

Clinical characterization of icotinib-induced chemoresistance in erlotinib-treated lung adenocarcinoma patient with EGFR mutations

A case report

Ka Wu, MPhil^a, Chao Guo, MPhil^b, Rong Li, MD^{c,*}

Abstract

Rationale: Mounting evidences reveal that mutation of epidermal growth factor receptor (EGFR) may induce the resistance of tyrosine kinase inhibitors (TKIs). TKI-resistant lung cancer cells are sensitive to inhibition of the EGFR pathway. This case report aimed to characterize the therapeutic benefits of erlotinib, a targeted drug, on an advanced lung cancer patient with somatic EGFR mutation.

Patient concerns: A 52-year-old non-smoking Chinese woman was suffered from pneumonia-based chest pains, and the patient was diagnosed as advanced lung cancer through medical imaging, thoracoscopy, and pathological examination.

Diagnoses: Blood tests, pathological examination, thoracoscopy, computed tomography (CT)/positron emission computed tomography (PET) scans, next-generation sequencing (NGS) testing were subjected to the patient's samples before and after targeted drug treatments.

Interventions: After icotinib-induced resistance, the chemoresistance mechanism was involved in EGFR mutations before being prescribed with erlotinib.

Outcomes: The therapeutic effectiveness of icotinib for 4-month showed undetected carcinomatous metastasis. The lung tumor sizes were reduced, and improved quality of life (QOL) was described by the patient. Followed by monotherapy with erlotinib for 1.5-year, the icotinib-resistant patient benefited from longer survival rate without tumor enlargement and neoplastic metastasis. In therapeutic duration of erlotinib, T790M mutation of EGFR, R248W mutation of tumor protein p53 (TP53), K844S mutation of retinoblastoma protein 1 (RB1) were identified through NGS test.

Lessons: In conclusion, the anti-cancer benefits of icotinib and erlotinib against advanced lung cancer may contribute to suppress neoplastic growth and metastasis. Further, erlotinib exerts potent efficacy for extended survival rate of patient because detectable mutations may not or limitedly induce erlotinib-resistance. In addition, reduced circulating hormones by menopause may enhance the therapeutic effectiveness of erlotinib.

Abbreviations: CA50 = cancer antigen 50, CEA = carcinoembryonic antigen, CT = computed tomography, CYFRA21-1 = cytokeratin fragment 19, EGFR = epidermal growth factor receptor, HE = hematoxylin-eosin, NGS = next-generation sequencing, NSCLC = non-small cell lung cancer, NSE = neuron-specific enolase, PET = positron emission computed tomography, QOL = quality of life, RB1 = retinoblastoma protein 1, TKIs = tyrosine kinase inhibitors, TP53 = tumor protein p53.

Keywords: drug resistance, EGFR mutation, erlotinib, lung cancer

Editor: N/A.

KW and CG contributed equally to this work.

Ethics approval and consent to participate: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Consent to publish: Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

The authors have no conflicts of interest to disclose.

^a Department of Pharmacy, The Second People's Hospital of Nanning City, The Third Affiliated Hospital of Guangxi Medical University, Guangxi, Nanning, ^b Department of Pharmacy, Guigang City People's Hospital, The Eighth Affiliated Hospital of Guangxi Medical University, Guigang, Guangxi, ^c Key Laboratory of Tumor Immunology and Microenvironmental Regulation, Guilin Medical University, Guilin, China.

* Correspondence: Rong Li, Key Laboratory of Tumor Immunology and Microenvironmental Regulation, Guilin Medical University, Huan Cheng North 2nd Road 109, Guilin 541004, China (e-mail: lirong1278@163.com).

Copyright © 2019 the Author(s). Published by Wolters Kluwer Health, Inc.

