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Severe adverse cutaneous reactions induced by gefitinib combined with antihypertensive and antihyperlipidemic drugs in lung cancer: a case report

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The incidence of lung cancer is increasing yearly worldwide, and targeted medicines are the main choice for lung cancer patients. However, there has been no relevant research about the analysis and adjustment of drug combinations for cancer patients with hypertension and hyperlipidemia until now. Here, we reported a case of medicine adjustment for a patient of lung cancer with hypertension and hyperlipidemia. The patient was diagnosed as right lung adenocarcinoma with lymph node metastasis and continued taking gefitinib tablets to maintain therapeutic efficacy after the end of chemotherapy. Severe paronychia and a high plasma concentration of gefitinib were noticed when the patient visited the hospital for reexamination. The clinical pharmacist found that the patient took nifedipine sustained-release tablets and simvastatin tablets simultaneously, and these medicines were all substrates of CYP3A4. The clinical pharmacist suggested replacing the medicines for hypertension and hyperlipidemia with valsartan capsules (Diovan) and rosuvastatin calcium tablets (Crestor), respectively. The adverse cutaneous reactions were greatly relieved, and the plasma concentration of gefitinib was decreased when another reexamination was performed. Therapeutic drug monitoring was an important method in our case and provided valuable information to develop individualized treatment strategies. For cancer patients suffering from other diseases such as hypertension and hyperlipidemia, it is necessary to pay special attention to the drug–drug interactions and metabolic pathways among drug combinations. *Anti-Cancer Drugs* 33: e802–e807 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.

Anti-Cancer Drugs 2022, **33**:e802–e807

Keywords: case report, drug–drug interaction, gefitinib, plasma concentration, therapeutic drug monitoring

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Received 8 August 2021 **Revised form accepted** 9 August 2021

Introduction

Lung cancer is becoming increasingly associated with cancer-related deaths worldwide [1]. Gefitinib, erlotinib, icotinib, and afatinib are the first-line treatments for lung cancer patients with epidermal growth factor receptor (EGFR) mutations, according to the Chinese Society of Clinical Oncology guidelines for the diagnosis and treatment of primary lung cancer [2]. Mild and moderate adverse cutaneous reactions are universal adverse drug reactions (ADRs) to gefitinib, mainly manifested as dry, itchy, and chapped skin as well as nail abnormalities. Paronychia was reported to be related to the use of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs). A total of 10–15% of patients developed paronychia after they took first-generation or second-generation EGFR-TKIs for 4–8 weeks [3]. It has also been reported that the incidence of paronychia, which may result from gefitinib, was approximately 9.8% [4].

When patients take two or more drugs at the same time or successively, the effect of one drug may be obviously changed by the influence of another drug and it is called drug–drug interactions (DDIs). It needs special attention for cancer patients as it may affect the therapeutic efficacy of anticancer medicines. Therapeutic drug monitoring (TDM) refers to collecting the blood (or urine, saliva, and other liquids) of patients and determining the drug concentration regularly during treatment [5]. We could understand the pharmacokinetic process of drugs in patients through TDM to infer the presence or influence of DDIs on the treatment effect. It could provide a reference for the following formulation of individualized drug treatment, optimize the treatment strategy and maximize the treatment effect of drugs [6]. The aim of individual treatment strategies was to achieve the most satisfactory outcome and avoid severe ADRs [7]. Therefore, TDM is

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an important way to obtain significant treatment effects and explore DDIs to ensure medication safety for cancer patients. Unfortunately, there are few systematic and comprehensive reports about TDM in cancer patients to date. Moreover, there is also no relevant clinical research report about TDM in cancer patients with hypertension and hyperlipidemia.

Here, we report a case of a clinical pharmacist who participated in the TDM of a lung cancer patient treated with gefitinib. The clinical pharmacist explored how to individualize the treatment strategy of cancer patients with hypertension and hyperlipidemia according to the TDM results. At the same time, the resolution of ADRs is another important aspect in the treatment process and provides some experience for the clinical treatment of these patients.

