect comparisons showed two to three fold elongation of overall survival when compared to chemotherapy [10]. TKIs differ from cytostatics with side effects and differ slightly in toxicity between themselves. These side effects are skin toxicity, mucositis and hepatic toxicity [11].

OBJECTIVE

The aim of this work is to present one single centre experience in treatment of NSCLC patients with *EGFR* activating mutation and who were eligible for TKI treatment.

MATERIAL AND METHODS

We retrospectively analysed the hospitalization data of patients treated between 2012 and 2016 for NSCLC with molecular targeted drugs: gefitinib, erlotinib or afatinib. Duration of the treatment depended on the efficacy and the tolerance of TKIs used. Eligibility criteria for molecular targeted therapy were:

1. Histologically confirmed diagnosis of NSCLC harboring activating *EGFR* mutation.
2. The presence of metastatic or locally advanced disease with no possibility of radical treatment.
3. The presence of target lesions or countable non-target lesions.
4. Lack of clinical significant co-morbidities.
5. Adequate blood test results confirmed normal bone marrow, liver and renal function.
6. Good Eastern Cooperative Oncology Group (ECOG) performance status (0–1). 0 performance status presented full activity – the patients were able to carry on all pre-disease performance without restriction. Patients with 1 performance status had activity limited by disease but were able to move or carry out work of light nature.

The exclusion criteria were brain metastases unless the patient received prior local treatment (surgery or radiotherapy) and his neurological status was stable. The treatment was continued until disease progression, non-acceptable toxicity or patient decision.

The efficacy of therapy was assessed using Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1) [13]. Furthermore we evaluated objective response rate (ORR) which is the sum of complete remission (CR) and partial remission (PR). The Kaplan–Meier estimate was used to determine survival curves and medians, 95% confidence interval (95% CI) for progression-free survival (PFS) and overall survival (OS). Median follow up was estimated using Schemper–Smith method [14]. The toxicity was evaluated by CTCAE v. 4.03 (Common Terminology Criteria for Adverse Events Version 4.03) [15]. Collection of patients data ended January 20, 2017.

RESULTS

16 patients were eligible for the study: 6 male and 10 female (tab. 1). Median age was 66.5 years (range: 30–80 years) (fig. 1). One female had locally advanced NSCLC beyond the possibility of radical therapy. The rest of the patients had metastatic disease. Most common site of metastases were other lung and bones, and subsequently pleura, liver, brain and adrenal glands (fig. 2). The majority of patients received erlotinib (10/62%) and 3 people were treated equally with gefitinib and afatinib. For most of the patients it was first line palliative therapy (13/81%), but 3 individuals had prior treatment with platinum based chemotherapy in other centres. Activating *EGFR* mutation was present in each case. It was mostly deletion on exon 19 and less often – activating mutation on exon 21 (4/25%) and on exon 18 (1/6%). ORR (PR + CR) was 50% (7 and 1 respectively). The rest of patients had stable disease (SD) as the best response (fig. 3).

TABLE 1.
Study group characteristics.

Gender	16 (100%)
female	10 (62%)
male	6 (38%)
Age (years; median, range)	66.5, 30–80
ECOG:	
0	3 (19%)
1	13 (81%)
Treatment:	
gefitinib	3 (19%)
erlotinib	10 (62%)
afatinib	3 (19%)
Prior treatment	3 (19%)
Later treatment	3 (19%)
Site of metastases:	
liver	5 (31%)
adrenal gland	4 (25%)
other lung	9 (56%)
pleura	6 (38%)
bones	9 (56%)
brain	5 (31%)
Patients without metastases	1 (6%)
Patients with one site metastases	3 (19%)
Patients with two sites metastases	5 (31%)
Patients with three sites metastases and more	7 (40%)
Type of mutation:	
Deletion on exon 19 (g.729_761del)	11 (69%)
Activating mutation on exon 21 (c.2573T>G) (L858R)	4 (25%)
Activating mutation on exon 18 (c.2156G>C)	1 (6%)

FIGURE 1.
Age of patients.

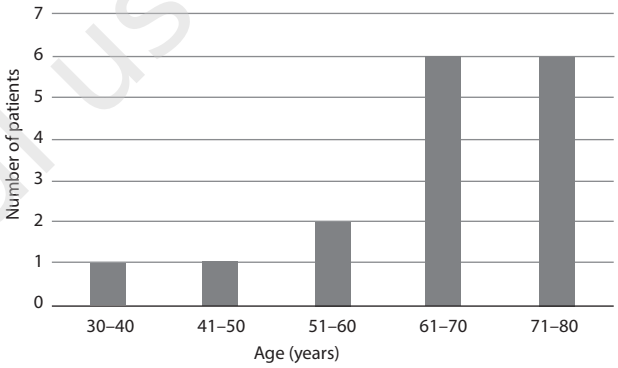


FIGURE 2.
Site of metastases.