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Medicine (2019) 98:18(e15489)

Received: 30 November 2018 / Received in final form: 3 April 2019 / Accepted: 10 April 2019

<http://dx.doi.org/10.1097/MD.00000000000015489>

1. Introduction

Epidemiological evidences have indicated that over 50% of patients with non-small cell lung cancer (NSCLC) in China are found with intracellular mutations of EGFR genes.^[1,2] Unexpectedly, around 30% of cases in lung adenocarcinoma may respond to therapeutic effectiveness of EGFR-tyrosine kinase inhibitors under producing EGFR-mutations.^[3] However, most of the patients with NSCLC develop drug resistance to EGFR-TKIs after about 6–12 months.^[4] Icotinib, a first generation of EGFR-TKI, is used for monotherapy of EGFR mutation-based patients with advanced-stage NSCLC in China.^[5,6] A clinical trial suggests poor overall response rate (30%) and unwanted side-effect event rate (31.5%) have shown in NSCLC cases treated with icotinib.^[7] Erlotinib is found marked survival benefit in monotherapy of advanced-stage and metastatic NSCLC, characterized by greater effectiveness against EGFR mutations.^[8,9,10] However, it is still unknown whether icotinib-resistant lung cancer cells with EGFR mutations will respond to clinical efficacy of erlotinib.

In this report, an interesting case described the icotinib-induced chemoresistance in an advanced NSCLC patient with EGFR mutations, followed by treatment with erlotinib. Further, clinical

characterization of therapeutic efficacy in erlotinib and potential benefits of extended survival rate in this patient would be discussed respectively.

2. Case report

A 52-year-old non-smoking Chinese woman was suffered from pneumonia-derived chest pains before hospitalization. As revealed in Fig. 1, biochemical assays showed markedly increased plasma contents of cancer antigen 50 (CA50, 10.9IU/ml), NSCLC associated antigen (CYFRA21-1 (cytokeratin fragment 19), 5.2 ng/mL), carcinoembryonic antigen (CEA, 28.6 ng/mL), neuron-specific enolase (NSE, 18.1 ng/mL) when referenced to clinical criteria. Thoracoscopy inspection showed visible pleural lumps and nodular deterioration. And the patient was medically diagnosed as NSCLC in stage IV by using chest computed tomography (CT) scan and pathological biopsy in March 2017, detecting a tumor volume of $4 \times 2.8 \text{ cm}^2$ in the right lung lower lobe. In addition, positron emission computed tomography (PET) scan suggested undetected tumorous metastases in lymph nodes, liver, pancreas, and brain. In biopsy sample, somatic EGFR mutation report found the mutations of exon18 G719X, exon20

