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# Late fatal recurrence in gefitinib-treated NSCLC patients

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## ÖZET

### ***Gefitinib ile tedavi edilen küçük hücreli dışı akciğer kanserli hastalarda geç ölümcül nüks***

*Gefitinib kanser hücrelerinin çoğalması ve sağkalımlarını kontrol eden signal iletim yollarını durduran selektif epidermal büyüme faktörü reseptör tirozin kinaz inhibitörüdür. Gefitinib ile tedavi edilen metastatik küçük hücreli dışı akciğer kanserli hastalarda uzun dönem sağkalım kısa bir süre önce bildirilmiştir. Gefitinib ile uzun süreli hastalık kontrolü sağlandıktan sonra nüks sonrası hızlı bir şekilde ölümcül seyreden iki olguyu sunuyoruz. Gefitinib ile tedavi edilen ölümcül agresif nükslerin biyolojisi yeterli olarak tanımlanmamıştır. Mekanizmadan bağımsız olarak, gefitinib tedavisi uygulayan doktorların bu ilaçla uzun süreli hastalık kontrolünün sağlanmasının ardından ölümcül hızlı nüks olasılığı hakkında dikkatli olmaları gerekmektedir.*

**Anahtar Kelimeler:** *Gefitinib, küçük hücreli dışı akciğer kanseri, nüks.*

## SUMMARY

### ***Late fatal recurrence in gefitinib-treated NSCLC patients***

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*Gefitinib is a selective epidermal growth factor receptor tyrosine kinase inhibitor, which blocks signal transduction pathways implicated in proliferation and survival of cancer cells. Long-term survival in patients with metastatic non-small-cell*

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lung carcinoma (NSCLC) treated with gefitinib has recently been reported. We showed herein two cases of fatal rapid recurrence after a long-term disease control by gefitinib. The biology of fatal aggressive recurrence of gefitinib-treated NSCLC is not well characterized. Regardless of the mechanism, however, physicians treating patients with gefitinib should be alert to the possibility of fatal rapid recurrence after a long-term disease control by this drug.

**Key Words:** Gefitinib, non-small-cell lung carcinoma, recurrence.

Gefitinib is indicated for the treatment of patients with inoperable non-small cell lung carcinoma (NSCLC), especially lung adenocarcinoma (1). We report fatal rapid recurrence after a long-term disease control by gefitinib in two patients with metastatic lung adenocarcinoma. Such a relapse seems to occur very rare, however, this phenomenon needs to be studied further through clinical trials on a larger series of patients.

### CASE REPORTS

#### Case 1

A 70-year-old Japanese woman was admitted for right supraclavicular and cervical lymph node adenopathies. She had no smoking history. A chest computerized tomography (CT) scan showed a 3 cm nodule in the right upper lobe with massive pericardial fluid. The resected lymph nodes and transbronchial biopsy specimens revealed adenocarcinoma. These specimens were found to be positive for thyroid transcription fac-

tor 1 and surfactant apoprotein. Performance status of the patient was evaluated as not good enough to receive platinum-containing chemotherapy and the patient and her family wanted to treat with gefitinib, therefore, chemotherapy with gefitinib was commenced as a first choice for the patient. Subsequently, she was treated with gefitinib 250 mg daily and achieved good partial response. After discharge, the patient regularly came to our hospital once or twice a month, and she was continued to treat with same dose of gefitinib. Physical examination and routine chest X-ray showed no recurrence. Eighteen months after the initiation of the therapy, however, the patient developed disturbance of consciousness. Until then, she continued to have gefitinib regularly. Head magnetic resonance imaging (MRI) revealed diffuse disseminated thickening of the dura mater (Figure 1). The patient was diagnosed as having meningitis carcinomatosa and she died two months after the recurrence.

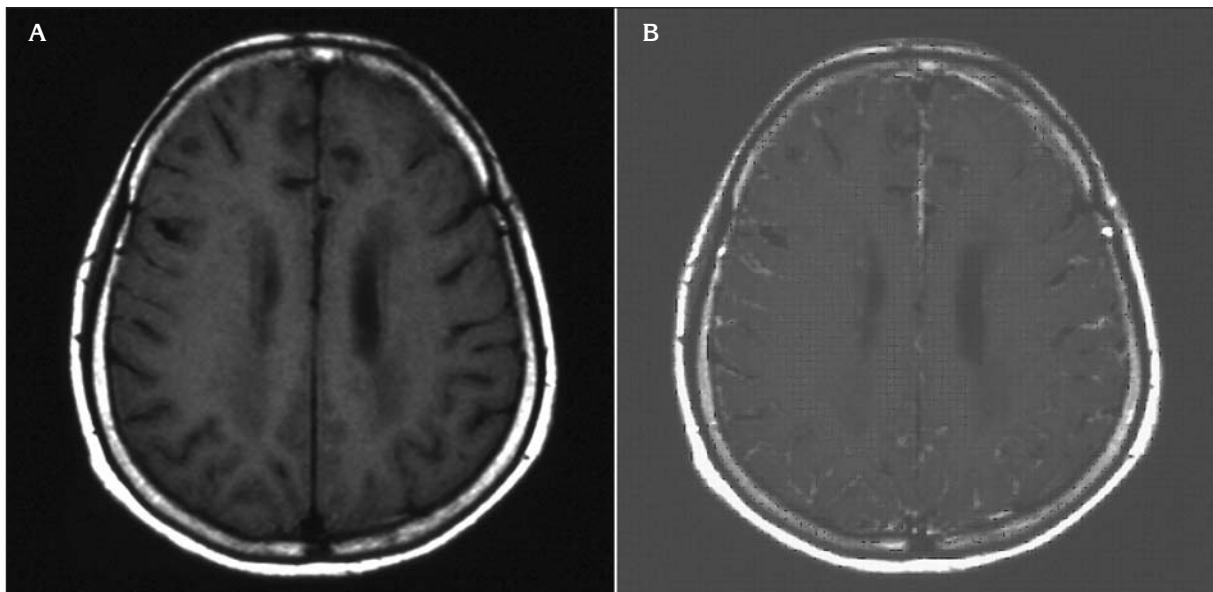


Figure 1. Head MRI at the time of first presentation showed no abnormal lesion (A), and MRI at the time of recurrence revealed diffuse disseminated thickening of the dura mater (B).

