OPEN

Hypotension from afatinib in epidermal growth factor receptor-mutated non-small cell lung cancer: a case report and literature review

Zhiwei Tang[a]*, XiuHai Ji[b]*, Guanghui Zhou[a], Ruhua Chen[a], Yan Fen[a,†] and Hui Ding[a]

Side effects of afatinib are a problem in patients with advanced non-small cell lung cancer (NSCLC). However, little is known about the occurrence of afatinib-induced hypotension. An 81-year-old man with NSCLC had an epidermal growth factor receptor-positive genotype with the p.L861Q mutation in exon 21. He was administered afatinib (40 mg/day) as anticancer therapy. Hypotension occurred twice after afatinib initiation. He suffered from dizziness and nausea. Blood pressure gradually returned to normal after afatinib cessation. Clinicians should be aware of hypotension in patients with NSCLC after afatinib initiation. ***Anti-Cancer Drugs*** **33: e840–e841 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.**

Anti-Cancer Drugs 2022, **33**:e840–e841

Keywords: afatinib, epidermal growth factor receptor, hypotension, lung cancer

[a]Department of Pulmonary & Critical Care Medicine, Affiliated Yixing People's Hospital, Jiangsu University, Yixing and [b]Department of Oncology, Affiliated Taicang Hospital of Traditional Chinese Medicine, Taicang, China

Correspondence to Hui Ding, Department of Pulmonary & Critical Care Medicine, Affiliated Yixing People's Hospital, Jiangsu University, Yixing, China
Tel: +86 13706156506; e-mail: dh1350519@163.com

*Dr. Zhiwei Tang and Dr. XiuHai Ji are first co-authors.
†Yan Fen is the co-corresponding author.

Received 26 July 2021 **Revised form accepted** 12 August 2021

Introduction

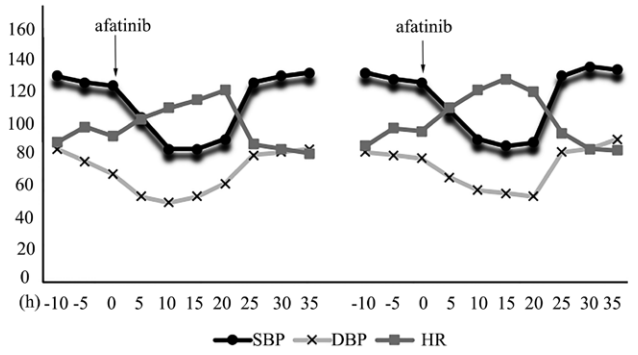
Patients with non-small cell lung cancer (NSCLC) still have a high incidence of poor outcomes because of late diagnosis at an advanced stage. Indeed, it is difficult to receive effective systemic treatments for NSCLC in the clinic. With the development of an in-depth understanding of molecular mechanisms of cancer growth and metastasis, some patients with NSCLC receive personalized care, especially those with mutations in the epidermal growth factor receptor (EGFR) gene. EGFR tyrosine kinase inhibitors (EGFR-TKIs), including first-generation (gefitinib and erlotinib), second-generation (afatinib) and third-generation (osimertinib) EGFR-TKIs, are currently accepted as the first-line treatments of NSCLC with activating mutations in the EGFR gene. Based on the differences in EGFR mutations and EGFR-TKI-related toxicities, the decision to personalize therapy should be fully confirmed in patients with NSCLC. A recent report has shown cardiac dysfunction as a side effect of afatinib [1]. Previously, we have presented a case of osimertinib-induced cardiomyopathy in a patient with advanced NSCLC. In this report, we introduce a case of afatinib-induced hypotension in a patient with advanced NSCLC to improve the understanding of cardiotoxicity related to afatinib.

