Good Clinical Response to Erlotinib in a Lung Adenocancer Patient and Grade 3 Skin Rash: A Case Report

Akciğer Adenokanserli Hastada Erlotinibe İyi Klinik Yanıt ve Evre 3 Cilt Döküntüsü: Olgu Sunumu

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Abstract
Epidermal growth factor receptor (EGFR) has received a particular attention in lung cancer treatment. Erlotinib, an orally available inhibitor of EGFR tyrosine kinase (EGFR-TKI), has been proven to prolong survival in non-small cell lung cancer (NSCLC) patients after first or second line chemotherapy. Skin rash is the most common adverse event associated with erlotinib treatment and a significant correlation between severity of rash and survival has been found. We report a case of lung adenocancer that we obtain good response together with severe skin rash by erlotinib therapy.

Key words: **Drug Eruptions; Erlotinib; Lung Neoplasms; Receptor Protein-Tyrosine Kinases.**

Özet
Akciğer kanseri tedavisinde epidermal büyüme faktörü reseptörü (EBFR) önemli bir ilgi görmektedir. Oral bir EBFR tirozin kinaz inhibitörü (EBFR-TKİ) olan erlotinibin, birinci veya ikinci sıra kemoterapi sonrasında küçük hücreli dışı akciğer kanseri (KHDAK) bulunan hastalarda sağkalımı uzattığı kanıtlanmıştır. Cilt döküntüsü erlotinib tedavisi ile ilişkili en sık yan etkidir ve döküntünün şiddeti ile sağkalım arasında önemli bir korelasyon olduğu bulunmuştur. Erlotinib tedavisi sonucu ciddi cilt döküntüsü ile beraber iyi cevap elde edilen bir akciğer adenokanseri olgusunu sunuyoruz.

Anahtar Kelimeler: **Akciğer tümörleri; Erlotinip; Erlotinib; İlaç döküntüleri; Reseptör Protein Tirozin Kinazlar.**

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Introduction

Erlotinib is a highly potent, orally available, reversible inhibitor of epidermal growth factor receptor (HER1/EGFR) tyrosine kinase. Erlotinib has been demonstrated to provide survival improvement in addition to control of the most distressing lung cancer symptoms and improvement in quality of life for patients with metastatic NSCLC after failure of at least one prior chemotherapy regimen (1).

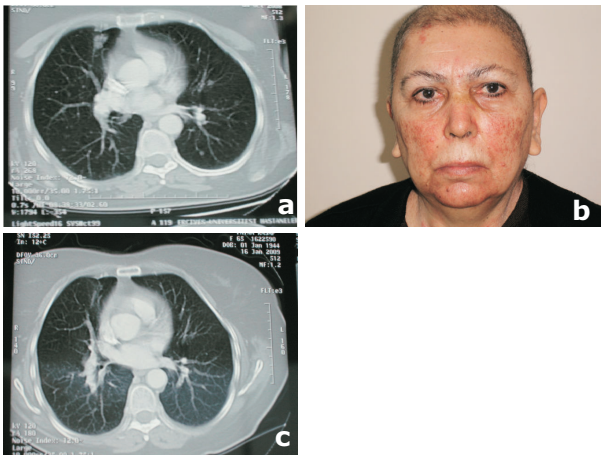
Skin rash is a common side-effect of all HER1/EGFR inhibitors occurring in at least %75 patients receiving erlotinib therapy (2-6). It has been suggested that rash could be used as an objective response to therapy. Skin rash seems to be a surrogate marker of clinical benefit (7). We report a case of lung adenocancer treated with erlotinib and in which we obtain a good response together with grade 3 skin rash.

Case Report

A 64-year old woman admitted to our hospital with the complaint of the left shoulder pain and tingle spreading to the arm. A smoother tissue mass painting with contrast was detected in the 5 and 6 cervical spine corpuses by the magnetic resonance imaging (MRI). She underwent corpectomy and surgical pathology demonstrated adenocancer metastasis.

We performed a comprehensive search for primary malignancy. Her medical history and physical examination did not have any features about malignancy. Total body bone scan revealed bone metastasis in 6–7 cervical spine corpuses and sakroiliac joint. Palliative radiation therapy performed including metastatic sites. There was no pathology in gynecologic and other systemic examinations, computerized tomography (CT) scans of the abdomen, mammography and breast ultrasonography.

