Resistance to Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitors by Transformation to Small Cell Lung Cancer in an EGFR-mutant Patient

EGFR Mutasyonu Olan bir Hastada Küçük Hücreli Akciğer Kanserine Dönüşüm Yoluyla Gelişen Epidermal Büyüme Faktörü Reseptörü-Tirozin Kinaz İnhibitör Direnci

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Abstract

It is important to determine the histological tumor type in non-small cell lung cancer (NSCLC). In patients with adenocarcinoma harboring the epidermal growth factor receptor (EGFR) exon 19 deletion mutation, targeted therapy can yield survival benefit. The epidermal growth factor receptor tyrosine kinase inhibitors gefitinib and erlotinib can provide survival benefit for advanced stage NSCLC patients. However, increasing evidence of acquired resistance to these drugs has been reported, and numerous molecular and biological mechanisms of acquired resistance have been detected. The present report is description of 1, such resistance mechanisms: transformation to small cell lung cancer in a patient who was in the 13th month of erlotinib therapy.

Key words: Non-small cell lung cancer, epidermal growth factor tyrosine kinase inhibitors, resistance mechanism, small cell carcinoma transformation.

Özet

Küçük hücre dışı akciğer karsinomunda subtiplendirmenin yapılması önemlidir. Epidermal growth factor reseptör (EGFR) Egzon 19 delesyonuna sahip adenokarsinomlu olgularda, gefitinib ve erlotinib olarak bilinen EGFR-Tirozin kinaz inhibitörü tedaviler ile ileri evre hastalarda sağkalımda fayda elde edilebilmektedir. Ancak birçok moleküler ve biyolojik mekanizmalar ile bu ilaçlara karşı direnç gelişebilmektedir. Bu yazıda, erlotinib tedavisinin 13. ayında, direnç mekanizmalarından biri olan küçük hücreli akciğer kanseri dönüşümünü, bir olgu eşliğinde sunmayı amaçladık.

Anahtar Sözcükler: Küçük hücre dışı akciğer kanseri, epidermal büyüme faktörü tirozin kinaz İnhibitörleri, rezistans mekanizmaları, küçük hücreli akciğer kanseri dönüşümü.

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RESPIRATORY CASE REPORTS

The ErbB family of proteins, and includes 4 different tyrosine kinase receptors: EGFR, ErbB-2, ErbB-3, and ErbB-4. They are activated in human carcinomas when an EGF-like peptide binds to an EGF receptor. EGFR plays a major role in tumor growth. Following EGFR signaling, many other angiogenic proteins are secreted into the tumor micro-environment, which may facilitate growth and metastasis of cancer tissue (1). EGFR may be over-expressed in many epithelial cancers, including NSCLC.

Some somatic deletions on the EGFR gene lead to amplified EGFR copies and worsen the prognosis (2). An L858R point mutation and the exon 19 deletion are the most frequently seen EGFR mutations (3). EGFR-tyrosine kinase inhibitors (TKIs) are used as targeted therapy in patients with NSCLC who have an active EGFR mutation. Erlotinib and gefitinib are first generation EGFR-TKIs drugs, and provide progression-free survival. The best response to these drugs is obtained in patients who are of Asian race, female gender, non-smokers, and have adenocarcinoma (4, 5). A significantly greater response rate and progression-free survival can be obtained with first generation EGFR-TKIs in first-line treatment than with platinum-based chemotherapy in EGFR-mutated NSCLC. But overall survival does not differ. The most common adverse effects of EGFR-TKIs are dry skin, diarrhea, skin rash, and elevated serum transaminases. According to studies investigating EGFR-TKIs in elderly patients with NSCLC, it has been reported that erlotinib and gefitinib may be considered as first-line treatment since the side effects are less serious and the drugs are generally well tolerated. There is no significant contribution to clinical response using EGFR-TKIs in combination with standard chemotherapy regimens (6).

