

## Case report

# Efficacy of dose modification of gefitinib after hepatotoxicity in late-line treatment of EGFR mutated advanced non-small cell lung cancer: A case report

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Targeted therapy with epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKI) is a standard treatment for advanced epidermal growth factor receptor (EGFR) mutated non-small cell lung cancer. There is information evidence demonstrating the efficacy of progression-free survival in either both first line treatment or and second-line treatment. However, there is only limited information on the efficacy of treatment and dose modification on the occurrence of medication side effects, especially in late-line treatment patients, and most is limited to case reports rather than clinical studies. In this study we describe the use of gefitinib in late-line treatment where the gefitinib dosage was adjusted reduced to 250 mg every 2 days after patients had developed hepatitis due to gefitinib. There was a 21 week progression free interval which included a 13 week progression-free interval of following dose modification.

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**Keywords:** gefitinib, hepatotoxicity, dose modification

## Introduction

The standard treatment for EGFR mutated advanced non-small cell lung cancer is targeted therapy with epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKI)(1). EGFR-TKIs, including gefitinib, erlotinib and afatinib, are a standard first-line treatments for EGFR gene mutated-positive non-small cell lung cancer (2-8). There is information evidence that they result in better progression-free survival (PFS) and response rate than chemotherapy compared to control groups (9). Common EGFR mutations with data confirming sensitive mutated to EGFR TKI are exon 19 deletion and exon 21 point mutated.

EGFR TKI therapy is effective in EGFR-

mutant lung cancer with a median duration of progression-free survival of 10 to 14 months (2-8) when EGFR TKI therapy is applied as a first line treatment, while progression-free survival is about 2 to 3 months when EGFR TKI therapy is applied as a late-line treatment (10, 11).

Information about the efficacy of EGFR TKI therapy with dose modification on the occurrence of medication side effects is limited to case reports; there have been no randomized control trials. Common side effects of EGFR TKI include rash, diarrhea, and hepatitis.

This study describes a dose modification approach and its treatment efficacy in advanced

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epidermal growth factor receptor (EGFR) mutated non-small cell lung cancer on exon 21 point mutated with EGFR TKI therapy late-line treatment, in a patient with hepatitis due to EGFR TKI whose dose was adjusted to 250 mg every 2 days. During the period of dose modification, the progression-free survival time was 13 weeks.

### Case history

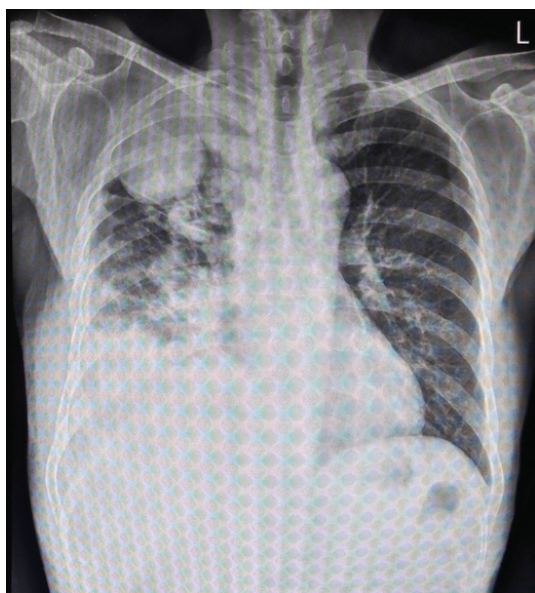
A 58-year-old non-smoking male was diagnosed with stage 4 lung adenocarcinoma in February 2015 and was given 6 cycles of first line chemotherapy with paclitaxel plus carboplatin in July 2015, and then a second-line chemotherapy treatment with 6 cycles of docetaxel complete in June 2016. As a relapse occurred, he was treated with third-line chemotherapy using oral etoposide from August to October 2016 after which he terminated his hospital treatment and moved to the Medical Oncology Clinic, Division of Medical Oncology, Department of Medicine, Buddhasothorn Hospital in November 2016.

