

CASE REPORT

Severe stomatitis caused by osimertinib combined with gefitinib: A case report

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Abstract

The 2017 NCCN Guidelines for NSCLC recommend epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) as the first-line treatment for patients with gene-sensitive mutations of pulmonary adenocarcinoma. The TKI combination can effectively inhibit the gene mutations caused by the drug resistance and enhance the antitumor effect. However, more clinical investigations are required of the efficacy and the adverse drug reactions (ADRs) of this combination. A 62-year-old female patient diagnosed as lung adenocarcinoma with brain metastasis, meningeal metastasis, multiple bone metastasis, and liver metastasis was treated with the combination of gefitinib and osimertinib. Evident improvement was observed after 10 days of combined treatment with these tyrosine kinase inhibitors (TKIs), including in the CT features and symptoms. The level of tumor marker CEA decreased significantly after 40 days. However, severe stomatitis occurred after 49 days. By analyzing the relationship between stomatitis and TKI combined treatment based on the temporal correlation, instructions and literature reports, mechanisms, and reaction, we discovered that the combination of the two TKI drugs can increase the incidence and severity of severe stomatitis. Following targeted treatment and drug withdrawal, the patient fully recovered. TKI combination may increase the incidence and severity of stomatitis, suggesting that closely care and timely withdrawal are necessary measures.

KEYWORDS

gefitinib, osimertinib, severe stomatitis

1 | WHAT IS KNOWN AND OBJECTIVE

The latest statistics from the National Cancer Center show that the morbidity rate for lung cancer is highest in China, with non-small-cell lung cancer (NSCLC) accounting for about 85% of cases.¹ The 2017 NCCN Guidelines

for NSCLC recommend epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) as the first-line treatment for patients with gene-sensitive mutations of pulmonary adenocarcinoma.^{2–5} Resistance due to the EGFR T790 M mutation will occur after 9–13 months of gefitinib treatment (a first-generation EGFR-TKI), which can then be replaced by the third-generation EGFR-TKI

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osimertinib (Tagrisso, AZD9291).^{3,4} However, osimertinib therapy will lead to resistance caused by a C797S site mutation in some patients. When C797S and T790 M are transmutational, the combination of gefitinib can effectively inhibit C797S and enhance the antitumor effect.^{6,7} However, more clinical investigations are required of the efficacy and the adverse drug reactions (ADRs) of this combination.

We applied pharmaceutical treatment to 80 NSCLC patients who had been using targeted drugs in our hospital since September 2013. We found that a combination of TKIs can prolong patient survival, but some serious side effects can occur such as skin reactions and oral inflammation. Patients with severe stomatitis experience unbearable pain and cannot eat orally, which seriously affects their quality of life. If this stomatitis is not identified and the drug withdrawn in time, it will aggravate rapidly to result in prolonging the hospital stay and increasing the treatment cost. The literature includes no cases of stomatitis with ADRs or the combination of TKI. We report a patient who received pharmaceutical treatment for severe stomatitis caused by the combination of osimertinib and gefitinib.

2 | CASE SUMMARY

Ms Wu, a 62-year-old female patient, was hospitalized on October 18, 2018, with the diagnosis of left lung adenocarcinoma (classification: T1NxM1 IV), brain metastasis, multiple bone metastasis, and liver metastasis. Her treatment history indicated that gefitinib was administered at 250 mg/day from February 25, 2017, while the DNA detection of peripheral blood tumors showed a mutation in exon L858R of EGFR exon 21. After 5 days of the treatment, her symptoms improved from coma to consciousness and fluent speech. CT performed 10 days later showed that the lesion in the left lung had reduced in size, and the therapeutic evaluation was of a partial response (Figure 1A). MRI performed 44 days later revealed a significant reduction in the number of lesions in the brain parenchyma compared with before treatment. However, during March 2018—after receiving 12.5 months of gefitinib treatment—her CEA increased progressively and her hearing decreased again as progressive disease (PD) (Figure 1A). The liver lesion was enlarged, and the puncture pathology showed the mutations of EGFR 21 L858R with KIT and KDR amplification. We replaced the treatment regimens with osimertinib at 80 mg/day, and on August 8, 2018, the CEA level had further increased to 260.8 ng/ml, and targeted combined treatment was started comprising docetaxel plus cisplatin. On August 13, 2018, after taking osimertinib at 80 mg/day for 4.5 months,