Tumor markers including CEA, CA15–3, CA–19, CA–125, hCG and AFP were normal. A few millimetric lymph nodules (the biggest one's diameter was 13 mm) in mediastine and bilateral millimetric subpleural and intraparenchymal nodules that the biggest one was in the right lung upper lobe anterior inferior segment and had 20 mm diameter were detected in CT scans of chest (Picture 1a). A positron emission tomography-computerized tomography (PET-CT) scan showed the elevated 18F-Fluorodeoxyglucose (FDG) uptake in the right lung middle lobe, right hilar region, right paratracheal lymph nodule, neighborhood of the 4–6 cervical spines and right iliac bone. So that it was thought to be NSCLC as primary tumor and then combination with paclitaxel (175 mg/m^2) and carboplatin (5AUC) was performed as an initial chemotherapy. Chemotherapy was planned to be administered intravenously every 21 days for up to 6 cycles. After 3 cycles we performed CT scans of chest to evaluate tumor response. There was minimal response so chemotherapy was completed to 6 cycles. After 6 cycles tumor response was evaluated as stable disease according to comparative CT scans of chest. In the follow up period, after 2 months, we repeated CT and progression was detected. Erlotinib (150 mg/day) was begun as second line chemotherapy. At the tenth day of the treatment grade 3 skin rash was occurred on the face, neck, upper chest and back as a common side effect of the drug (Picture 1b). We continued chemotherapy with symptomatic treatment for rash (topical corticosteroid and antihistaminic). Evaluation at the second month of erlotinib therapy with Response Evaluation Criteria In Solid Tumors (RECIST) was revealed regression (Picture 1c) with skin rash recovery. Because of the good response and manageable toxicity our patient's treatment is still going on.



Picture 1. (a) Bilateral millimetric subpleural and intraparenchymal nodules. The biggest one is in the right lung upper lobe anterior inferior segment and has 20 mm diameter. **(b)** Grade III skin rash (Generalized erythroderma and pustular eruption) was occurred by erlotinib on the face at the tenth day of the treatment as drug side effect. The skin rash was graded according to the National Cancer Institute: Common Terminology Criteria for Adverse Events. **(c)** Two months after erlotinib treatment. Regression of subpleural and intraparenchymal nodules.

Discussion

Erlotinib, a quinazolinamine, is a highly potent, orally available, reversible inhibitor of EGFR tyrosine kinase. In a phase III randomized placebo-controlled trial (TRIBUTE), erlotinib has been proven to prolong survival in NSCLC patients after first or second line chemotherapy (8). Following this trial, erlotinib has been approved by Food and Drug Administration and Committee for Medicinal Products for Human use in chemotherapy-pretreated advanced NSCLC. In a phase III trial subgroup analysis showed that all patient subgroups demonstrated benefit from second-line erlotinib treatment; improved benefit was observed in patients who developed rash, in female patients, in never smokers, in Asian patients, in patients with positive EGFR status, and in patients with adenocarcinoma histology (9). In our patient we began erlotinib as a second line treatment after first line platinum-based chemotherapy failure due to coincide with mentioned criteria above of adenocarcinoma histology, female sex, never smoker and Asian origin.

The most common side-effects in patients receiving erlotinib are skin rash and diarrhea (10). Skin rash generally develops within 7–10 days of starting treatment and commonly affected areas include the face (nose, cheeks, nasolabial folds, chin and forehead), the upper chest and/or back and less frequently on the scalp, arms and/or legs, abdomen and buttocks, but sparing palms, soles and mucosa (8, 10,11). Similarly our patient developed rash on her face at the tenth day of the erlotinib treatment.

The skin reaction is increasingly considered an indirect marker of relevant in vivo EGFR targeting. Pharmacokinetic studies have shown that rash parallels saturation of receptor clearance and may be used as an indirect measure of effective receptor saturation and blockade at the higher dose levels or as an indicator for optimum biologic dose (12). However, this raises the question of why about one third of patients do not develop skin toxicity. It has been suggested that the variability in skin toxicity may be related to pharmacokinetic and pharmacodynamic differences and EGFR polymorphisms among patients (13-15).

In three phase II trials of erlotinib in patients with advanced NSCLC, advanced head and neck squamous cell carcinoma and advanced ovarian cancer, a significant correlation between rash and survival was found, with the median duration of survival increasing with severity of rash (16).

As consistent with literature, we obtained good response together with grade III skin rash in our patient. Finally, for patients with advanced NSCLC who progressed following first-line platinum-based chemotherapy have adenocarcinoma histology, female sex, never smoker and Asian origin, the data demonstrate that second-line EGFR-TKI treatment is efficacious and well-tolerated in this chosen group.

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