Physical examination at the Medical Oncology Clinic found the patient was still healthy, with ECOG performance status 1 and chest x-rays found massive right pleural effusion. Pleural fluid

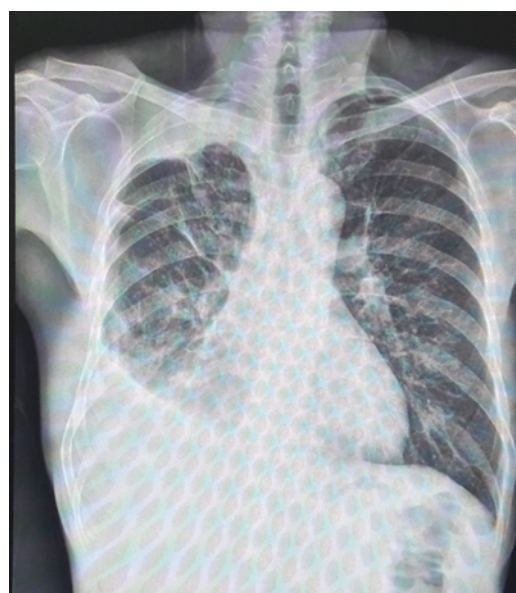
cytology identified it as metastatic adenocarcinoma which is consistent with lung primary lung cancer. An intercostal drain (ICD) was inserted and pleurodesis was performed. Molecular tests for EGFR mutated detected exon 21 L858R.

Gefitinib, which is in the EGFR TKI group, was given as a late-line treatment, starting at 250 mg per day. Following a 2-week follow-up chest x-ray, it was found that there was a response to treatment. After taking gefitinib for 8 weeks, chest x-rays showed response to treatment (Figure 1-2), but also showed drug-induced hepatotoxicity grade 3 with AST 341 U/L and ALT 480 U/L had developed, so gefitinib was stopped. No other potential causes of liver toxicity were found.

After stopping gefitinib for 2 weeks, the hepatotoxicity improved to grade 1 with AST 88 U/L and ALT 174 U/L. At that time, gefitinib was restarted at a reduced dose of 250 mg every 2 days and a follow-up CT scan was scheduled. After 6 weeks of dose modification (14 weeks after starting treatment), an imaging study showed that the lung cancer had been reduced by 63.1% which is a partial response according to RECIST criteria 1.1 (Figure 3-4). A follow-up chest x-ray at 13 weeks after dose modification found the cancer



**Figure 1.** Chest x-ray before starting gefitinib



**Figure 2.** Chest x-ray after a standard dose of gefitinib for 8 week



**Figure 3.** Chest x-ray at the restart of gefitinib at a modified dose following discontinuation for 2



**Figure 4.** Chest x-ray after 5 weeks of gefitinib dose modification showing continued response to treatment



**Figure 5.** Chest x-ray at date of detection of disease progression (increased multiple lung nodules at upper right lung). (13 weeks after dose modification and 21 weeks after initial dose.)

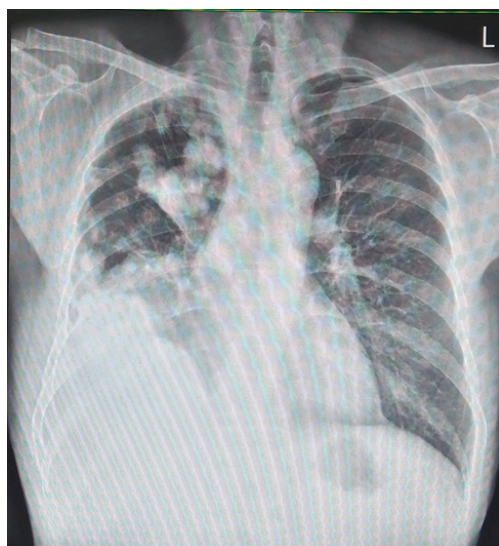


**Figure 6.** Chest x-ray at date of second re-challenge with dose modification of gefitinib after disease progression. (17 weeks after dose modification)

had increased in size and that the hepatitis was more than 5 times larger (Figure 5). Again, the medicine was stopped for 3 weeks until the severity of the hepatitis was below grade 1.

After that 3 week period, gefitinib was started again because the patient had no symptoms of cancer (Figure 6). Several studies have demon-

strated the promise of continuation of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) beyond progression in asymptomatic patients with EGFR-mutant non-small-cell lung cancer (12). Gefitinib 250 mg was given every 3 days for 2 weeks, then adjusted to 250 mg every 2 days for 12 weeks. Gefitinib was stopped



**Figure 7.** Chest x-ray at date gefitinib was stopped. Total duration of treatment 39 weeks including 31 weeks of gefitinib dose modification

again because CT scans showed the cancer had increased by 78%, compatible with progression disease progression according to RECIST 1.1 criteria and because the patient was more tired and had a cough (chest symptom) symptomatic of a chest problem (Figure 7).