Although they have great clinical efficacy, primary or acquired resistance is inevitable. There are currently limited data about primary resistance. The coexistence of a T790M mutation with exon 19 deletion, BIM deletion polymorphism, and mesenchymal-epithelial transition (MET) amplification, are the pathways most suspected in primary resistance (7). EGFR T790M substitution, MET and ERBB2 gene amplification, overexpression of hepatocyte growth factor, down regulation of phosphatase and tensin homolog (PTEN) and transformation to SCLC are well-defined pathways of acquired resistance usually seen between months of 9 and 14 of EGFR-TKI treatment (8). In this instance afatinib and dacomitinib, second generation EGFR-TKIs, which bind irreversibly to EGFR receptors, may be considered as targeted therapy for patients who have resistance to first-line EGFR-TKIs (9, 10). T790M is the most common secondary mutation and it prevents binding of first-line EGFR-TKIs to receptors, but afatinib can block the adenosine 5'-triphosphate-binding site of a tyrosine kinase receptor and the cancer cell goes to apoptosis (6). According to the LUX-Lung 1 study comparing afatinib to a placebo in patients with acquired resistance to first-line EGFR-TKIs, afatinib was superior to placebo in terms of median progression-free survival and response rate (11).

SCLC transformation in patients with adenocarcinoma is rarer than other resistance mechanisms; fewer than 30 cases have been reported so far. There are some reports demonstrating the importance of a PTEN M2641 mutation and the PI3K-AKT pathway in SCLC transformation, but these molecular anomalies do not suffice to explain the mechanism; hence, the subject is still unclear (8).

Presently described is the case of an NSCLC patient with mutant EGFR developing SCLC transformation in the 13th month of EGFR-TKI treatment, and a review of the literature.

CASE

A 59-year-old male who was a non-smoker with chronic cough was referred to the hospital due to suspected lung cancer. Chest X-ray revealed pleural effusion in the left hemithorax, and diagnostic thoracentesis was performed (Figure 1d). Based on the cell-block examination, the diagnosis was metastasis of lung adenocarcinoma with thyroid transcription factor-1 (TTF-1) positivity. 18F-Fluorodeoxyglucose-positron emission tomography-computed tomography (18F-FDG PET-CT) revealed a 2.9x2.5 cm mass on the left lung apical lobe with maximum standardized uptake value (SUV-max) of 12.3, 4.3x3.3 cm aorta-pulmonary lymphadenopathy with SUV-max of 13.9, locally increased FDG uptake in the left parietal pleura, hypermetabolic lesions in the left surrenal gland (SUV-max: 15.4), and multiple bone metastases, including left ischium and neck of femoral bone (Figure 1a,b, and c). The patient underwent first-line chemotherapy with 4 cycles of cisplatin-gemcitabine followed by palliative radiotherapy at 2000 centigray in 5 fractions to an existing lytic lesion causing pain on the left hip. Pleural effusion and lesion on the left upper lobe demonstrated partial response, according to the Response Evaluation Criteria in Solid Tumors criteria (Figure 1e).
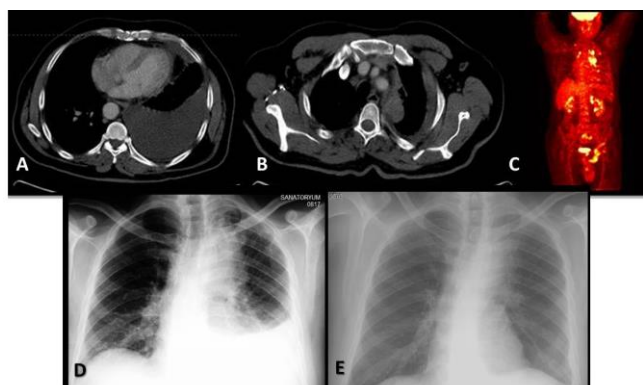
Figure 1a, b, c, d, and e: Left apical mass with ipsilateral pleural effusion and multiple bone metastases (a, b, c), Chest X-ray demonstrates left hilar enlargement and left pleural effusion (d), Regression of pathological findings illustrated on chest X-ray after 4 cycles of cisplatin-gemcitabine (e)