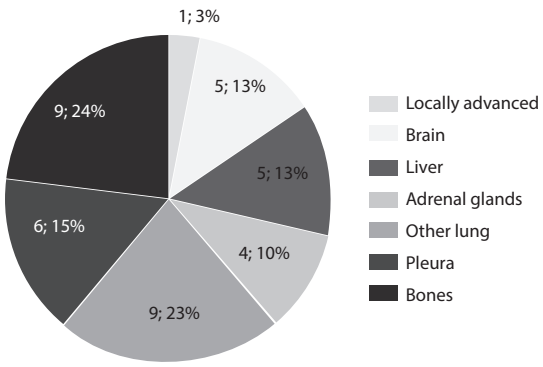
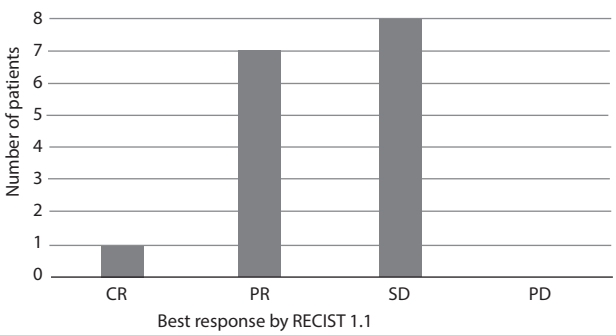


FIGURE 3.
The efficacy of the treatment.



Median follow-up time was 21.8 months. 2 individuals are still being treated. Median PFS was 8.7 months (95% CI: 5.1–25.8). Median OS was 22.9 months (95% CI: 7.0–not reached) (fig. 4, 5). Average number of cycles was 12 (range 3–44). Side effects were observed in grade 1 and 2 toxicity (CTCAE), most often: hyponatraemia, hyperbilirubinemia, anaemia, skin toxicity and mucositis. One patient did not experienced any toxicity. In 8 cases (50%) we observed serious side effects (grade 3 and 4 toxicity) which required hospitalization, dose reduction or temporary withdrawal of drugs (tab. 2). These were hyperbilirubinemia (2/12%), hypertransaminasemia (1/6%), hyponatremias (1/6%), skin toxicity (2/12%), diarrhoea (1/6%) and anaemia (1/6%). One death from pneumonia and limbic encephalitis was reported. The cause of death was confirmed by autopsy. Furthermore it was the patient in complete remission of lung cancer which was proven by PET CT scan performed prior to death and autopsy examination.

FIGURE 4.
Kaplan–Meier curve for progression free survival.

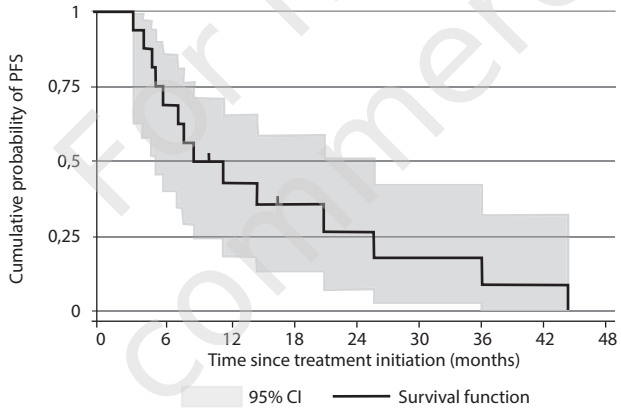
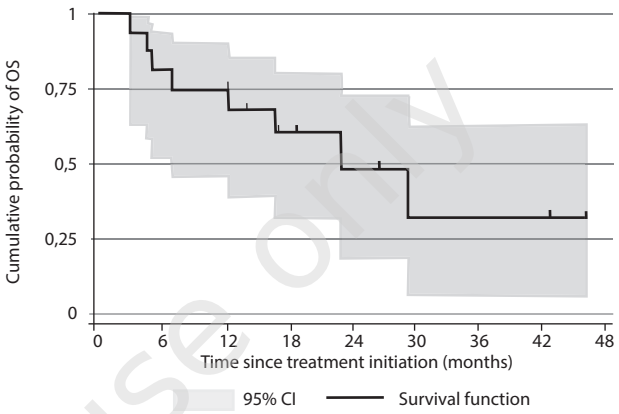


FIGURE 5.
Kaplan–Meier curve for overall survival.



