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Case report

Alkalescent soda beverage caused the disappearance of gefitinib-induced rashes and decreased efficacy in a non-small-cell lung cancer patient treated with gefitinib: A case report

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ABSTRACT

Oral anticancer drugs have the advantages of convenient and flexible administration, however, they also face some new problems related to their oral preparation. Herein we describe a case of advanced non-small-cell lung cancer patient treated with gefitinib who had long-term adverse reactions of rashes and diarrhea, and his rashes disappeared after taking alkaline soda, and then reappeared after stopping drinking it. Imaging progress was also observed. To our knowledge, this is the first report on the effect of alkaline food on gefitinib-induced rashes dynamic change. In this case, the rash acted as a signal of therapeutic efficacy. Clinicians and pharmacists should be aware of potential and common factors that affect drug efficacy and strive to achieve the best therapeutic results.

1. Introduction

With the development of tumor molecular biology technology, the emergence of small molecular targeted drugs (SMTD) has brought a new therapeutic approach to patients with advanced non-small-cell lung cancer (NSCLC). Gefitinib is the first-generation epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI). Compared with traditional chemotherapy drugs, gefitinib improves the prognosis and survival of NSCLC patients with EGFR mutation with fewer adverse reactions [1]. And rash caused by gefitinib may be a maker of its efficacy [2]. As an oral anticancer drug, its oral preparation is convenient and flexible for administration. However, along with these advantages, oral administration also faces some new problems related to this. Herein we describe a case of advanced NSCLC patient treated with gefitinib who had long-term adverse reactions of rashes and diarrhea, and his rashes disappeared after taking alkaline soda, and then reappeared after stopping drinking it. Imaging progress was also observed. To our knowledge, this is the first report on the effect of alkaline food on gefitinib-induced rashes dynamic change.

1.1. Case report

A 52-year-old male smoking patient was found with a mass of right upper and middle lung during physical examination in September 2017, and underwent surgical resection. Rapid intraoperative pathology showed right upper middle lung adenocarcinoma. Then right upper and middle lobectomy with systematic mediastinal and hilar lymph node dissection were performed, and pathology showed no cancer metastasis in lymph nodes. Pemetrexed plus cisplatin was given 6 cycles after operation. Eleven months after operation, chest CT showed enlarged multiple mediastinal lymph nodes, and lymph node metastasis was considered. So docetaxel plus cisplatin was given 2 cycles and paclitaxel plus cisplatin was given 2 cycles. CT examination after chemotherapy showed enlargement of the anterior superior mediastinal lymph node, which was evaluated as ineffective. In December 2018, when EGFR L858R mutation was detected from the original surgical specimen, he switched to gefitinib targeted therapy. Subsequent multiple CT examinations showed reduced mediastinal lymph nodes. Treatment with gefitinib was effective, accompanied with long-term tolerable adverse reactions such as rashes and diarrhea. The patient bought soda water (an alkaline beverage containing sodium bicarbonate) accidentally in June 2019. When he drank it the next day, the rashes subsided. The patient

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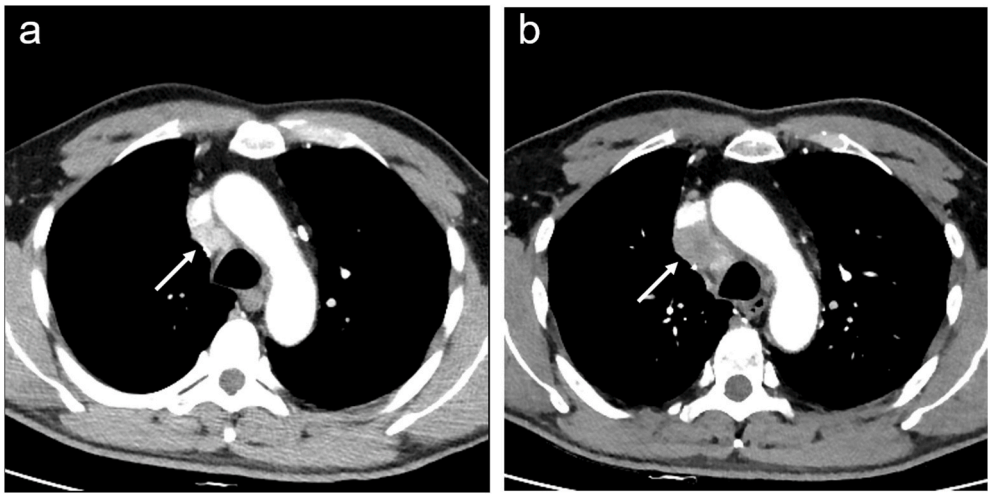

