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Targeted Therapy in Patients With Non–small Cell Lung Cancer Previously Treated With Chemotherapy

Monika Drobnienė[1], Audronė Cicėnienė[1], Teresė Pipirienė Želvienė[1], Rūta Grigienė[2], Nadežda Lachej[1], Laura Steponavičienė[1], Eduardas Aleknavičius[1]

[1]Radiotherapy and Drug Therapy Center, Institute of Oncology, Vilnius University,
[2]Diagnostic Radiology Department, Institute of Oncology, Vilnius University, Lithuania

Key words: *lung adenocarcinoma; targeted therapy; erlotinib.*

Summary. *A case of successful and prolonged treatment of metastatic non–small cell lung cancer with the epidermal growth factor receptor antagonist erlotinib is presented. A never-smoker female was diagnosed with stage IV lung cancer in December 2005. A chest CT scan showed soft tissue mass 35×34 mm in size in the right lung with metastases in the lymph nodes and in the left lung. A biopsy revealed a poorly differentiated adenocarcinoma. The disease showed poor response to the first-line and second-line chemotherapy. Targeted therapy with erlotinib was started in February 2007. The most severe adverse event observed was grade 3 skin rash. The disease was stable until February 2009 when brain metastases were detected. Erlotinib was continued until May 2009 when disease progression in the lungs was confirmed. The patient died due to ongoing disease progression in December 2009. Retrospective genetic analysis of a tumor specimen was performed, and no mutations in EGFR exons 18–21 were detected.*

The patient had a significant clinical benefit for the period of 24 months. These results are consistent with previous reports in literature that clinical characteristics such as female gender, nonsmoker, adenocarcinoma histology, and severe cutaneous toxicity seem to predict good response to erlotinib. In the present case, erlotinib proved to be effective even in heavily pretreated, chemotherapy-resistant lung adenocarcinoma. So far, no exact predictive biomarkers of erlotinib effectiveness have been determined; and their further analyses are essential.

Introduction

Lung cancer is the leading cause of cancer death worldwide. Non–small cell lung cancer (NSCLC) accounts for approximately 80% of these cases. Most of the patients present with locally advanced or metastatic disease, and the outcomes of these patients are poor despite advances in treatment. The 5-year age- and area-adjusted relative survival of all lung cancer patients in Europe is low – 11%. In Lithuania, lung cancer is the second most common cancer among men. In contrast, lung cancer incidence rates in women are much lower. In 2009, there were 277 newly diagnosed cases among women (31.8% of cases with stage IV cancer). The 5-year overall survival in women is only 9.2% (1). The survival rate of women with NSCLC treated at the Institute of Oncology, Vilnius University, during 1996–2005 was 8.4 months (2).

Therefore, new agents are investigated and come into practice in the hope to reduce the death rate attributable to lung cancer.

Case Report

A 56-year-old female presented with chronic bronchitis in December 2005 complaining of persistent dry cough and dyspnea for about 2 months. She was treated with antibiotics for about a month for a suspected pneumonia in an outpatient department. As her condition was not improving, the patient was admitted to hospital for examination and treatment. There was no previous history of smoking, comorbidities, or any known risk factors for lung cancer.

A chest x-ray revealed a peripheral tumor with centralization in segment VI of the right lung. Pulmonary metastases were seen in the left lung (Fig. 1). A chest CT scan (December 29, 2005) revealed soft tissue mass 35×34 mm in size and uneven polycyclic contour with the centralization in segment VI of the right lung as well as enlarged hilar and mediastinal lymph nodes and metastases in the left lung (Fig. 2). Fiberoptic bronchoscopy showed narrowed SVI and SX bronchi of the lower lobe of the right lung and infiltrated bronchial mucosa. A biopsy was performed.