DISCUSSION

NSCLC in metastatic stage is a malignant neoplasm with very poor prognosis. In such cases oncological treatment is palliative and aims to prolong life and improve quality of life. The use of palliative chemotherapy results in 20–40% of objective response rate with median OS of 8–12 months. The most effective is platinum doublet chemotherapy. This treatment is toxic so the patients should be in good performance status and have no serious co-morbidities. After disease progression they can be eligible for second line palliative chemotherapy (monotherapy with docetaxel or pemetrexed). The patients with adenocarcinoma or NSCLC with predominant adenocarcinoma histology harboring activating *EGFR* mutation can be treated with molecular targeted therapy. Epidermal growth factor receptor mutations are present in about 10–20% of Caucasian patients and in 50% of Asian patients with metastatic NSCLC of adenocarcinoma histology –

TABLE 2.
The toxicity of the treatment (CTCAE).

Toxicity	Grade 1 (No. of patients [%])	Grade 2 (No. of patients [%])	Grade 3 (No. of patients [%])	Grade 4 (No. of patients [%])
Anaemia	4 (25%)	1 (6%)	1 (6%)	-
Thrombocytopenia	-	-	-	-
Neutropenia	-	-	-	-
Hyperbilirubinemia	4 (25%)	3 (19%)	2 (12%)	-
Hypertransaminasemia	-	-	1 (6%)	-
Hyponatraemia	7 (40%)	-	1 (6%)	-
Hyperglycaemia	5 (31%)	-	-	-
Nephrotoxicity	5 (31%)	-	-	-
Diarrhea	1 (6%)	3 (19%)	-	1(6%)
Mucositis	3 (19%)	-	-	-
Skin toxicity	7 (40%)	5 (31%)	2 (12%)	-

more often in non-smokers, former smokers and women [6, 16]. EGFR tyrosine kinase inhibitors in first line treatment in selected NSCLC patients with activating *EGFR* mutation TKIs improve ORR (56–83%), quality of life (QL) and PFS (9.5–13.1 months) when compared to standard chemotherapy (ORR: 15–47%, PFS: 4.6–6.9 months) [5–7, 17]. No benefit has been demonstrated in terms of overall survival. And the reason of this may be that in clinical trials the patients treated with chemotherapy after disease progression could be treated subsequently with anti-EGFR drug. The use of TKIs in advanced NSCLC allowed to prolong average survival from 9 months, observed over decade ago, to 2 years today [18].

The use of TKIs in second line of NSCLC treatment in population with unknown *EGFR* status demonstrated objective response rate of 8–8.9% and prolong median OS by 2 months when compared to placebo (only erlotinib) [19, 20].

In Poland there are 3 EGFR TKIs available in treatment of advanced NSCLC patients harboring activating *EGFR* mutation. These are: gefitinib, erlotinib (first generation TKIs) and afatinib (second generation TKIs). All 3 drugs are registered in first line of NSCLC palliative treatment. Additionally erlotinib or gefitinib can be used in second line of NSCLC treatment after progression after standard chemotherapy.

Recently the efficacy of the third generation TKIs was proved. Osimertinib and rociletinib are effective after failure of first and second generation TKIs due to acquired *EGFR* resistance mutation c.2369C>T (T790M) [21, 22].

The treatment with small-molecule tyrosine kinase inhibitors in NSCLC patients is available in Poland only within therapeutic program of National Health Found.

The study presents results of treatment of NSCLC patients with tyrosine kinase inhibitors in one of multiprofile oncological wards in Warsaw. Results show high efficacy and relatively low toxicity of TKIs, which is comparable to previous reports. All patients benefited from the treatment. The minimal best response was stable disease (in half of study group). There were some long responders with stabilization as the best response. The longest PFS (44 months) was reported in male treated with erlotinib in second line. Stable disease is frequent response observed in molecular targeted treatment, which although is not spectacular though results in improve of quality of life, prolong time to disease progression and survival time. In follow up time one death was reported due to pneumonia in female with limbic encephalitis. This patient was in complete remission which was confirmed in autopsy. Few reports describe such complication after TKI treatment [23, 24]. The most common toxicities were skin toxicity, mucositis and hepatic disorders – mainly in grade 1 or 2 (CTCAE). These results are similar given by the literature [23].

The limitation of the study is small group of patients – over 4 years only 16 patients with NSCLC were eligible to TKIs treatment. The reason is that the ward is multiprofile and there are very few patients with NSCLC who are eligible to TKI treatment (rarity of *EGFR* mutation).