the patient's meningeal metastasis progressed with convulsion occurring more than 10 times accompanied by transient disturbances of consciousness. We adjusted the osimertinib dosage to 160 mg/day, and on September 1, 2018, her consciousness became sleepiness with speech ambiguity (PD) (Figure 1A). The treatment regimen was therefore adjusted to osimertinib at 80 mg/day plus gefitinib at 250 mg/day. After 10 days of this revised treatment, her symptoms had surprisingly improved significantly, including clear consciousness, increased dietary consumption, ambulation, and a significant decrease in CEA. On September 19, 2018, her consciousness was clear and she could consume food by herself after the nasogastric tube was removed. CT performed on October 20, 2018, showed that the hepatic lesions were now significantly smaller.

On October 23, 2018, after receiving osimertinib combined with gefitinib for 49 days, the patient experienced severe stomatitis, whose both quarrel had a skin ulcer about 3 cm in diameter and some parts of the tongue also had ulcers (Figure 1B). She suffered from pain and could not eat orally. A nasogastric tube was placed for nasogastric feeding, and she was given oxycodone sustained-release tablets to relieve her pain as well as recombinant bovine basic fibroblast growth factor gel to promote wound healing. On November 5, 2018, a second course of pemetrexed was started, but the ulcer on her mouth remained unchanged. Clinical pharmacists reminded the doctor that the stomatitis could be a side effect of the TKI combination, and so that was stopped. Three days later, her stomatitis had improved significantly, with the ulcer gradually changing to a scab and falling off. The patient was discharged from hospital on December 2, 2018. The timeline of the treatment process and the clinical responses is shown in Figure 1.

3 | WHAT IS NEW AND CONCLUSION

The patient had a pathological diagnosis of NSCLC lung cancer, with gene testing indicating the presence of EGFR gene mutation and appropriateness for EGFR-TKI treatment. The patient progressed after taking gefitinib at 250 mg/day for 12.5 months, while the nervous system symptoms progressively worsened after switching to osimertinib at 80 mg/day. According to BLOOM research, patients with brain metastasis and meningeal metastasis of NSCLC lung cancer with EGFR mutations respond better to oral osimertinib at 160 mg/day than at 80 mg/day, with this also allowing ADRs to be controlled.³ The efficacy remained unsatisfactory even after increasing the dosage to 160 mg/day. Financial reasons resulted in the patient refusing to take anlotinib. Based on the T790 M