Case

Case presentation

A 63-year-old woman went to the local hospital for examination in February 2019 due to dry cough without obvious inducement. She was diagnosed as right lung adenocarcinoma with lymph node metastasis according to the imaging and pathological results. The genetic test results demonstrated that the patient had the EGFR exon-21 L858R mutation, and then she underwent six cycles of AL chemotherapy (pemetrexed + lobaplatin) and gefitinib (Iressa; AstraZeneca, Cheshire, UK) from February to June. The specific dosage was 800 mg pemetrexed on the first day + 40 mg lobaplatin on the first day + 0.25 g gefitinib each day, and chemotherapy was cycled every 3 weeks. The evaluation results of the chemotherapy efficacy were stable disease both in April and May 2019. The patient continuously took gefitinib 0.25 g each day for maintenance treatment after the end of chemotherapy, and the evaluation result was partial response (PR) in August 2019. At present, the patient takes 0.25 g gefitinib orally for maintenance therapy and is hospitalized for reexamination every 3 months. The patient had hypertension for more than 20 years and regularly took 20 mg nifedipine sustained-release tablets orally every day. Moreover, the patient had no special medical, personal or family histories.

Admission examination

The patient was 156 cm in height and 61 kg in weight, temperature was 37.0°C and blood pressure was 142/88 mmHg. Serious adverse cutaneous reactions were found when the patient was admitted to the hospital for physical examination in November 2019. The patient's skin around the whole body was dry, and many scales fell off, especially on the face, hands, and feet. Moreover, both the patient's hands and feet had serious pigmentation as well as a small amount of blood oozing from the nail seam. The fingertip was slightly peeled, and the situation was more serious in the patient's feet and accompanied by the nail cavity falling off, as well as local infection and even suppuration (Fig. 1).

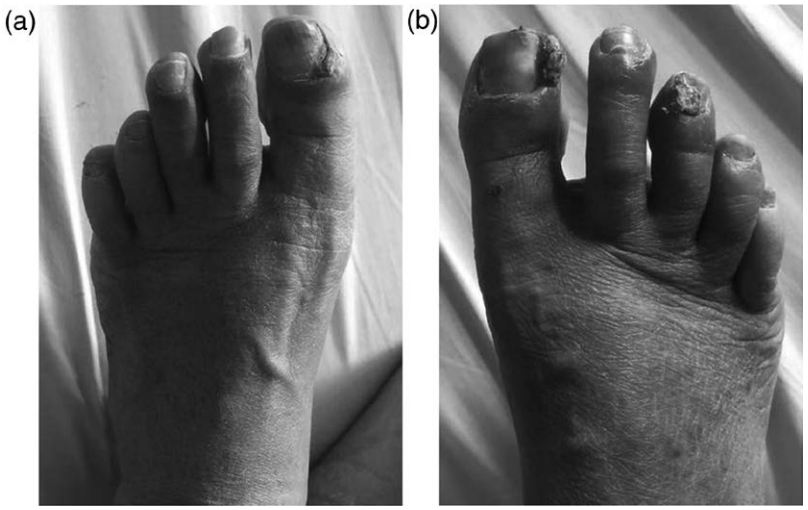
The biochemical examination showed that the serum total cholesterol was 3.39 mmol/L, serum triglycerides were 0.90 mmol/L and other indicators were all normal, including renal and hepatic organ function. There were also no remarkable findings from the blood test, immune test, urine analysis, electrocardiogram, chest X-ray or tumor marker test. The chest enhanced computed tomography scan revealed similar results compared with the last scan (Fig. 2). The brain was further evaluated with a brain MRI scan, and there were no abnormal results.