Correspondence to M. Drobnienė, Radiotherapy and Drug Therapy Center, Institute of Oncology, Vilnius University, Santariškių 1, 08660 Vilnius, Lithuania
E-mail: monika.drobniene@gmail.com

Adresas susirašinėti: M. Drobnienė, VUOI Spindulinės ir medikamentinės terapijos centras, Santariškių 1, 08660 Vilnius
El. paštas: monika.drobniene@gmail.com

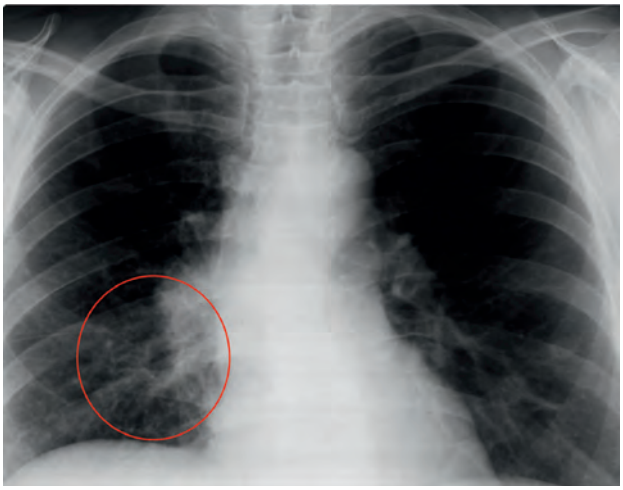

Fig. 1. Chest x-ray (December 29, 2005)
A peripheral tumor with centralization in segment VI of the right lung. Pulmonary metastases are seen in the left lung.

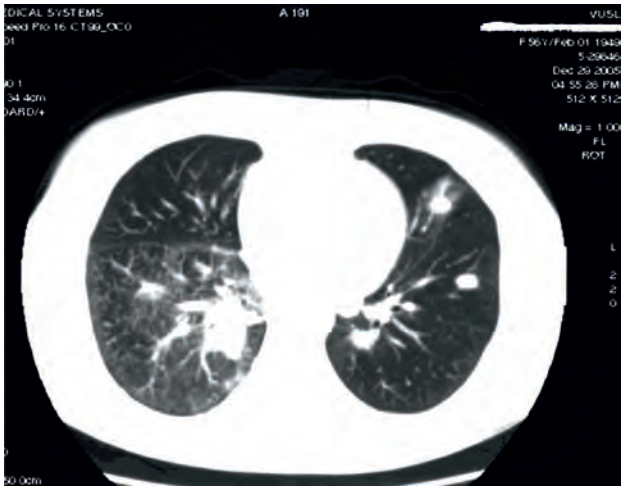

Fig. 2. A chest CT scan (December 29, 2005) revealing soft tissue mass 35×34 mm in size and uneven polycyclic contour with centralization in segment VI of the right lung
Enlarged hilar and mediastinal lymph nodes are not clearly seen in this view. Metastases in the left lung.

