

Treatment of severe rash caused by crizotinib with both traditional Chinese medicine and Western medicine

Two case reports and literature review

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Abstract

Rationale: Lung adenocarcinoma is the most common pathologic pattern of lung cancer. During the past decades, a number of targeted agents have been explored to treat advanced lung adenocarcinoma. Recently, Crizotinib, the antagonist of anaplastic lymphoma kinase (ALK), has been widely used in ALK-rearranged lung cancer treatment. Crizotinib is generally well tolerated while its most frequent adverse events include visual disorders, gastrointestinal disturbances, cardiac and endocrine abnormalities. Rash caused by crizotinib is rarely seen, and there are few case reports of severe rash caused by crizotinib.

Patient concerns and diagnoses: Here we report cases of an 81-year-old man and a 66-year-old woman with ALK-rearranged advanced lung adenocarcinoma. When patients came to our department, they both had crizotinib-induced severe rash.

Interventions: Crizotinib was initiated as the 1st-line treatment without other therapies. We treated severe rash with traditional Chinese medicine (TCM) therapy called Zhiyang Pingfu liquid along with Western medicine. Zhiyang Pingfu liquid consists of *Scutellaria baicalensis* 20g, *Portulaca oleracea* 30g, *Cortex Dictamnii* 30g, *Sophora flavescens* 30g, and other substances. Western medicine includes Minocycline hydrochloride tablets and Aprepitant capsules.

Outcomes: Both patients achieved a partial response when treated with crizotinib, and suffered from severe rash. With Zhiyang Pingfu liquid and Western medicine, their rash gradually disappeared with no sign of cancer progression. Also the male patient did not relieve after taking only antibiotics (standard therapy) and anti-allergic medicine.

Lessons: Despite the dramatic benefit of crizotinib for patients with ALK rearrangement, crizotinib-induced severe rash needs to be dealt with caution. This is the 1st case in which TCM and Western medicine are used to successfully treat crizotinib-induced severe rash. The mechanism of crizotinib-induced rash deserves further attention in future research.

Abbreviations: ALK = anaplastic lymphoma kinase, CT = computed tomography, EGFR = epidermal growth factor receptor, EGFRIs = epidermal growth factor receptor inhibitors, MRI = magnetic resonance imaging, NCI-CTCAE v4.0 = National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0, NSCLC = nonsmall-cell lung cancer, PET-CT = positron-emission computed tomography, TCM = traditional Chinese medicine, TKIs = tyrosine kinase inhibitors.

Keywords: anaplastic lymphoma kinase gene rearrangement, crizotinib, rash, Zhiyang Pingfu liquid

Editor: N/A.

SYZ and WS are co-first authors.

Informed written consent was obtained from both the patients for publication of this case report and accompanying images. This case report was supported by Capital's Funds for Health Improvement and Research (2018-2-4065) and China-Japan Friendship Hospital.

The authors have no conflicts of interest to disclose.
nothing to disclose.

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Medicine (2018) 97:48(e13088)

Received: 25 May 2018 / Accepted: 11 October 2018

<http://dx.doi.org/10.1097/MD.0000000000013088>

1. Introduction

Lung cancer is the leading cause of cancer-related death worldwide. For certain patients with nonsmall-cell lung cancer (NSCLC), molecularly targeted therapies have transformed treatment and improved overall survival. The most-studied driver pathways are the epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK). For these 2 genetic subtypes, targeted therapies represent the standard care for the superior efficacy and improved tolerability, as compared with cytotoxic chemotherapy.^[1,2] Crizotinib is a multi-targeted tyrosine kinase inhibitor (TKI), which is proved to be safe and effective for ALK-rearranged patients with NSCLC.^[3,4] In clinical practice, common adverse events associated with crizotinib are vision disorders, gastrointestinal disturbances, cardiac, and endocrine abnormalities and most of them are grade 1 or 2 in severity. It is reported that the occurrence rate of rash is 10%, and with no grades 3 to 4 cutaneous reaction.^[5] The mechanism of rash caused by crizotinib remains unclear and there is a lack of relevant literature. This report, in addition to a literature review, presents 2 cases of patients with severe rash (≥grade 3) caused by crizotinib who have been treated with the combination of Zhiyang Pingfu liquid and Western medicine.

2. Case reports

2.1. First case

In December, 2016, an 81-year-old yellow-raced male smoker (700 packs of cigarettes per year) started to have progressively aggravated syndromes of coughing with phlegm and weakness. Computed tomography (CT) scans of chest was obtained on February 4, 2017 in Beijing Hepingli Hospital, which showed multiple nodules in the inferior lobe of his left lung whose maximum diameter was approximately 19 mm. Positron-emission CT (PET-CT) revealed lymphatic metastasis. A week later, adenocarcinoma was diagnosed by fine-needle aspiration biopsy under ultrasonic bronchoscope. Fluorescence in situ hybridization suggested ALK (2p23) chromosome translocation. The patient was diagnosed with adenocarcinoma in the inferior lobe of left lung in the IV period, according to the American Joint Committee on Cancer Staging System, 7th edition.^[6]

On February 17, 2017, the patient started to take crizotinib 200 mg PO twice daily. Then the dose was increased to 250 mg 2 weeks later since no obvious side effects were found. However, after 6 days, the patient developed lots of rash which formed like

acne. Before seeking medical advice from our department, he had taken a variety of antibiotics (amoxicillin, erythrocin, itraconazole) and anti-allergic medicine (antihistamine), which did not help alleviate the symptoms. Continuous rash severely affected the patient's quality of life. He suffered from insomnia, depression, and even considered a withdrawal of crizotinib treatment.