In the second month of follow-up, the patient was admitted with dyspnea. CT of thorax revealed progression of the primary lesion and newly formed pleural effusion in the left hemithorax (Figure 2a and b). He had EGFR exon 19 deletion, so EGFR-TKI therapy of erlotinib 150 mg/day was initiated as second-line treatment. There was good radiological response seen on CT performed in ninth month of erlotinib therapy (Figure 2c and d). In the 13th month of EGFR-TKI treatment, disease progressed in both the primary lesion and metastatic sides, according to results of 18F-FDG PET-CT (Figure 3a), so 5 cycles of pemetrexed-cisplatin were administered as third-line chemotherapy. After the latest session, the mass in the left apical lobe progressed (Figure 3b and c) again and re-biopsy was performed with transthoracic fine needle aspiration (TTFNA). His new pathological diagnosis was, surprisingly, high-grade neuroendocrine carcinoma combined with SCLC (Figure 3d). Following standard procedures, DNA obtained using a cobas DNA sample preparation kit (Roche Molecular Systems, Inc., Pleasanton, CA, USA) from the biopsy was analyzed using the cobas EGFR mutation test (Roche Molecular Systems, Inc., Pleasanton, CA, USA), and direct sequencing and EGFR exon 19 deletion were identified. But no other mutation, including T790M, was detected. After 2 cycles of cisplatin-etoposide there was minimal radiological response, but his medical condition worsened and he could not continue chemotherapy. The patient died while in a supportive care program, 23 months after the beginning the therapy.

DISCUSSION

At present, EGFR-TKIs can provide remarkable tumor regression in NSCLC patients who have somatic EGFR exon mutations. However, acquired or secondary re-

sistance to EGFR-TKIs is inevitable. Some alternative treatment options are currently available, depending on the resistance mechanisms (8). But the main dilemma lies in how to assess in which patient EGFR-TKI resistance may develop and for which patient to do a re-biopsy. According to the relevant literature, the criteria to expect a probable secondary TKI resistance are single-agent treatment with EGFR-TKI for EGFR mutations and related drug sensitivity, systemic progression under TKI treatment, and other systemic chemotherapies after cessation of TKIs (12). However most often, the responsibility for TKI resistance lies in particular mutations, overexpression of growth factors, amplification of some oncogenes, histopathological transformation to SCLC, and squamous cell cancer and NSCLC with neuroendocrine morphology (13, 14, 15).
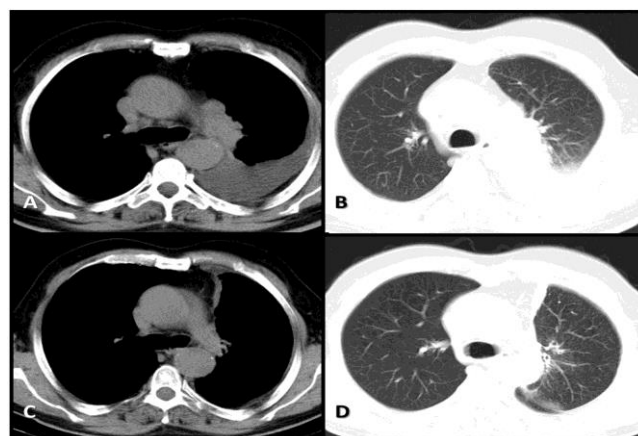

Figure 2a, b, c, and d: Progression of primary lesion before erlotinib treatment (a, b), Radiological response in the ninth month of erlotinib treatment (c, d)
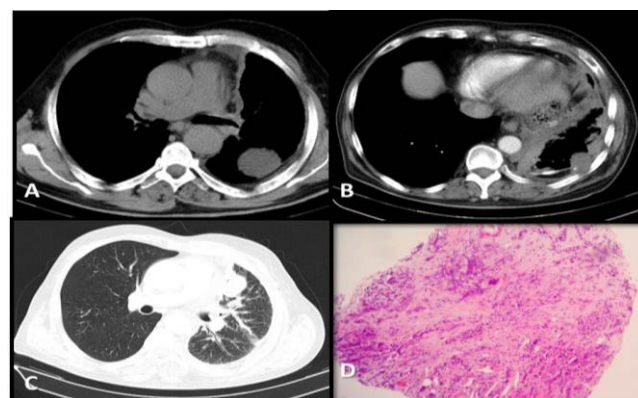