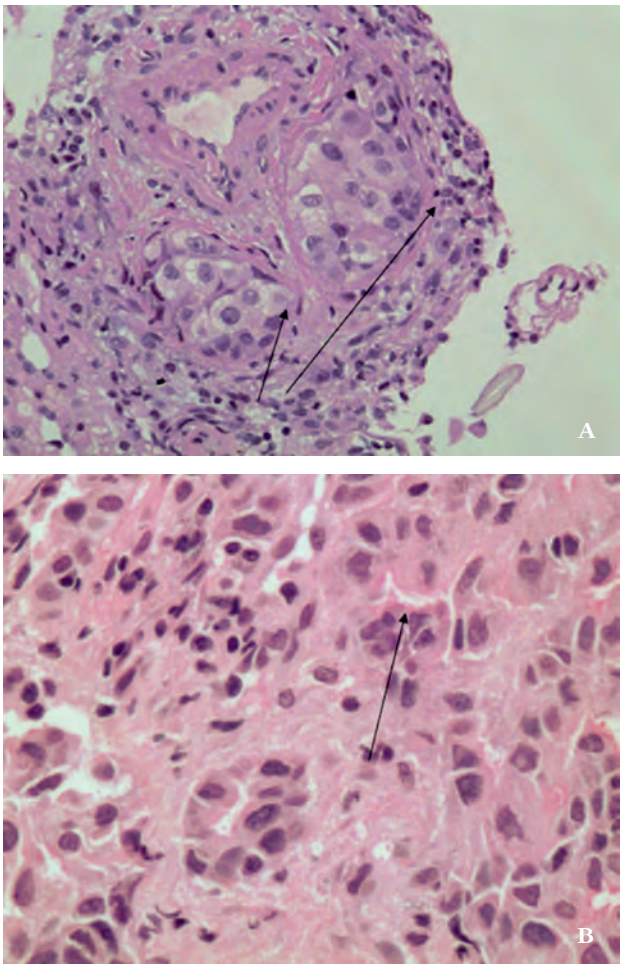

Fig. 3. Neoplastic cells showing poor glandular formation
A, hematoxylin (×200); B, mucicarmine (×200).

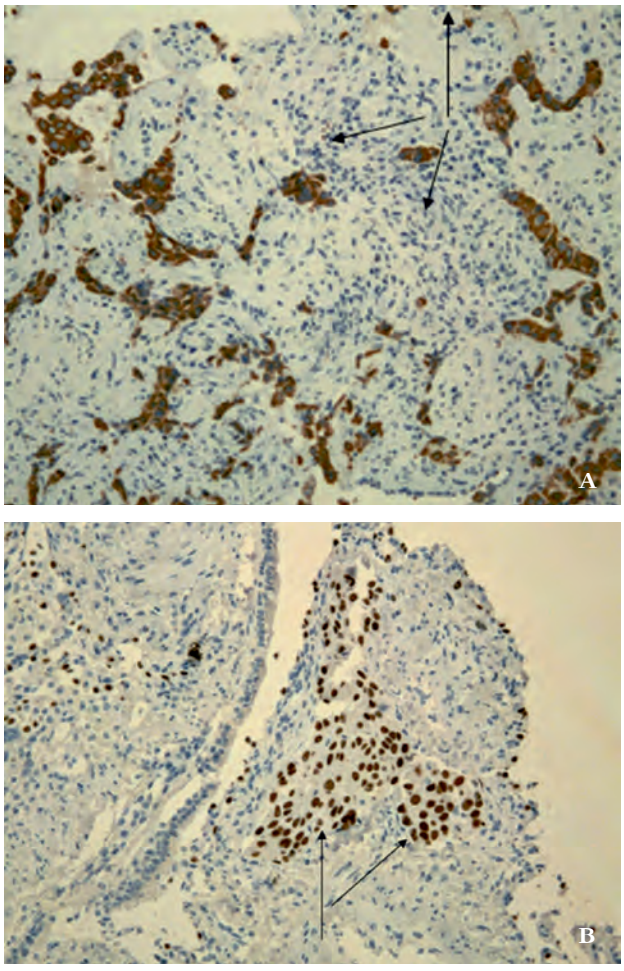

Fig. 4. Epithelial tumor with poor glandular formation
A, positive for cytokeratin 7 (×100); B, positive for thyroid transcription factor 1 (×100).

It revealed G3 adenocarcinoma (Fig. 3 and 4).

According to the clinical and histological findings, stage IV central adenocarcinoma of the right lung (cT2 N2 M1) with metastases to the left lung was diagnosed. The patient had ECOG performance status of 0. There were no pathological changes in other organ systems and laboratory values.

From January 2006 until May 2006, 6 cycles of palliative chemotherapy with paclitaxel (175 mg/m^2, on day 1) and carboplatin (300 mg/m^2, on day 1) were administered every 3 weeks.

After chemotherapy, a chest CT scan showed partial response (Fig. 5): peripheral soft tissue mass in the right lung decreased up to 19.4×23.3 mm in size. Pulmonary metastases in the left lung also decreased in size. Mediastinal and hilar lymph nodes did not change. As such a partial response was considered insufficient and due to grade 2 neurotoxicity caused by paclitaxel, it was decided to continue chemotherapy with cisplatin (60 mg/m^2, on day 1) and gemcitabine (1000 mg/m^2, on days 1 and 8).