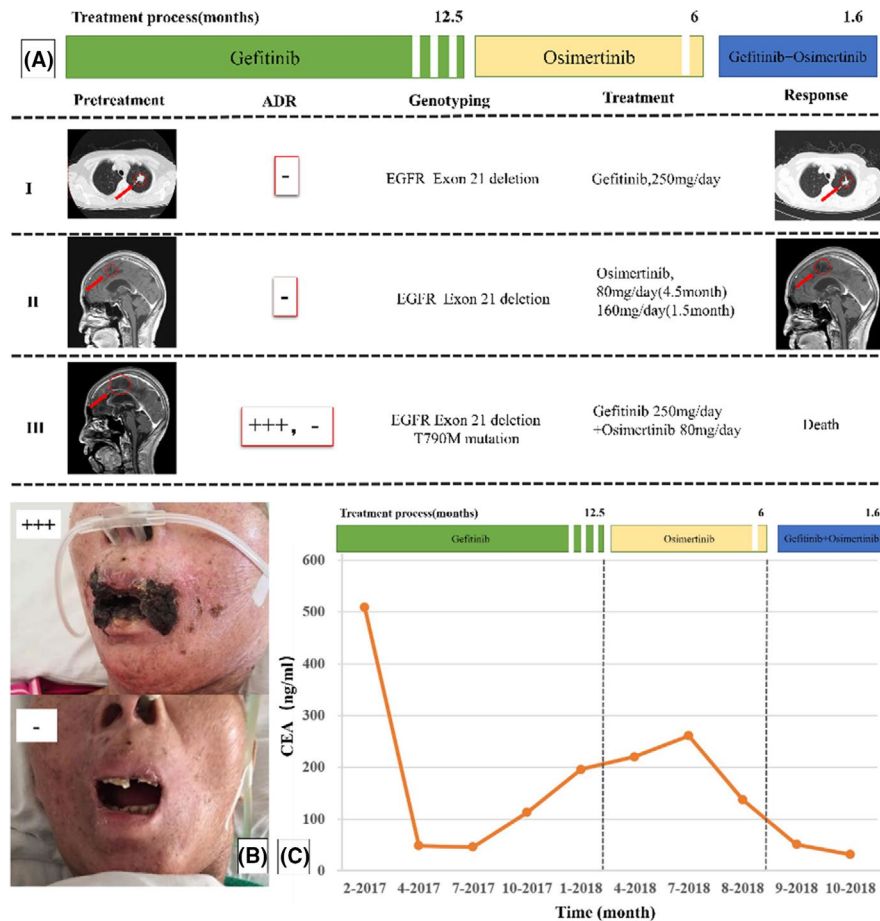


FIGURE 1 Treatment process and clinical responses to gefitinib in combination with osimertinib. (A) Stage I: Gefitinib at 250 mg/day. The patient exhibited a partial response, with CT showing that the lesion in her left lung had reduced in size after 1 month of gefitinib treatment. There was no adverse effect of stomatitis. Stage II: Osimertinib at 80 mg/day for 4.5 months followed by 160 mg/day for 1.5 months. The patient experienced PD after 12.5 months of gefitinib treatment. Based on gene test results, we replaced the treatment regimen with osimertinib at 80 mg/day for 4.5 months followed by 160 mg/day for 1.5 months. Head MRI showed PD with no adverse effect of stomatitis. Stage III: Gefitinib at 250 mg/day plus osimertinib at 80 mg/day. The patient achieved a partial response with head MRI showing PD, and so the treatment regimen was changed. The patient experienced severe stomatitis after receiving osimertinib combined with gefitinib for 49 days. (B) Severe stomatitis (+++), both quarrel had a skin ulcer about 3 cm in diameter, and some parts of the tongue also had ulcers. At 3 days after withdrawing the TKI combination, her stomatitis had improved significantly, with complete recovery after 1 month. (C) Dynamic monitoring of CEA during the treatment of EGFR-TKIs. The changes in CEA were essentially identical to those in the symptoms

mutation of the CSF gene being detected, we tried osimertinib combined with gefitinib. After 10 days, the patient's consciousness had improved significantly and she was able to get out of bed, while after 40 days her CT features, symptoms, and the tumor marker CEA had all improved significantly.

Arulananda et al. were the first to report on the clinical efficacy of the combination of first- and third-generation EGFR-TKIs for transmutations of T790 M and C797S.⁵ A 41-year-old Asian male patient who had NSCLC with mediastinal and bone metastases improved within 3 days after starting the combination therapy. Although the mutation sites of the two cases are different, the effectiveness of the combination therapy is highly significant and indicates

that the underlying mechanism needs further investigation. Combining first- and third-generation EGFR-TKIs is a common clinical treatment for patients with lung cancer and brain metastasis. However, no stomatitis occurred in the case report of Arulananda et al., and there have been no reports of the adverse effect of stomatitis induced by TKI combination therapy.⁵ This might be due to there being very few TKI combination cases reported and also the treatment times being short.