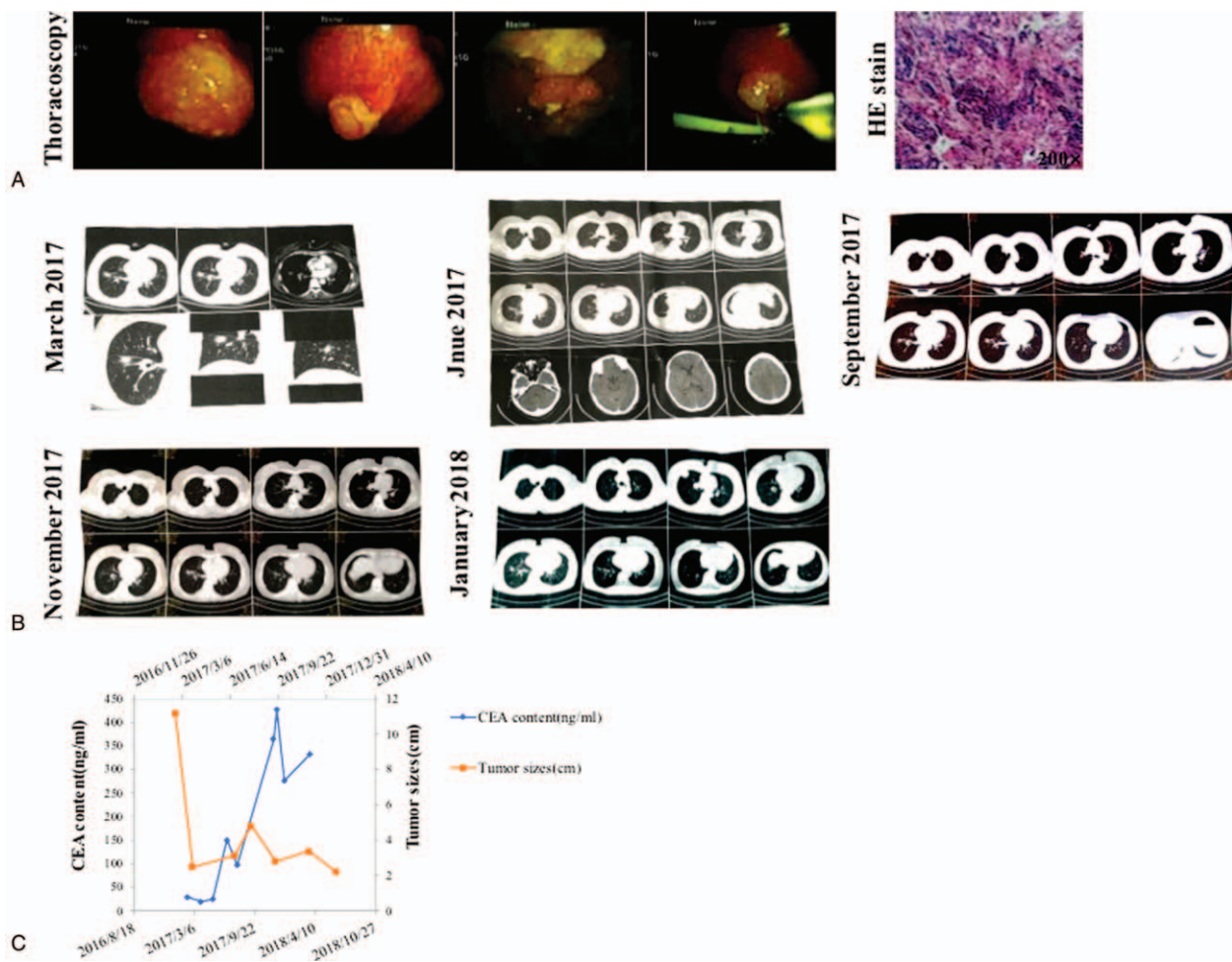


Figure 1. Clinical characterization of non-small cell lung cancer (NSCLC) patient with EGFR mutations. A: Visible nodular neoplasm in pleura through thoracoscopy, and malignant lung adenocarcinoma in pleura through hematoxylin-eosin (HE) stain-based clinicopathologic diagnosis. B: Medical CT images monitored the neoplastic development during chemotherapy periods. C: Periodical tests of serological tumor biomarker (CEA) contents and lung tumor sizes during chemotherapy periods.

S768I T790M, exon21 L816Q L858R, followed by icotinib (125 mg/day; Roche, Switzerland; Lot No. B0104M2) treatment.

After around 4-month icotinib monotherapy, assay to biopsy lung sample by using NGS was employed to reveal panoramic gene monitoring of this patient. The omics data showed L858R A871G mutations (mutation frequency, MF, 9.66%) and T790M mutation (MF, 5.82%) of EGFR, exon7 R248W mutation (MF, 5.82%) of TP53, exon25 K844S mutation (MF, 12.28%) of RB1. Due to icotinib-inducible chemoresistance, the patient was recommended to take erlotinib (80 mg/day; Betta Pharmaceuticals, Hangzhou, China; Lot No. A180805) from July 2017 when the tumor size was $3.2 \times 1.5 \text{ cm}^2$. As results, lung tumor size was reduced gradually although circulating CEA biomarker was altered. In addition, clinical symptoms and quality of life of the patient were reduced and improved progressively, lasting for approximate 1.5 years (November 2018). And the erlotinib therapy might cause some slight side-effects, such as rash, inappetence. However, the patient is still survival without neoplastic metastasis (November 2018).

3. Discussion

In this case report, NSCLC patient with EGFR mutations benefited from initial monotherapy of icotinib, an EGFR-targeting tyrosine kinase inhibitor, contributing to reduced lung tumor size and improved quality of life. In addition, carcinomatous metastasis in other organs was undetected by imaging scans. However, around 4-month icotinib treatment resulted in chemoresistance-related recurrence, showing growth of lung tumor. This chemoresistance mechanism was involved in EGFR mutations with concurrent MET amplification, as revealed in NGS assays. Therefore, the patient was prescribed with another TKI drug, erlotinib, for reducing chemoresistance. Although some undesired side effects were occurred, such as rash, the tumor sizes were decreased and improved quality of life was maintained. Therefore, drug-induced resistance of targeted therapy warrants to be monitored to benefit from TKI-based treatment in NSCLC.