After completion of 6 cycles of this chemotherapy regimen, a CT scan was performed on December 20, 2006, which did not show any significant changes, i.e., the disease was stable (Fig. 6). According to a good performance status of the patient and laboratory findings, it was decided to continue treatment with targeted therapy. Erlotinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), at a dosage of 150 mg/day was administered on February 27, 2007. After 6 days of this therapy, grade 3 (according to the Common Terminology Criteria for Adverse Events version 3.0, CTCAE v3.0) rash (acneiform dermatitis) developed. Bacterial culture grew *Staphylococcus* (coagulase-negative) and *Micrococcus luteus*.

Papulopustular eruptions improved with temporal discontinuation of erlotinib until April 11, 2007, and with the application of topical antibiotics. After the improvement of skin condition, the treatment was renewed with a dosage reduced to 100 mg/day. The patient also experienced other undesirable grade 1/2 (according to the CTCAE v3.0) erlotinib-specific side effects such as pruritus, dry skin, conjunctivitis, fatigue, paronychia, and loose nails.

A control CT scan (July 23, 2007) showed a very good clinical effect on all pulmonary lesions; tumor mass was not seen clearly (Fig. 7). After 15-month therapy, a CT scan (May 10, 2008) showed a suspicious nodule in the left lung with a background of fibrosis, which minutely increased up to 13 mm in size in September (Fig. 8). Since the patient was of good ECOG performance status and there were no changes of other pulmonary lesions, the treatment with erlotinib was further administered.

Stable disease was observed until February 2009 when the patient began to complain of severe headache and vertigo. Multiple brain metastases were detected by brain CT scan. The surgical treatment of metastases was discussed, but due to the prolonged disease and poor prognostic criteria, it was not chosen. Salvage whole-brain radiotherapy was administered. Erlotinib was continued until May 2009 when the progressive disease in lungs was confirmed by a CT scan. Then, 6 cycles of palliative chemotherapy with docetaxel were given until October 2009. Brain and chest CT scans showed minimal effects of the chemotherapy.

The patient died due to ongoing disease progression in December 2009.

Discussion

The current standard of care of the patients presented with locally advanced or metastatic lung

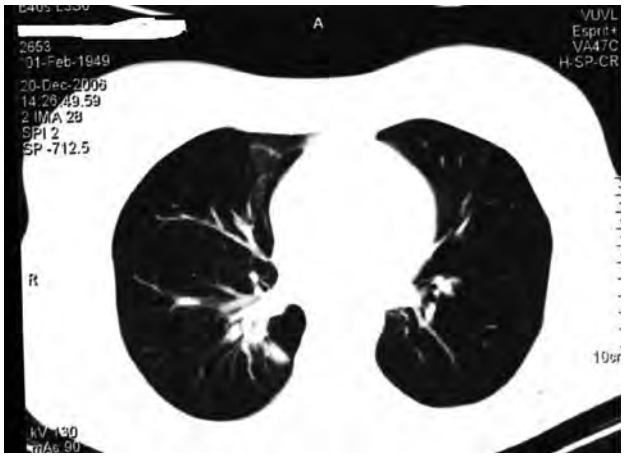

Fig. 5. A CT scan (May 17, 2006): peripheral soft tissue mass in the right lung decreased up to 19.4×23.3 mm in size

Pulmonary metastases in the left lung also decreased in size. Mediastinal and hilar lymph nodes did not change. Partial response.