In summary, the clinical data on this patient show there was a total of 39 weeks of treatment with gefitinib and 21 weeks of progression-free interval during which includes a progression-free interval of 13 weeks with dose modification.

## Discussion

Based on historical data, hepatitis due to gefitinib is found occurs in 25-39% of cases; the incidence of hepatitis grade 3 is approximately 4% (13). The average duration of hepatitis is 4 months. Hepatitis is more commonly found in patients given gefitinib for a long period (over 14 months) (13).

In patients with hepatitis due to gefitinib, it is recommended to temporarily stop taking gefitinib when hepatotoxicity is at grade 3, and rechallenge when hepatotoxicity is less than grade 1 with AST and ALT less than 3 times normal (13). There are no clear recommendations for gefitinib

dose modification in cases of hepatitis, only case reports which provide a variety of information. According to Chen et al. (14), a Chinese woman with stage 4 lung cancer after developed hepatitis grade 4 and temporarily stopped the medication for 3 months. The patient then rechallenged with gefitinib at the same dose of 250 mg a day and continued to show good therapeutic response for more than 6 months.

Similarly, according to Ho et al. (15) in 2005, a patient with lung cancer treated with gefitinib had a better good response. Later, however, the patient developed hepatitis grade 3, so gefitinib was temporarily stopped after which a 250 mg dose of gefitinib every 5 days was instituted. The patient showed a near complete response with an 8 week progression-free interval.

A study of the relationship between drug exposure and gefitinib response in 87 patients with lung cancer was reported by Xin et al. (16). They found the median C trough was 173.9 ng/mL. They also found that progression-free survival (PFS) of patients who had a C trough < 200 ng/mL and patients who had a C trough >200 ng/mL were not significantly different at 17.3 months and 14.8 months, respectively. Those results showed that the PFS in the lower trough concentration group was not inferior to that in higher trough concentration group and that dose reduction is a rational suggestion reasonable option. Further clinical studies are required to explore the precise dose schedule of gefitinib.

Currently available information on dose modification and efficacy of gefitinib for hepatotoxicity is based on case reports. There have been no published clinical studies providing information on dose modification, although recent data do provide evidence on the rechallenge process with dose modification.

Information on the response of lung cancer patients treated with gefitinib as a late-line treatment following development of hepatitis grade 3 with dose modification to 250 mg every 2 days for 13 weeks, is useful for evaluating treatment of patients.