Case presentation

An 81-year-old male, nonsmoker, was confirmed to have primary lung adenocarcinoma based on histological evidence obtained by bronchoscopy and lymph node biopsy. Molecular testing of lung tissue and blood revealed an EGFR-positive genotype with the p.L861Q mutation in exon 21. Chest computed tomography (CT) showed a lung space-occupying lesion with brain metastasis. Before administration of afatinib, heart echocardiography showed a left ventricular ejection fraction of 63%, without structural abnormalities. Laboratory examination showed that the *N*-terminal-pro-B-type natriuretic peptide (NT-proBNP) level was 23 pg/mL. The levels of serum myocardial enzymes were normal. The patient's blood pressure was stable for several days. Therefore, treatment with oral afatinib 40 mg once daily was started. The patient suffered from dizziness and nausea 8 h after taking afatinib medication. The instant monitoring of blood pressure indicated hypotension. Immediate echocardiography indicated a left ventricular ejection fraction of 64%, without structural abnormalities. Meanwhile, the NT-proBNP level was 22 pg/mL. The serum myocardial enzymes had normal levels. The condition of this patient was evaluated by a cardiologist, who considered the association of hypotension with afatinib and proposed that the drug be stopped. After 22 h of cessation, the blood pressure gradually returned to a normal level. Several days later, the patient took afatinib again on his own. Dizziness and nausea returned again 7 h after taking afatinib. Immediate echocardiography showed a left ventricular

0959-4973 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc. DOI: 10.1097/CAD.0000000000001244

Fig. 1



Changes of blood pressure and heart rate during treatment with afatinib. HR, heart rate.

ejection fraction of 63%, without structural abnormalities. Meanwhile, the NT-proBNP level was 24 pg/mL. The serum myocardial enzymes were at normal levels. We stopped his treatment, and blood pressure became normal within 24 h (Fig. 1). Therefore, afatinib was discontinued, and alternative therapy with almonertinib (110 mg/d) was started. There was no recurrence of hypotension.

Discussion

To the best of our knowledge, there are no reports indicating that oral afatinib induces hypotension in patients with NSCLC. As a second-line TKI, afatinib prevents tumor growth by inhibiting the phosphorylation of tyrosine kinase. The antitumor value of afatinib is widely accepted in patients with EGFR-mutated NSCLC [2,3]. Despite its beneficial effects, a high incidence of afatinib-induced adverse events is a problem. Certain adverse events, such as skin rash, paronychia and stomatitis, were reported in patients with NSCLC treated with afatinib. In the Lux-Lung 3 trial, the incidence of mucositis was almost 70% [2]. Matsumoto *et al*., [4] reported a rare case of afatinib-induced acute esophageal necrosis. More interestingly, cardiac dysfunction with a left ventricular ejection fraction of 40–60% was found in patients with NSCLC taking afatinib for 1 month [1]. Afatinib-induced cardiac dysfunction is associated with erb-b2 receptor tyrosine kinase 2 (Her2) inhibition. In addition to EGFR, afatinib irreversibly inhibits Her2 [5]. However, the explicit mechanism is unclear.

To our knowledge, there are no other case reports on blood pressure changes related to afatinib. Complex considerations, including the efficacy, side effects, patient feedback and other factors, provide valuable information for clinical treatment. Dizziness and nausea due to afatinib-related hypotension severely influenced the continuance and effect of the oral targeted drug and even threatened the patient's life. The instant monitoring indicated that hypotension occurred twice after taking afatinib. Blood pressure improved after the discontinuation of afatinib in our case. No cardiac toxicity was detected by heart echocardiography monitoring or a myocardial zymogram. Hence, we recognized that afatinib was the causative drug, although this was an extremely rare incidence.

In conclusion, awareness of life-threatening side effects related to afatinib is crucial. Clinicians should be alert of the possibility of hypotension in patients with NSCLC after afatinib initiation.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References

1 Nuvola G, Dall'Olio FG, Melotti B, Sperandi F, Ardizzoni A. Cardiac toxicity from Afatinib in EGFR-mutated NSCLC: a rare but possible side effect. *J Thorac Oncol* 2019; **14**:e145–e146.
2 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**:3327–3334.
3 Ke EE, Wu YL. Afatinib in the first-line treatment of epidermal-growth-factor-receptor mutation-positive non-small cell lung cancer: a review of the clinical evidence. *Ther Adv Respir Dis* 2016; **10**:256–264.
4 Matsumoto Y, Kuroki S, Yamada H. Gastrointestinal: Afatinib-induced acute esophageal necrosis. *J Gastroenterol Hepatol* 2018;**11**. doi: 10.1111/jgh.14308
5 Li D, Ambrogio L, Shimamura T, Kubo S, Takahashi M, Chirieac LR, *et al.* BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in preclinical lung cancer models. *Oncogene* 2008; **27**:4702–4711.