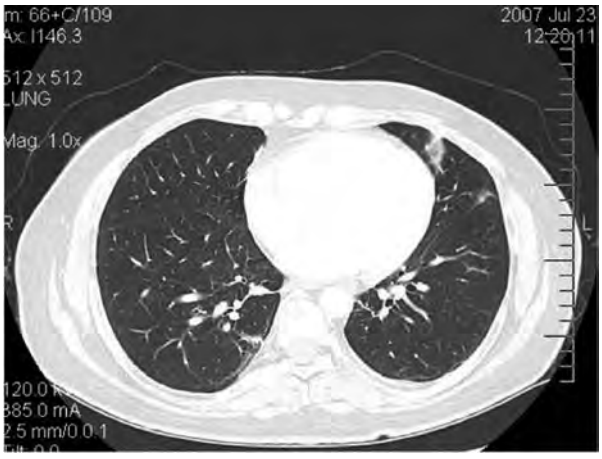

Fig. 6. A CT scan (December 20, 2006): stable disease

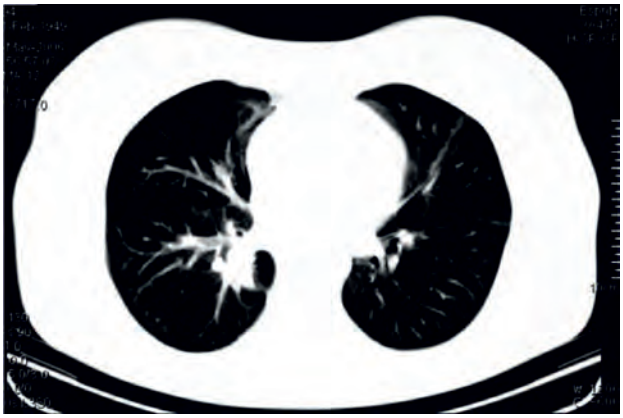

Fig. 7. A CT scan (July 23, 2007): after 5-month treatment with erlotinib, narrowed SVI bronchus, deformed hilum of the lung, and pulmonary fibrosis without clear tumor mass are seen

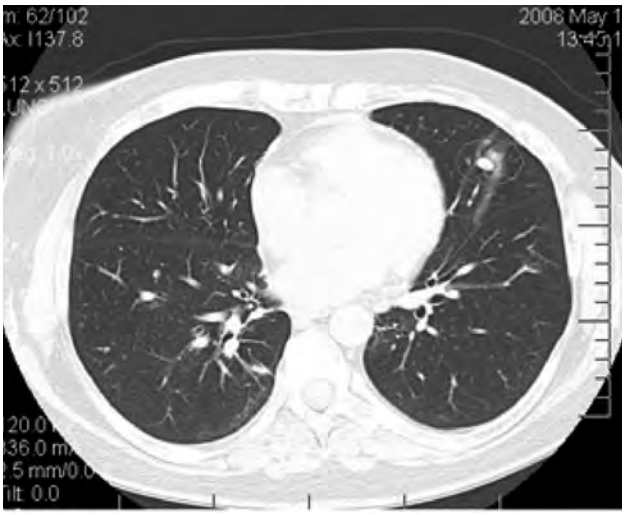

Fig. 8. A CT scan (May 10, 2008): after 15-month treatment with erlotinib, a suspicious nodule in the left lung with a background of fibrosis was documented

cancer is the systemic chemotherapy with two-drug combination regimens that includes a platinum agent, such as cisplatin plus paclitaxel; cisplatin plus gemcitabine; cisplatin plus docetaxel; and carboplatin plus paclitaxel, etc. The overall response rates comparing all these regimens range from 17% to 22%; the median survival varies from 7.4 to 8.1 months (3).

The median survival of untreated patients is only 4 to 5 months. The 1-year overall survival rate is 33% (the 1-year survival rate of untreated patients is only 10%), and the 2-year overall survival rate is 11%. None of the regimens appeared to be superior to the others (3, 4). As the regimen of carboplatin and paclitaxel is less toxic than the other regimens, the patient received it as the first-line chemotherapy and achieved partial response. She also did not benefit significantly from the second-line chemotherapy and proceeded with the third-line therapy – EGRF antagonist erlotinib.

EGFR is expressed in 40% to 80% of lung cancers, which makes this an attractive target for molecular intervention in this disease. Erlotinib and gefitinib were the first two agents to target the tyrosine kinase of the EGFR (5). Erlotinib is a small-molecule EGFR tyrosine kinase inhibitor, which blocks EGFR autophosphorylation and downstream signaling.