## References

1. Nan X, Xie C, Yu X, Liu J. EGFR TKI as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer. *Oncotarget*. 2017;8: 75712-26.
2. Fukuoka M, Wu YL, Thongprasert S, Sunpawaravong P, Leong SS, Sriuranpong V, et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in asia (IP-ASS). *J Clin Oncol*. 2011;29:2866-74.
3. Han JY, Park K, Kim SW, Lee DH, Kim HY, Kim HT, et al. First-signal: first-line single-agent iressa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung. *J Clin Oncol*. 2012;30: 1122-8.
4. Mitsudomi T, Morita S, Yatabe Y, Negoro S, Okamoto I, Tsurutani J, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomized phase 3 trial. *Lancet Oncol*. 2010;11:121-8.
5. Inoue A, Kobayashi K, Maemondo M, Sugawara S, Oizumi S, Isobe H, et al. Updated overall survival results from a randomized phase III trial comparing gefitinib with carboplatin-paclitaxel for chemo-naïve non-small cell lung cancer with sensitive EGFR gene mutations (NEJ002). *Annals of Oncology*. 2013;24:54-9.
6. Rosell R, Carcereny E, Gervais R, Alain V, Bartomeu M, Enriqueta F, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EORTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. 2012;13:239-46.
7. Zhou C, Wu YL, Chen G, Jifeng F, Xiao-Qing L, Changli W, 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;12:735-42.
8. Sequist LV, Yang JC, Yamamoto N, O'Byrne K, Hirsh V, Mok T, et al. Phase III Study of Afatinib or Cisplatin Plus Pemetrexed in Patients With Metastatic Lung Adenocarcinoma With EGFR Mutations. *J Clin Oncol*. 2013;31:3327-34.
9. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med*. 2009;361: 947-57.
10. Frances AS, José RP, Tudor C, Eng HT, Vera H, Thongprasert S, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med*. 2005; 353:123-32.
11. Shao YY, Shau WY, Lin ZZ, Chen HM, Kuo R, Yang JC, et al. Comparison of gefitinib and erlotinib efficacies as third-line therapy for advanced non-small-cell lung cancer. *Eur J Cancer*. 2013;49:106-14.
12. Nishie K, Kawaguchi T, Tamiya A, Mimori T, Takeuchi N, Matsuda Y, et al. Epidermal growth factor receptor tyrosine kinase inhibitors beyond progressive disease: a retrospective analysis for Japanese patients with activating EGFR mutations. *J Thorac Oncol*. 2012;7:1722-7.
13. Wang J, Wu Y, Dong M, He X, Wang Z, Li J, et al. Observation of hepatotoxicity during long-term gefitinib administration in patients with non-small-cell lung cancer. *Anticancer Drugs*. 2016;27:245-50.
14. Chen X, Pan Y, Zhang S, Chen D, Yang S, Li X, et al. Re-challenge with gefitinib following severe drug-induced hepatotoxicity in a patient with advanced non-small cell lung cancer: A case report and literature review. *Oncol Lett*. 2014;7:878-80.
15. Ho C, Davis J, Anderson F, Bebb G, Murray N. Side effects related to cancer treatment: CASE1. Hepatitis following treatment with gefitinib. *J Clin Oncol*. 2005;23: 8531-33.
16. Xin S, Zhao Y, Wang X, Huang Y, Zhang J, Guo Y, et al. The dissociation of gefitinib trough concentration and clinical outcome in NSCLC patients with EGFR sensitive mutations. *Sci Rep*. 2015;31:12675.

## ประสิทธิภาพของการปรับลดขนาดยา gefitinib ภายหลังเกิดผลข้างเคียงต่อตับในผู้ป่วยมะเร็งปอดชนิดไม่ใช้เซลล์ขนาดเล็กในระยะลุกลามที่ผ่านการรักษามาหลายขนาน : รายงานผู้ป่วย

ชัยชนะ จันทระคิด

หน่วยมะเร็งวิทยา กลุ่มงานอายุรกรรม โรงพยาบาลพุทธโสธร

การใช่มุ่งเป้า (targeted therapy) กลุ่ม epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKI) เป็นการรักษามาตรฐานในการรักษาโรคมะเร็งปอดระยะที่ 4 ที่มี epidermal growth factor receptor (EGFR) mutation ซึ่งมีข้อมูลที่ได้ผลในการควบคุมโรค (progression free survival) ทั้งในการรักษาขนานที่ 1 หรือการรักษาขนานที่ 2 แต่ข้อมูลประสิทธิภาพของการรักษาและวิธีการปรับยาในกรณีที่เกิดผลข้างเคียงของยา โดยเฉพาะในกลุ่มผู้ป่วยที่ผ่านการรักษามาหลายขนานยังมีข้อมูลจำกัดและส่วนใหญ่ยังเป็นเพียงรายงานผู้ป่วย ดังนั้นจึงรายงานการรักษามะเร็งปอดระยะที่ 4 ด้วยยา gefitinib ในการรักษาขนานที่ 4 (late line treatment) และต่อมา มีการปรับลดขนาดยา gefitinib เป็นขนาด 250 มิลลิกรัม รับประทานทุก 2 วัน เมื่อผู้ป่วยมีภาวะตับอักเสบจากการรักษาด้วยยา gefitinib ซึ่งพบว่ามีประสิทธิภาพในการควบคุมโรค (progression free interval) ได้ทั้งหมด 21 สัปดาห์ ซึ่งในช่วงระยะเวลาดังกล่าวเป็นช่วงเวลาที่สามารถควบคุมโรคจากขนาดยาที่ปรับลดลง (progression free interval of dose modification) 13 สัปดาห์ **เชียงใหม่เวชสาร 2562; 58(2):99-104.**

**คำสำคัญ:** gefitinib ตับอักเสบ การปรับขนาดยา