Fig. 1. As indicated by the arrows,(a)CT showed the enlarged but gradually shrunken lower paratracheal lymph node of the patient treated with gefitinib 2 months before soda consumption; (b) The patient drank soda for 1 month, CT showed the lower paratracheal lymph node was significantly enlarged compared with the last time.

believed that soda water can counteract the adverse reaction of rashes, so he insisted on drinking it for 1 month, with intake about 300ml per day, during which rashes did not occur again. He didn't stop drinking soda water until July 2019, when CT showed mediastinal lymph nodes were larger than the last time (Fig. 1). After that, his rashes gradually developed but were not as obvious as before. Unfortunately, we did not record a comparative photograph of his rashes.

2. Discussion

The absorption of gefitinib is affected by a variety of factors. The first prerequisite for its absorption in vivo is its dissolution in the gastrointestinal tract. For oral SMTD, gastric pH is an important factor affecting the dissolution of drugs. Changes in gastric pH can be influenced by foods and antacids, which can affect the dissolution and absorption of a number of TKIs, including gefitinib, erlotinib, crizotinib, dasatinib, lapatinib, and pazopanib, thus affecting the bioavailability and efficacy of drugs [3,4].

Gefitinib has pKa values of 5.4 and 7.2 and therefore ionizes progressively in solution as the pH falls [5,6]. Clinical study of healthy volunteers demonstrated that the bioavailability of a single oral dose of gefitinib 250 mg is reduced by approximately 50% when gefitinib is administered under conditions of a sustained elevated gastric pH level ($pH > 5$) [6].

Gefitinib-induced rash is considered to be a marker of the efficacy and clinical outcome of EGFR-TKIs treatment to some extent [2]. In this case, initial gefitinib treatment was effective, accompanied by adverse reactions of rashes and diarrhea, his rashes subsided the second day after taking soda, and gradually developed after he stopped drinking it, then CT showed progression. The disappearance of rashes may represent a decrease in efficacy, reflecting the fact that soda can decrease the bioavailability and efficacy of gefitinib by raising gastric pH. However, we cannot rule out that disease progression is due to gefitinib resistance in the patient himself.

Since EGFR-TKIs exhibit pH-dependent solubility, drug interactions with acid suppressant (AS) occur by gastric acid suppression. A study showed the intake of erlotinib with an acidic beverage (cola) enhanced bioavailability by almost 40% in patients also taking esomeprazole [7]. It further suggests that changes in gastric pH have an effect on EGFR-TKIs bioavailability. However, a number of previous studies on the clinical impact of AS include proton pump inhibitors (PPIs) and H2-receptor antagonists (H2RAs) on the treatment outcome of EGFR-TKIs remains controversial [8–11].

In clinical practice, the use of AS, including PPIs and H2RAs, is common in patients with advanced lung cancer, due to the treatment or prevention of gastrointestinal disease, for many patients take non-steroidal anti-inflammatory drugs (NSAIDs) to control pain. If concomitant use is unavoidable, then staggering the dose of the EGFR-TKIs and AS by several hours may help to reduce the extent of the interaction, but the effect of this solution is uncertain because of the long-acting acid inhibition effect of AS [12]. It is worth mentioning that studies have shown that food has no particularly significant effect on the bioavailability of gefitinib, and gefitinib can therefore be taken with food [13]. However, from the above discussion, it should be noted that gefitinib is not suitable for taking with alkaline food that elevate gastric pH. In addition, during EGFR-TKIs treatment, concomitant medication should also be considered comprehensively to achieve optimal therapeutic outcome [14].

3. Conclusions

The dissolution and absorption of gefitinib is pH dependent. Factors that elevate gastric pH can affect the bioavailability of gefitinib and may reduce its efficacy. When gefitinib-induced long-term rashes subside or disappear, clinicians should consider whether there exist factors that cause the decline in bioavailability and efficacy. When lung cancer patients are treated with EGFR-TKIs, clinicians and pharmacists should consider not only drug interactions, but also the influence of the food pH on pharmacokinetics. Identify common but easily overlooked pharmacokinetic factors to achieve optimal therapeutic outcomes.

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Declaration of competing interest

The authors declare no conflict of interests.

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