Erlotinib was approved by the FDA in November 2004 and by the EMEA in September 2005 for the treatment of patients with non–small cell lung cancer as a second- or third-line therapy based on the results of the National Cancer Institute of Canada Clinical Trials Group BR.21 trial, a phase 3, randomized, double-blind, placebo-controlled study published by Shepherd et al. in July 2005. In this study, patients with stage IIIB or IV NSCLC who had progressed through one or two prior regimens of chemotherapy were randomized to receive placebo or erlotinib. Erlotinib increased the median survival by approximately 2 months. Erlotinib is now also indicated as monotherapy for maintenance treatment in patients with locally advanced or metastatic NSCLC with stable disease after 4 cycles of standard platinum-based first-line chemotherapy.

Since only a subgroup of patients with cancer had a clinical benefit from the treatment with EGFR inhibitors, there was an urgent need for identification and clinical validation of useful criteria for selecting patients for such treatment (6).

Most clinical studies of gefitinib or erlotinib in NSCLC have suggested that Asian ethnic background, female sex, absence of a history of smoking, and a tumor with histological features of adenocarcinoma are the potential predictors of positive clinical response to anti-EGFR therapy (7, 8)

Moreover, the presence or absence of cutaneous toxic effects and their severity were the most important clinical correlates of the efficacy of anti-EGFR therapy (9).

At that time our patient was treated in Lithuania, it was difficult to determine and use in clinical practice exact molecular markers to select the patients who would be most likely to benefit from EGFR antagonists. Thus, only indicated clinical predictors of a positive clinical response to erlotinib were used. Retrospectively, when preparing this article, molecular genetic and immunohistochemical analyses of a patient's histological sample were performed.

It has been proven that efficacy of gefitinib therapy strongly depends on *EGFR* mutation status in Asian patients with NSCLC (10).

The association between EGFR expression and mutations, and a response to erlotinib has been investigated in several clinical studies (6). In the

BR.21 trial, the overall response rate was 8.9%, and this study was the first to demonstrate a significant survival advantage for treatment with EGFR-TKI in previously treated patients with NSCLC (hazard ratio [HR]=0.70, $P<0.001$). Analysis of the subsets of BR.21 patients showed that response rates were 7% for wild type and 27% for mutant *EGFR* ($P=0.03$). A significant survival benefit from erlotinib therapy was observed in patients with wild-type *KRAS* (HR=0.69, $P=0.03$) and *EGFR* fluorescent in situ hybridization (FISH) positivity (HR=0.43, $P=0.004$), but not in patients with mutant *KRAS* (HR=1.67, $P=0.31$), wild-type *EGFR* (HR=0.74, $P=0.09$), mutant *EGFR* (HR=0.55, $P=0.12$), and *EGFR* FISH negativity (HR=0.80, $P=0.35$). In multivariate analysis, only *EGFR* FISH-positive status was prognostic of poorer survival ($P=0.025$) and predictive of differential survival benefit from erlotinib ($P=0.005$). This indicates that erlotinib therapy might be also beneficial in terms of survival irrespective of *EGFR* mutation status (10, 11).

Molecular genetic analysis of a tumor sample of our patient revealed that there were no mutations in exons 18–21 of *EGFR*. In these exons, the mutations are most frequently detected. This finding might be interpreted as a presence of unknown active mutations in other exons of *EGFR* genes, high *EGFR* gene copy number, a presence of another potential pathway related to antitumor activity rather than EGFR pathway, or other specific predictive factors. Thus, further studies in such patient settings are essential. In our case, the clinical benefit achieved using erlotinib lasted 24 months.

Immunohistochemically, EGFR was moderately expressed in 40% of the patient's cancer cells. Although this test or analysis of *EGFR* gene copy number by fluorescent in situ hybridization is not recommended for routine clinical use, the latest clinical guidelines still recommend *EGFR* somatic mutation testing to be carried out to identify the patients eligible for treatment with EGFR-TKIs (12).

Moreover, in a phase 2 prospective biomarker study, which evaluated erlotinib monotherapy in pretreated Japanese patients with *EGFR* wild-type tumors, 1 of the 30 patients responded to erlotinib therapy. No mutations were detected in the tumor specimens of this female patient. This phenomenon suggests that physicians should be aware that a patient could respond well to the TKI therapy even when mutation analysis reveals a "mutant-negative" result (10).