Treatment

Due to the patient continued taking the targeted drug gefitinib, the clinical pharmacist suggested measuring the plasma concentration of gefitinib as well as conducting pharmaceutical ward rounds. The results revealed that the plasma concentration of gefitinib was 589 ng/mL, which was much higher than the valley concentration reported in the literature [8–11]. Through the pharmaceutical ward round, it was worth noting that the patient described that she also took 20 mg simvastatin tablets before going to bed at night every day, which she did not mention before. However, the clinical pharmacist noticed that nifedipine, gefitinib, and simvastatin were all substrates of the hepatic drug-metabolizing enzyme CYP3A4. The clinician and clinical pharmacist considered that it was necessary to adjust the drug treatment strategy of the patient. We proposed the following adjustment plans after discussion: (1) reduce the dosage of gefitinib by half, possibly by administering either half of the tablet every day or one tablet every other day. (2) Stop administering antihypertensive medicine as the patient's blood pressure was not particularly high. (3) Replace antihypertensive and antihyperlipidemic drugs with those metabolized without a hepatic drug-metabolizing enzyme system. (4) Continue to maintain the current situation since the treatment efficacy of the anticancer agent is quite satisfactory, and adverse cutaneous reactions do not seriously affect the patient's daily life. After obtaining the understanding and consent of the patient and her family through full communication, the clinician and clinical pharmacist finally decided to replace the medicines for hypertension and hyperlipidemia with valsartan capsules and rosuvastatin calcium tablets, respectively.

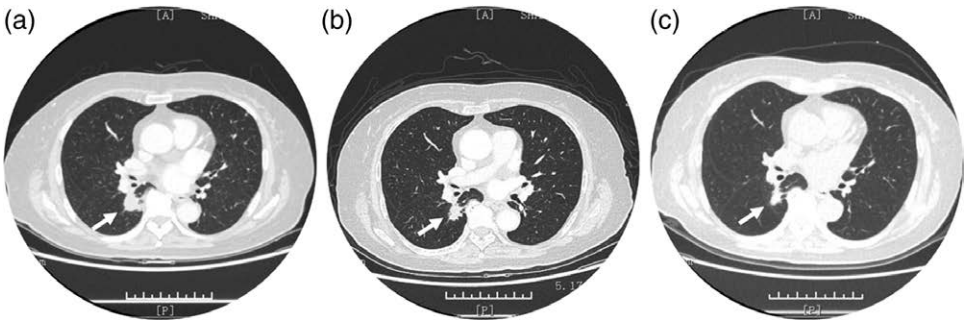
The efficacy evaluation result was PR this time, and gefitinib maintenance treatment was continued (Fig. 2a and b). The patient was discharged with the following medicines: (1) (Iressa; AstraZeneca) gefitinib tablets (DL), one tablet per time, once a day; (2) (Crestor; AstraZeneca) rosuvastatin calcium tablets, one tablet per time, once a day; and (3) (Diovan; Novartis, Beijing, China) valsartan capsules, one capsule per time, once a day. The clinical pharmacist educated the patient and her family on the correct use of these medicines and told

Fig. 1



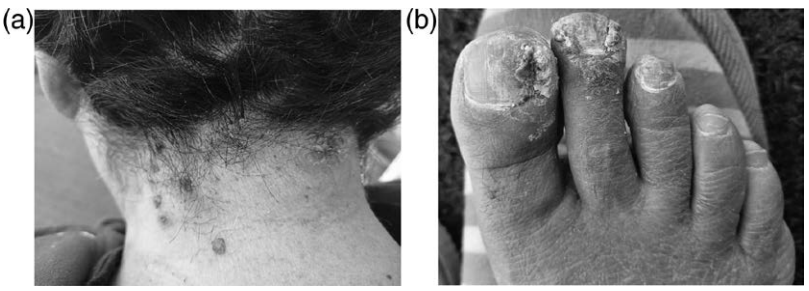
Severe adverse cutaneous reactions on the patient's feet when she was hospitalized on 30 November 2019. (a) Obvious pigmentation, dry skin and nail cavity on the patient's left foot. (b) The adverse cutaneous reactions were more serious on the patient's right foot.

Fig. 2



The chest CT scan showed a trend of gradual improvement. (a) The imaging showed a space-occupying lesion with a size of 32 × 18 mm that was located in the right lower lobe on 30 May 2019. (b) The lesion on 2 December 2019 and it was 21 × 12 mm in size. (c) The lesion was further reduced and the size was 14 × 11 mm on 20 April 2020. The part indicated by the arrow is the lesion.