Figure 3a, b, c, and d: Left apical sub pleural mass showing progression in the 13th month of erlotinib treatment (a), Multiple, newly developed nodules on the left lung after 5 cycles of sisplatin-pemeterexed. d: Re-biopsy specimen showing small cell lung cancer (b, c)

SCLC transformation is relatively rare. In previous reports, most of the patients were female and were diagnosed in the fourth or fifth decade of life. But there are not enough

data to comment on age or gender predominance. The present case is a male and was in his sixth decade. Patient smoking habits weren't mentioned in any of the prior reports; however, some cases did not have a history of smoking. In our patient, diagnosis was obtained from pleural cytological analyses. Synchronous tumor was excluded due to response of both pleural effusion and left upper lesion to platinum-based chemotherapy and erlotinib. Overall survival is less than 6 months for an SCLC patient without treatment (19). In the current case, it was nearly 16 months to second progression.

Acquired resistance is mostly seen after 9 to 14 months of EGFR-TKI therapy (8). Similarly, in the present case, tumor progression occurred in the 13th month of erlotinib therapy. SCLC transformation is mostly seen with the genotype Exon 19 deletion or L858R, which are sensitive to EGFR-TKI therapy (16). Similarly, in present case, while the SCLC specimen was positive for exon 19 deletion, it was negative for a T790M mutation. There are several opinions about the underlying mechanisms of SCLC transformation in EGFR-mutation patients in autopsy and genotype studies. In a study analyzing 122 SCLC patients in terms of EGFR mutation, it was detected in only 5 (4%) patients. Combined histopathology with adenocarcinoma was notable in these patients. Both SCLC and adenocarcinoma subtype harbored EGFR mutations, but only the adenocarcinoma component had gene amplification. Investigators reported partial response with gefitinib in an EGFR-mutant SCLC patient (17). In clinical practice, perhaps, since the beginning of treatment both histopathological types are present. It can be explained by tumor heterogeneity, but it's difficult to detect this combined histopathology using small biopsy specimens. Our patient was first diagnosed with cytoblock examination, and SCLC was diagnosed with TTFNA.

Another possible explanation for acquired resistance to TKIs is phenotypic transformation. Under first-line EGFR-TKI treatment, changes in gene amplification may lead to prominence of the existing SCLC component. In this instance, some specific genomic changes may have a role in SCLC transformation. In a patient with EGFR mutation, while liver metastasis showing SCLC phenotype had PTEN M2641, metastasis of adenocarcinoma phenotype didn't have this mutation (8). Sequist et al. (18) reported a PI3K-AKT mutation with SCLC transformation, but a presence of only 5% of NSCLC cases. Therefore, both mutations are not specific to SCLC. In the present case, PTEN M2641 and PI3K-AKT mutations were not studied. In short, the SCLC transformation mechanism is still unclear.

Currently, there is no algorithm for how to manage SCLC transformation. The efficacy of standard chemotherapy regimens is unclear. Watanabe et al. reported partial response with carpoplatin-etoposid in a patient with SCLC transformation (16). In our case, 2 cycles of cisplatin-etoposide were administered with partial radiological response, but the treatment had to be discontinued due to the patient's poor medical condition.

In conclusion, due to the possible benefit of standard cytotoxic agents against SCLC transformation, clinicians shouldn't hesitate to re-biopsy in the case of progression under EGFR-TKI therapy.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - D.K., P.A.K., T.I.C., Ü.Y., H.E.Ö., Ö.E., N.A., S.K.; Planning and Design - D.K., P.A.K., T.I.C., Ü.Y., H.E.Ö., Ö.E., N.A., S.K.; Supervision - D.K., P.A.K., T.I.C., Ü.Y., H.E.Ö., Ö.E., N.A., S.K.; Funding - P.A.K.; Materials - D.K.; Data Collection and/or Processing - Ü.Y.; Analysis and/or Interpretation - T.I.C.; Literature Review - S.K.; Writing - D.K.; Critical Review - P.A.K.

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