Clinical trials have shown that erlotinib has an important clinical activity and manageable side effects in patients with metastatic, chemorefractory NSCLC (13, 14). Dose-dependent and reversible diarrhea and acneiform rash have been the most prominent side effects. The histological characteristics of rash differ from typical acne and are common to all EGFR-targeted drugs (15). Skin toxicity is generally observed within 2 to 3 weeks after the start of treatment, and it gradually resolves continuing treatment or after dose reduction.

In the BR.21 clinical trial, toxic effects were mild; there were 5% of patients who discontinued treatment due to drug-related adverse events. The most frequent grade 3 and 4 adverse events in the erlotinib arm were skin rash (9%) and diarrhea (6%), with 19% of patients in the erlotinib group requiring dose reductions (mostly due to skin rash and diarrhea). There were similar rates of pneumonitis and pulmonary fibrosis in the two groups (<1%) (16). The patient described in this case report experienced grade 3 rash within the first week.

Conclusions

The results of the present study are consistent with and confirm previous reports from literature that clinical characteristics such as female gender, nonsmoker, adenocarcinoma histology, and severe cutaneous toxicity seem to predict response to erlotinib. Retrospective genetic analysis for *EGFR* status of a patient's tumor specimen was performed to show a negative result. In the present case, erlotinib still proved to be effective in pretreated, chemotherapy-resistant lung adenocarcinoma. Further studies in such patient settings evaluating predictive factors are needed.

Statement of Conflict of Interest

The authors state no conflict of interest.

Nesmulkialąstelinio plaučių vėžio gydymas taikinių terapija po anksčiau taikytos chemoterapijos

Monika Drobnienė[1], Audronė Cicėnienė[1], Teresė Pipirienė Želvienė[1], Rūta Grigienė[2], Nadežda Lachej[1], Laura Steponavičienė[1], Eduardas Aleknavičius[1]

[1]Vilniaus universiteto Onkologijos instituto Spindulinės ir medikamentinės terapijos centras,
[2]Vilniaus universiteto Onkologijos instituto Diagnostinės radiologijos skyrius

Raktažodžiai: plaučių adenokarcinoma, taikinių terapija, erlotinibas.

Santrauka. Pristatomas metastazavusio nesmulkialąstelinio plaučių vėžio sėkmingo gydymo epidermio augimo faktoriaus antagonistu erlotinibu klinikinis atvejis. Niekada nerūkiusiai moteriai 2005 m. gruodį diagnozuotas IV stadijos plaučių vėžys. Krūtinės ląstos kompiuterinėje tomogramoje dešiniojo plaučio S6 segmente rastas 35×34 mm skersmens minkštųjų audinių tankio darinys su padidėjusiais tarpuplaučio, dešiniosios šaknies limfmazgiais ir metastazėmis kairiajame plautyje. Bronchoskopijos metu atlikus biopsiją, nustatyta blogai diferencijuota adenokarcinoma. Po pirmos ir antros eilės chemoterapijos pastebėtas nepakankamas gydomasis poveikis. Biologinės taikinių terapijos epidermio augimo faktoriaus receptorių tirozinkinazės inhibitoriumi erlotinibu metu, kuris buvo skirtas 2007 m. vasarį, konstatuotas labai geras klinikinis poveikis. Gydymo metu ryškiausias šalutinis reiškinys buvo 3 laipsnio odos išbėrimas. Geras poveikis išliko iki 2009 m. vasario, kai buvo nustatytos metastazės galvos smegenyse. Gydymas erlotinibu tęstas iki 2009 m. gegužės, kai, atlikus kompiuterinės tomografijos tyrimą, nustatytas ligos progresavimas plaučiuose. Pacientė mirė 2009 m. gruodį nuo tolesnio ligos progresavimo. Retrospektyviai atlikus genetinį naviko tyrimą, EGFR geno 18–21 egzonų mutacijų nenustatyta.