Fig. 3



Adverse cutaneous reactions became more serious. (a) Pustula and rupture occurred even on the patient's neck when she continued to take nifedipine sustained-release tablets and simvastatin tablets. (b) The paronychia became more serious on the patient's feet.

them to remember that grapefruit was not recommended. If other medicines need to be taken at home, it is better to consult with the doctor or pharmacist first.

Outcome and follow-up

However, the patient continued taking nifedipine sustained-release tablets and simvastatin tablets after discharging for personal reasons. The adverse cutaneous reactions were obviously aggravated during this period, and the plasma concentration of gefitinib was 716 ng/mL (Fig. 3). The clinicians and clinical pharmacist educated the patient and her family about drug usage and then she replaced the drugs according to our advice. Blood samples were collected again 2 weeks later, and the plasma concentration of gefitinib was 480 ng/mL. The patient continued taking gefitinib, valsartan, and rosuvastatin calcium tablets until 20 April 2020, when she was admitted to the hospital again. Physical examination showed that the adverse cutaneous reactions were greatly reduced (Fig. 4). The plasma concentration of gefitinib was detected again during hospitalization and the result was 426 ng/mL, which was significantly lower than that of previous. The outcome of the efficacy evaluation was PR this time (Fig. 2c).

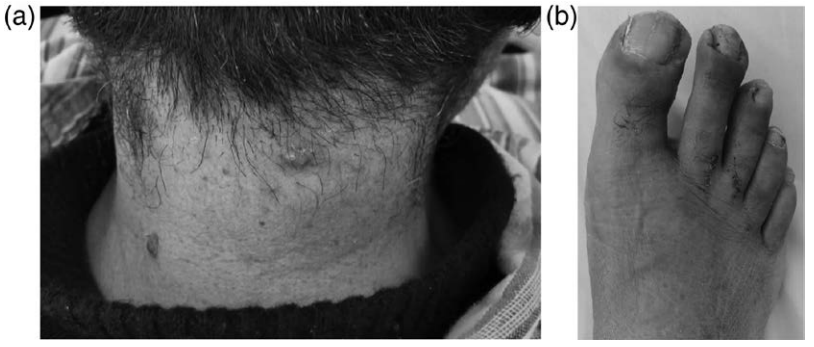
Discussion

Here, we reported a case that the patient with lung cancer had serious adverse cutaneous reactions as well as high plasma concentration of gefitinib, and the reason is worthy of further study. The clinical pharmacist first analyzed from drug pharmacokinetics [12]. The patient's daily diet was regular, and food had no significant effect on the absorption of gefitinib. Gefitinib is widely distributed in the body during homeostasis, mainly binding with serum albumin and α1-acid glycoprotein, and the binding rate is approximately 90%. The P450 isoenzyme CYP3A4 was the major enzyme involved in drug metabolism, and gefitinib could inhibit CYP2D6 *in vitro*. Drug excretion was mainly through feces, less than 4% of which was eliminated by kidneys in the form of prototypes and metabolites. The biochemical examination results showed that the patient's liver and kidney functions were normal when she was hospitalized.

Considering that the patient took antihypertensive and antihyperlipidemic drugs at the same time and most drugs need the hepatic drug-metabolizing enzyme P450 system for metabolism, the clinical pharmacist focused on drug metabolism and DDIs. As CYP3A4 is the only P450 isoenzyme involved in the oxidative metabolism of gefitinib, CYP3A4 inducers/inhibitors or other medicines metabolized by CYP3A4 may influence the metabolism of gefitinib. It was reported that nifedipine was oxidized *in vivo* via a hepatic microsomal drug-metabolizing enzyme system including cytochrome P450 monooxygenase. The combination of CYP3A4 inhibitors would elevate the exposure of simvastatin, as there was some definitive evidence that simvastatin was metabolized by CYP3A4 [13,14]. A pharmacokinetic test showed that taking simvastatin and amlodipine at the same time would increase the plasma concentration of simvastatin [15]. In conclusion, almost all three medicines are metabolized by CYP3A4, and they might compete for the CYP3A4 enzyme when taken together. The outcome was the increase in drug exposure, which manifested as the abnormal elevation of drug concentration.