CONCLUSION

The treatment of NSCLC patients with small-molecular tyrosine kinase inhibitors is safe and efficient in selected group of individuals. It is necessary to determine EGFR mutation in all NSCLC patients with predominant adenocarcinoma histology so the optimal antitumor treatment could be initiated. First line treatment with TKIs should be a standard therapy for NSCLC patients with activating *EGFR* mutation.

References

1. Krajowy Rejestr Nowotworów. [online: http://onkologia.org.pl/nowotwory-zlosliwe-oplucnej-pluca-c33-34/].
2. Krzakowski M. Nowotwory płuca, opłucnej i śródpiersia. In: Krzakowski M, Potemski P, Warzocha K, Wysocki P (ed.). Onkologia Kliniczna. Via Medica, Gdańsk 2015: 546-553.
3. Schulze WX, Deng L, Mann M. Phosphotyrosine interactome of the ErbB-receptor kinase family. Mol Syst Biol 2005; 1: 2005.0008.
4. Mendelsohn J, Baselga J. Epidermal growth factor receptor targeting in cancer. Semin Oncol 2006; 33(4): 369-385.
5. Rosell R, Carcereny E, Gervais R et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012; 13: 239-246.
6. Mok TS, Wu YL, Thongprasert S et al. Gefitinib or carboplatin–paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009; 361: 947-957.
7. Sequist LV, Yang JC, Yamamoto N et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013; 31: 3327-3334.
8. Lee JK, Hahn S, Kim DW et al. Epidermal growth factor receptor tyrosine kinase inhibitors vs conventional chemotherapy in non-small cell lung cancer harboring wild-type epidermal growth factor receptor: a meta-analysis. JAMA 2014; 311(14): 1430-1437.
9. Petrelli F, Borgonovo K, Cabiddu M et al. Efficacy of EGFR tyrosine kinase inhibitors in patients with EGFR-mutated non-small cell lung cancer: a meta-analysis of 13 randomised trials. Clinical Lung Cancer 2012; 13: 107-114.

10. Krzakowski M. Nowotwory płuca, opłucnej i śródpiersia. In: Krzakowski M, Potemski P, Warzocha K, Wysocki P (ed.). Onkologia Kliniczna. Via Medica, Gdańsk 2015: 557-558.
11. Zhang Y, Sheng J, Yang Y et al. Optimized selection of three major EGFR-TKIs in advanced EGFR-positive non-small cell lung cancer: a network metaanalysis. Oncotarget 2016; 7(15): 20104.
12. Krzakowski M, Jassem J. Zasady oceny wartości leczenia systemowego w onkologii. In: Krzakowski M. (ed.) Onkologia kliniczna. Borgis Wydawnictwo Medyczne, Warszawa 2006: 655-656.
13. Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45(2): 228-247.
14. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Control Clin Trials 1996; 17: 343-346.
15. Common Terminology Criteria for adverse events (Version 4.0). [online: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf].
16. Rosell R, Moran T, Queralt C et al. Screening for epidermal growth factor receptor mutations in lung cancer. N Engl J Med 2009; 361(10): 958-967.
17. Zhou C, Wu YL, Chen G et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2011; 12(8): 735-742.
18. Schiller JH, Harrington D, Belani CP et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002; 346(2): 92-98.
19. Shepherd FA, Rodrigues Pereira J, Ciuleanu T et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005; 353(2): 123-132.
20. Thatcher N, Chang A, Parikh P 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): 1527-1537.
21. Sequist LV, Soria JC, Goldman JW et al. Rociletinib in EGFR-mutated non-small-cell lung cancer. N Engl J Med 2015; 372(18): 1700-1709.
22. Mok TS, Wu YL, Ahn MJ et al. Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. N Engl J Med 2017; 376(7): 629-640.
23. Product characteristic: Tarceva. [online: http://ec.europa.eu/health/documents/community-register/2005/200509199999/anx_9999_pl.pdf].
24. Okyuama T, Akazawa Y, Uchida J et al. Subacute transient encephalopathy induced by erlotinib. Oncol Res 2011; 19(8-9): 399-402.

Authors' contributions:
Joanna Kardas: 50%; Agnieszka Buraczewska: 10%; Paweł Chrom: 10%; Anna Waśko-Grabowska: 10%; Beata Młot: 10%; Cezary Szczylik: 10%.
Conflict of interests:
None.
Financial support:
None.
Ethics:
The paper complies with the Helsinki Declaration, EU Directives and harmonized requirements for biomedical journals.