Pasiektas reikšmingas klinikinis atsakas, kuris išliko 24 mėn. Šie duomenys atitinka analogiškus publikuotus, kad nerūkanti moteris, serganti plaučių adenokarcinoma, bei išreikštas odos pažeidimas leidžia tikėtis gero atsako į epidermio augimo faktoriaus receptorių tirozinkinazės inhibitorius, netgi esant chemoterapijai atspariam vėžiui. Iki šiol nėra tikslių predikcinių erlotinibo veiksmingumo biožymenų, todėl būtini tolesni jų tyrinėjimai.

References

1. Smailytė G, Aleknavičienė B. Vėžys Lietuvoje 2009 metais. Vėžio registras, Vėžio kontrolės ir profilaktikos centras, Vilniaus universiteto Onkologijos institutas. 2011. p. 9-39.
2. Cicėnas S, Kurtinaitis J, Smailytė G. Outcome and treatment strategy in female lung cancer: a single institution experience. Adv Med Sci 2010;55(2):273-80.
3. Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002;346:92-8.
4. Rapp E, Pater JL, Wilan A, Cormier Y, Murray N, Evans WK, et al. Chemotherapy can prolong survival in patients with advanced non-small-cell lung cancer – report of a Canadian multicenter randomized trial. J Clin Oncol 1998;6:633-41.
5. DeVita VT, Hellman S, Rosenberg SA, editors. Cancer: principles and practice of oncology. 8th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2008. p. 936.
6. Ciardiello F, Tortora G. EGFR antagonists in cancer treatment. N Engl J Med 2008;358:1160-74.
7. Karamouzis MV, Grandis JR, Argiris A. Therapies directed against epidermal growth factor receptor in aerodigestive carcinomas. JAMA 2007;298:70-82.
8. Sridhar SS, Seymour L, Shepherd FA. Inhibitors of epidermal-growth-factor receptors: a review of clinical research with a focus on non-small-cell lung cancer. Lancet Oncol 2003;4:397-406.
9. Wacker B, Nagrani T, Weinberg J, Witt K, Clark G, Cagnoni PJ. Correlation between development of rash and efficacy in patients treated with the epidermal growth factor receptor tyrosine kinase inhibitor erlotinib in two large phase III studies. Clin Cancer Res 2007;13:3913-21.
10. Yoshioka H, Hotta K, Kiura K, Takigawa N, Hayashi H, Harita S, et al. A phase II trial of erlotinib monotherapy in pretreated patients with advanced non-small cell lung cancer who do not possess active EGFR mutations. J Thorac Oncol 2010;5:99-104.
11. Zhu CQ, da Cunha Santos G, Ding K, Sakurada A, Cutz JC, Liu N, et al. Role of KRAS and EGFR as biomarkers of response to erlotinib in National Cancer Institute of Canada Clinical Trials Group Study BR.21. J Clin Oncol 2008;26:4268-75.
12. Felip E, Gridelli C, Baas P, Rosell R, Stahel R; Panel Members. Metastatic non-small-cell lung cancer: consensus on pathology and molecular tests, first-line, second-line, and third-line therapy: 1st ESMO Consensus Conference in Lung Cancer; Lugano 2010. Ann Oncol 2011;22:1507-19.
13. Ranson M, Hammond LA, Ferry D, Kris M, Tullo A, Murray PI, et al. ZD1839, a selective oral epidermal growth factor receptor-tyrosine kinase inhibitor, is well tolerated and active in patients with solid, malignant tumors: results of a phase I trial. J Clin Oncol 2002;20:2240-50.
14. Hidalgo M, Siu LL, Nemunaitis J, Rizzo J, Hammond LA, Takimoto C, et al. Phase I and pharmacologic study of OSI-774, an epidermal growth factor receptor tyrosine kinase inhibitor, in patients with advanced solid malignancies. J Clin Oncol 2001;19:3267-79.
15. Lacouture ME. Mechanisms of cutaneous toxicities to EGFR inhibitors. Nat Rev Cancer 2006;6:803-12.
16. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005;353:123-32.

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