The patient had a history of hypertension for more than 20 years, which was routinely controlled with oral medicines. So was oral antihyperlipidemic drugs, and it was not suitable to suddenly withdraw those drugs. To maintain treatment efficacy, it was not appropriate to adjust the dosage or frequency of gefitinib and the ADRs should be minimized. Taking all of the above factors into consideration, the best solution was to replace the medicines with those metabolized without the hepatic drug-metabolizing enzyme CYP3A4. The clinical pharmacist studied the metabolic pathways of common antihypertensive and antihyperlipidemic drugs (Tables 1 and 2). Finally,

Fig. 4



The symptoms were greatly relieved after taking valsartan and rosuvastatin calcium tablets for 1 month. (a) The rupture on the neck was smaller than before and almost disappeared. (b) The dry skin and nails were both greatly relieved on the patient's feet.

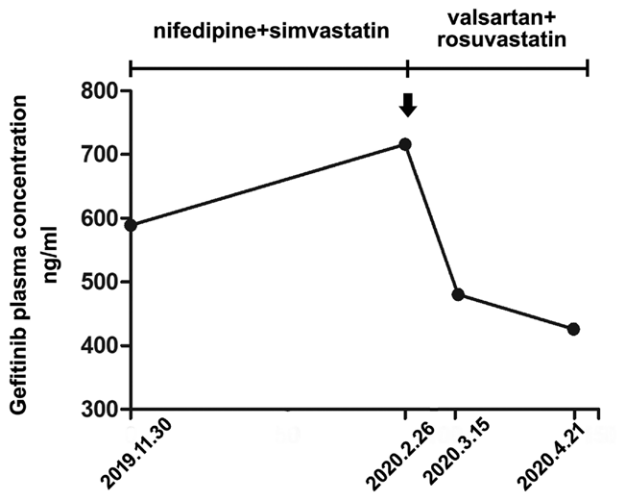
Table 1 **Metabolic pathways of common antihypertension medicines**

Trade name	Generic name	Metabolic pathways
Aprovel	Irbesartan tablets	In-vitro experiments showed that Irbesartan was mainly oxidized and metabolized by cytochrome P450 enzyme CYP2C9, and CYP3A4 isoenzyme almost had no effect.
Diovan	Valsartan capsules	About 70% of Valsartan is excreted as prototype in bile and most of them will not undergo biotransformation. About 20% of them will transform into metabolites with no pharmacological activity.
Norvasc	Amlodipine besylate tablets	About 90% is extensively metabolized into inactive metabolites through the liver. The strong CYP3A4 inhibitor may significantly increase the plasma concentration of amlodipine. The combination of amlodipine may elevate the exposure of simvastatin and cyclosporine tacrolimus.
Nifedipine	Nifedipine sustained-release tablets	The medicine is oxidized into three kinds of metabolites without pharmacological activity through the hepatic microsomal drug-metabolizing enzyme system (including cytochrome P450 monooxygenase) in vivo.
Betaloc ZOK	Metoprolol succinate sustained-release tablets	It is mainly metabolized by cytochrome P450 2D6 in the liver.
Plendil	Felodipine sustained release tablets	It is the substrate of CYP3A4.
Vilya	Candesartan cilexetil tablets	Precious few of them is metabolized by liver, and also not by P450 hepatic drug-metabolizing enzyme system, as well as has no effect on P450 metabolism.
Lacipil	Lacidipine tablets	It is mainly metabolized by liver, including P450 CYP3A4.