## Case 2

A 53-year-old Japanese woman was admitted for a nodular lesion in the right lung noted on a chest X-ray. She was a non-smoker and had no history of pulmonary disease. A chest CT scan showed a 3.5 cm nodule in the right lower lobe with pleural dissemination and brain metastasis. Bronchoscopic biopsy revealed adenocarcinoma. She received one course of first-line chemotherapy with cisplatin and vinorelbine, but no response was achieved. Subsequently, the patient was treated with gefitinib 250 mg daily and achieved good partial response. After discharge, the patient regularly attended our hospital once or twice a month, and she was continued to treat with same dose of gefitinib. Physical examination and routine chest X-ray showed no recurrence. Thirty-one months after the initiation of the therapy, the patient developed right chest pain and dyspnea, and she admitted to our hospital again. Chest CT two weeks after the second admission revealed massive pleural fluid with disseminated large pleural mass (Figure 2). The pleural mass enlarged rapidly and she died two months after the recurrence.

## DISCUSSION

The optimal treatment strategy for refractory and recurrent NSCLC patients remains to be defined. Local radiotherapy, systemic chemotherapy or combinations of the two, or molecular-targeted therapies using gefitinib or erlotinib have been tried. Gefitinib is a selective epidermal growth factor receptor (EGFR) tyrosine kinase

inhibitor, which blocks signal transduction pathways implicated in proliferation and survival of cancer cells (2,3). Recently, some authors reported long-term survival in patients with metastatic NSCLC treated with gefitinib (4,5).

In this report, we showed two cases of fatal rapid recurrence after a long-term disease control by gefitinib. With regard to this drug, the effect of re-treatment with gefitinib after acquisition of resistance has also been reported (6,7). Recurrent lesions in their patients did not enlarge so rapid that they could be treated either other cytotoxic drugs or gefitinib. On the other hand, however, there is fatal rapid recurrence after a long-term disease control by gefitinib. Such cases are very rare but recurrent lesions in their patients did enlarge so rapid that they may not be treated easily. Pao et al. reported that acquired resistance of lung adenocarcinomas to gefitinib is associated with a second mutation in EGFR (8). Recent study by Greulich et al. revealed that oncogenic transformation of cells by different EGFR mutations causes differential sensitivity to gefitinib (9). However, the precise mechanism by which gefitinib may cause rapid recurrence after a long term disease control is not known. Regardless of the mechanism, however, physicians treating patients with gefitinib should be alert to the possibility of fatal rapid recurrence after a long-term disease control by this drug.

In patients with small cell lung cancer as well as hematological malignancies, it is known that late-relapsing patients have a better prognosis

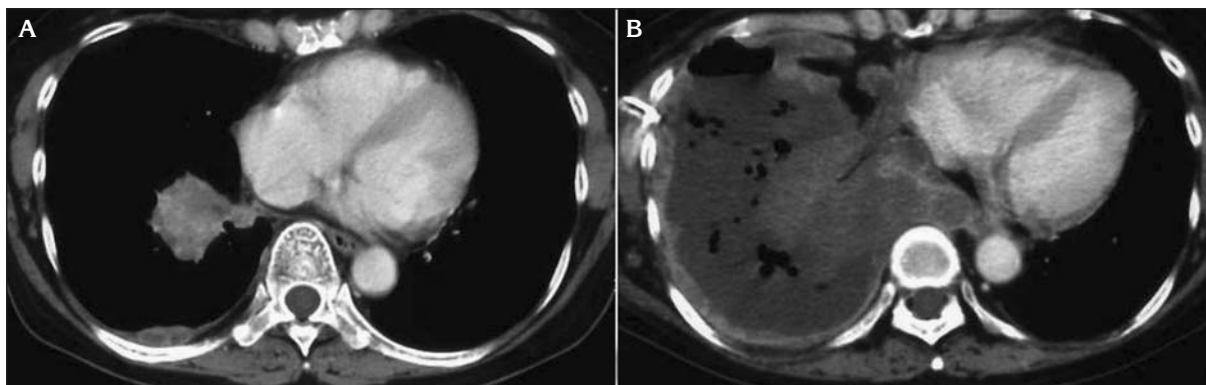


Figure 2. Chest CT at the time of 31-month after the initiation of gefitinib therapy showed primary lesion (A), and CT two weeks after the admission revealed massive pleural fluid with disseminated large pleural mass (B).

than those who relapse earlier (10-12). Our cases suggested the need for an individualized approach in the clinical follow up of NSCLC patients who respond to gefitinib to detect early signs of relapse or progression. The use of imaging techniques including CT, MRI and standard radiography should be emphasized to detect relapses, but all of them can not detect aggressive relapse. These tumors, however, seem to be resistant to other chemotherapeutic drugs because they have already exposed one or more cytotoxic drugs, therefore, early detection of such relapse cannot lead to appropriate treatment.

We showed there is fatal rapid recurrence after a long-term disease control by gefitinib as observed in our cases. The biology of fatal aggressive recurrence of gefitinib-treated NSCLC is not well characterized. Although this phenomenon seems to be vary rare, prospective clinical and biological data need to be collected on a larger series of patients before definitive conclusions on the effective treatment approaches can be made.

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