The clinical pharmacists provided full pharmaceutical treatment to the present patient for 678 days. After carefully analysis of the medication history, no stomatitis occurred when gefitinib was applied as a monotherapy for more than 1 year or when osimertinib was applied as a

monotherapy for more than 6 months. In terms of medication time, docetaxel was suspended for 21 days, which can exclude the associated ADRs. Severe stomatitis only occurred when gefitinib was combined with osimertinib. According to previous reports, an ADR to gefitinib is most likely to appear within 31–90 days,^{8,9} and the severe stomatitis occurred in the present case at 49 days after starting the TKI combination treatment of osimertinib and gefitinib.

According to the latest Expert Consensus on Adverse Reaction Management of EGFR-TKI¹⁰ and edition 5.0 of the CTCAE (American Common Terminology Criteria for Adverse Events), a patient who suffers from severe pain and is put on a nasogastric tube for nutrition support can be diagnosed as having severe stomatitis worse than grade 3. Clinical studies have found that the incidence of severe stomatitis in both gefitinib and osimertinib is very low, <1%.^{10–15}

The mechanism via which EGFR-TKIs induce stomatitis may involve the abundance of EGFR in undifferentiated keratinocytes playing a key role in the proliferation, migration, differentiation, and survival of keratinocytes, keratinization, and follicular development. Treatment with EGFR-TKIs will reduce EGFR phosphorylation of the basal-layer stem cells and increase the expansion and differentiation of cells in the oral mucosal epithelia. The activation of PI3K-Akt and Ras-Raf-MAPK signaling pathways was initially inhibited. Cyclin-dependent kinase inhibitor p27 was subsequently up-regulated, resulting in arrest of the G1/S cycle while inhibiting DNA synthesis. However, apoptotic proteins BCL2 and BCL-XL were up-regulated in normal keratinocytes, which promoted cell apoptosis and eventually led to significant changes and thinning of the epidermis. Apoptotic cells provide favorable conditions for the reproduction of bacteria, viruses, and fungi. *Streptococcus* and *Staphylococcus* species proliferate in areas such as the buccal mucosa, tongue, gingiva, and maxilla, which aggravates inflammatory reactions and leads to further acute damage to the oral mucosa.^{16,17}

In addition, the target of the first-generation EGFR-TKI gefitinib (Mg-ATP) differs from that of the third-generation osimertinib (C797S). The combination of these two TKIs enhances the inhibition of EGFR signal transduction and promotes the apoptosis of tumor cells, but also promotes the apoptosis of epidermal keratinocytes. The combination of TKIs may also accelerate the apoptosis of keratinocytes, leading to an increase in the incidence and severity of severe stomatitis. Other studies have shown that ADRs to gefitinib and osimertinib are dosage-dependent, and that the incidence of ADRs to osimertinib is significantly lower than that of the first- and second-generation EGFR-TKIs.¹² Therefore,

the present patient did not experience adverse effects when taking high dosages of osimertinib alone, but severe stomatitis occurred when this was combined with gefitinib.

Following the above analysis, we stopped the TKI medication, and 3 days later, the patient's stomatitis improved significantly and most of the scabs on the mouth corners fell off. The condition of the patient improved, and she was discharged. We therefore conclude that the stomatitis that this patient experienced may have been related to the combination of gefitinib and osimertinib. On May 17, 2019, the patient died of lung cancer cachexia, giving a total time course of 2 years and 3 months.

In conclusion, careful and complete pharmaceutical treatment applied in this study allowed clinical pharmacists to assist physicians in identifying the ADRs to the TKI combination in a timely manner. It was found that this regimen may increase the incidence and severity of severe stomatitis. This report provides reference information for TKI combination treatments, reminding doctors and clinical pharmacists to pay attention to the possible occurrence of the adverse effect of stomatitis in order to improve both the effectiveness and safety of these treatments.

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CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTION

Lei Yu composed the background section of the manuscript and contributed to editing. Zhu Ya-ning, Li li, Zhang Peng, Zuo Yan, Bai Jun, and Cao Lu edited the manuscript. Guo Zhen-Jun composed the remainder of the manuscript and is the corresponding author. All authors read and approved the final manuscript.

ETHICAL APPROVAL

Consent was obtained from the patient described in this report.

CONSENT

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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