Table 2 **Metabolic pathways of common antihyperlipidemic drugs**

Trade name	Generic name	Metabolic pathways
Crestor	Rosuvastatin calcium tablets	It is the weak substrate of cytochrome P450 metabolism. CYP2C9 is the main isoenzyme involved in metabolism and the participation of CYP2C19, CYP3A4, and CYP2D6 are relatively low.
Mevalotin	Pravastatin sodium tablets	It is mainly metabolized by liver, but not by cytochrome P450 3A4.
Zocor	Simvastatin tablets	It is highly selective for liver and the concentration in the liver is significantly higher than other tissues. Most of them is absorbed in the liver due to the first pass effect, mainly works in the liver and then excreted through bile.
Lescol	Fluvastatin sodium capsules	It mainly works in the liver, which is also the major organ of its metabolism. The biotransformation of fluvastatin is accomplished by many alternative pathways of cytochrome P450. The inhibition of cytochrome P450 has little effect on the metabolism of fluvastatin. Fluvastatin only inhibits the metabolism of compounds that metabolized through CYP2C9.
Lipitor	Atorvastatin calcium tablets	Atorvastatin calcium and its metabolites are mainly metabolized by liver and/or extrahepatic and then eliminated through bile. In-vitro studies have shown the importance of cytochrome P450 3A4 in the metabolism of atorvastatin calcium.

Fig. 5



The gefitinib plasma concentration was significantly decreased when the antihypertensive and antihyperlipidemic drugs were changed to valsartan and rosuvastatin, respectively.

Diovan (valsartan capsules) without biotransformation and the more commonly used Crestor (rosuvastatin calcium tablets) were selected. The patient continued to take nifedipine sustained-release tablets and simvastatin after discharging, during which the adverse cutaneous reactions gradually became severe and even began to involve the face and neck. The plasma concentration of gefitinib reached 716 ng/mL and later, the patient took valsartan and rosuvastatin calcium tablets according to the advice of the clinicians and clinical pharmacist. Both the adverse cutaneous reactions and plasma concentration of gefitinib have been greatly improved later (Fig. 5). However, the plasma concentration failed to decline to the desired level and the reason may be complex. On the one hand, the possible cause might be the individual differences in age, sex and other patients. On the other hand, the hepatic drug-metabolizing enzyme system is only part of the reason, among which there are some unknown factors.

Considering that the main reason of ADRs was drug metabolism in this case, we further explored the hepatic drug-metabolizing enzyme. It is well known that CYP3A4 and CYP3A5 are the main hepatic drug enzymes involved in the metabolism of gefitinib [16–18], while CYP2D6 is associated with the production of gefitinib, an inactive metabolite [19,20]. Regretfully, many studies have shown that CYP3A5 has no obvious relationship with the plasma concentration, clearance rate and effect of gefitinib [21,22]. However, it has been reported that poor

metabolizer phenotypes for CYP2D6 and CYP3A5 were associated with an increased risk of severe hepatotoxicity induced by gefitinib [23]. Importantly, a study found that patients with reduced CYP2D6 activity treated with gefitinib had a significantly higher frequency of rash than did patients with functional CYP2D6, and CYP2D6 phenotypes are a risk factor for the development of rash in gefitinib therapy [24]. Furthermore, several SNPs in P450 associated with skin rash and diarrhea in Chinese NSCLC patients treated with Gefitinib, including CYP3A4 [25]. In order to improve our research, we genotyped patient's hepatic drug enzymes. The results showed that CYP3A4 was wild type, which was more prone to adverse cutaneous reactions. CYP2D6 genotype was weak metabolic type, which was related to the high incidence of rash, and could not completely convert gefitinib into inactive products.

Conclusion

Take all above into consideration, we thought the phenotype of the patient's hepatic drug-metabolizing enzyme and at the same time she took the three drugs, which had DDIs, led to the high plasma concentration of gefitinib and severe adverse cutaneous reactions in this case. Our experience in this case suggested that it was necessary to take DDIs into consideration for cancer patients with other diseases. The clinical pharmacist's effort not only ensures the safety of patients' medicines, but also provides some reference for the future work of clinicians.

Acknowledgements

The research was supported by the National Natural Science Foundation of China (grant no. 82003844) and Suzhou science and technology development project (grant no. SYSD2019175).

The blood drug concentration monitoring technology of molecular targeted drugs had been passed by the ethics committee of Shanghai General Hospital and the acceptance number is: 2019-N-021. Written informed consent to participate was obtained from the parents of the patient.

Conflicts of interest

There are no conflicts of interest.

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