As reported previously,^[8] the study described therapeutic benefits of combination therapy of erlotinib (150 mg/day)/ crizotinib (250 mg/day) in a 36-year-old non-smoking female NSCLC patient with EGFR mutations on exon 21 L858R. In addition, multiple metastases in lymph nodes, liver, and brain were detected before chemotherapy. As results, this patient suffered from severe pneumonia and infection, and finally died around 10-month combination therapy. Compared to this case, reporting 51-year-old non-smoking female NSCLC patient with EGFR mutations was given the monotherapy of icotinib (125 mg/day) or erlotinib (80 mg/day), resulting in more than 1.5-year survival time (to November 2018). The therapeutic efficacy may benefit from free of neoplasm metastasis when icotinib and erlotinib exert effective pharmacologic activities. In addition to EGFR L858R, previous case report showed terminal occurrence of novel mutations of NRAS Q61H, KRAS G12D, and MET G1108C, eventually inducing erlotinib-resistance and

patient's death. In this case, resultant T790M mutation of EGFR, R248W mutation of TP53, K844S mutation of RB1 were found by NGS tests. Taken together, we reasoned that these somatic mutations in the lung might not or limitedly induce erlotinib-resistance in over 9-month monotherapy. Further, in this case, the patient was menopause before monotherapy, implying that reduced circulating hormones might affect or benefit this type of targeted treatment. As limitations in current report, the further clinical trial with greater population sizes should be conducted for validating the proposed hypothesis.

Acknowledgments

This report is supported by National Natural Science Foundation of China (No. 81560134, 81860097).

Author contributions

Data curation: Ka Wu, Chao Guo.

Formal analysis: Chao Guo.

Investigation: Rong Li.

Methodology: Ka Wu, Chao Guo, Rong Li.

Resources: Ka Wu, Chao Guo.

Supervision: Rong Li.

Validation: Ka Wu.

Writing – original draft: Rong Li.

Writing – review & editing: Rong Li.

References

- [1] Molina JR, Yang P, Cassivi SD, et al. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. *Mayo Clin Proc* 2008;83:584–94.
- [2] O’Kane GM, Bradbury PA, Feld R, et al. Uncommon EGFR mutations in advanced non-small cell lung cancer. *Lung Cancer* 2017;109:137–44.
- [3] Ahn MJ, Sun JM, Lee SH, et al. EGFR TKI combination with immunotherapy in non-small cell lung cancer. *Expert Opin Drug Saf* 2017;16:465–9.
- [4] Song T, Yu W, Wu SX. Subsequent treatment choices for patients with acquired resistance to EGFR-TKIs in non-small cell lung cancer: restore after a drug holiday or switch to another EGFR-TKI? *Asian Pac J Cancer Prev* 2014;15:205–13.
- [5] Liang S, Xu Y, Tan F, et al. Efficacy of icotinib in advanced lung squamous cell carcinoma. *Cancer Med* 2018;7:4456–66.
- [6] Tan F, Shi Y, Wang Y, et al. Icotinib, a selective EGF receptor tyrosine kinase inhibitor, for the treatment of non-small-cell lung cancer. *Future Oncol* 2015;11:385–97.
- [7] Guan YS, He Q, Li M. Icotinib: activity and clinical application in Chinese patients with lung cancer. *Expert Opin Pharmacother* 2014;15:717–28.
- [8] Kobayashi K, Hagiwara K. Epidermal growth factor receptor (EGFR) mutation and personalized therapy in advanced nonsmall cell lung cancer (NSCLC). *Target Oncol* 2013;8:27–33.
- [9] Yang Z, Hackshaw A, Feng Q, et al. Comparison of gefitinib, erlotinib and afatinib in non-small cell lung cancer: a meta-analysis. *Int J Cancer* 2017;140:2805–19.
- [10] Li YQ, Song SS, Jiang SH, et al. Combination therapy of erlotinib/crizotinib in a lung adenocarcinoma patient with primary EGFR mutation plus secondary MET amplification and a novel acquired crizotinib-resistant mutation MET G1108C. *Ann Oncol* 2017;28:2622–4.