Later, the patient was recommended to our Department of Integrative Oncology in China-Japan Friendship Hospital for the treatment of skin toxicity (Fig. 1A–C). Papules were concentrated on his chest and back. Pustules were mainly on his cheeks and the top of his head. The skin lesion totally covered >30% body surface area. Therefore, the level of adverse event was evaluated as grade 3, referring to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0 (NCI-CTCAE v4.0).^[7] The therapeutic effect for tumors was also reviewed. CT scans of chest revealed that multiple nodules whose maximum diameter was approximately 4.5 mm were found in the inferior lobe of his left lung. The patient achieved a partial response compared to the last CT result. Zhiyang Pingfu liquid and Western medicine were jointly used to treat skin toxicity.



Figure 1. Pustules on cheeks and the top of the head were like impetigo, the skin of which was thin, easily frangible and having suppurating pus with black thick scab (A). There were scattered dark red papules on chest and back (B and C). After 3 days of treatment, the black thick scab on the head gradually fell off, and no new pustules occurred (D). The rash on the cheeks, chest, and back all faded in color; the area of rash shrank (E and F).



Figure 2. Rash and pustules disappeared and the skin recovered to normal, only with few scars in light color (A and B).

Zhiyang Pingfu liquid^[8–11] consisted of *Scutellaria baicalensis* 20 g, *Portulaca oleracea* 30 g, Cortex Dictamni 30 g, and *Sophora flavescens* 30 g. First, Chinese medical herbs were extracted with water twice, then decompressed and concentrated to the density of 1.10 (60°C), finally centrifugated. Second, medical soup, glycerol, and honey were prepared in a proportion of 2.2:1:2, and then compressed the compound into facial masks. Zhiyang Pingfu liquid could be kept at normal temperature. The Chinese herbs were provided by Tongrentang of Beijing (a time-honored TCM pharmacy in China), and the herbal preparation was completed by pharmacists in the chemical chamber of China-Japan Friendship Hospital.

Zhiyang Pingfu liquid was for topical application. We used the facial mask made of Zhiyang Pingfu liquid for 30 minutes twice or thrice a day on the patient's cheeks. The liquid was also applied to the pustules on the scalp and the papules on his chest and back directly for 30 minutes twice or thrice a day. The patient was required not to clear excretion. Due to the large area of rash, we suggested the patient drop Zhiyang Pingfu liquid into bath water and soak in it for 30 minutes before going to sleep. We also asked the patient to take Minocycline hydrochloride tablets (Wyeth Pharmaceuticals Company, Suzhou, China; approval number: H10960010) 100 mg bid and Aprepitant capsules (Merck Sharp & Dohme Australia Pty Ltd, Hangzhou, China; approval number: H20130545) 125 mg day 1, 80 mg day 2, 80 mg day 3 in the morning orally.

Three days later, the skin rash and itching, especially the pustules on the head, relieved, then the patient could fall asleep. The skin toxicity (Fig. 1D–F) was graded as Cutaneous G2 reaction. The rash and itching disappeared and the skin returned to normal (Fig. 2) after another 7 days.

2.2. Second case

A 62-year-old female, nonsmoker, complained of coughing with little white phlegm, chest distress, and short of breath. CT scans of her chest in the local hospital revealed that there was an

unknown neoplasm in the inferior lobe of her left lung. On September 10, 2013, poorly differentiated adenocarcinoma with metastatic carcinoma of lymph nodes was diagnosed by fine-needle aspiration biopsy under ultrasonic bronchoscope in Cancer Hospital Chinese Academy of Medical Sciences. Immunohistochemistry staining revealed ALK-VentanaD5F3 (3+) expression. PET-CT revealed adenocarcinoma in the inferior lobe of her left lung, with metastasis of mediastinal lymph node, bone, abdominal lymph nodes, and liver.

At 1st, the patient received the 1st-line chemotherapeutic regimen of pemetrexed 776 mg day 1 and carboplatin 651 mg day 1, every 21 days, totally 6 periods. During the chemotherapy, she once had grade II bone marrow suppression and grade II gastrointestinal reaction. Terminally, she had a partial response. Then, the patient was treated with crizotinib, 250 mg twice a day. During the treatment, the patient had regular reviews of the CT scans of her chest and abdomen and got a partial response (Fig. 3).

After being treated with crizotinib for about 3 months, the patient developed multiple erythematous rash that spread to upper limbs, cheeks, and neck. Later, she was recommended to our Department of Integrative Oncology in China-Japan Friendship Hospital. Her skin toxicity was observed (Fig. 4A–D). There were multiple rash and erythema on her upper limbs, cheeks, neck, and auricle, some of which were in escharosis and exfoliation, covering >30% body surface area. Simultaneously, the patient complained of the photosensitivity of rash and erythema, which would aggravate when exposed to sunshine. Also, she had skin itching and dryness which severely affected her sleep and daily activities. The skin toxicity was evaluated as grade 3, referring to NCI-CTCAE v4.0.^[7]

The skin biopsy specimen (Fig. 5) showed perivascular lymphocytic infiltrates in the upper dermis. The patient was offered the same therapeutic schedule as the 1st case. After 5 days of treatment, rash and erythema (Fig. 4E–H) relieved evidently. Without skin itching, the patient was able to fall asleep. The 2-month follow-up showed the skin toxicity (Fig. 6) disappeared.

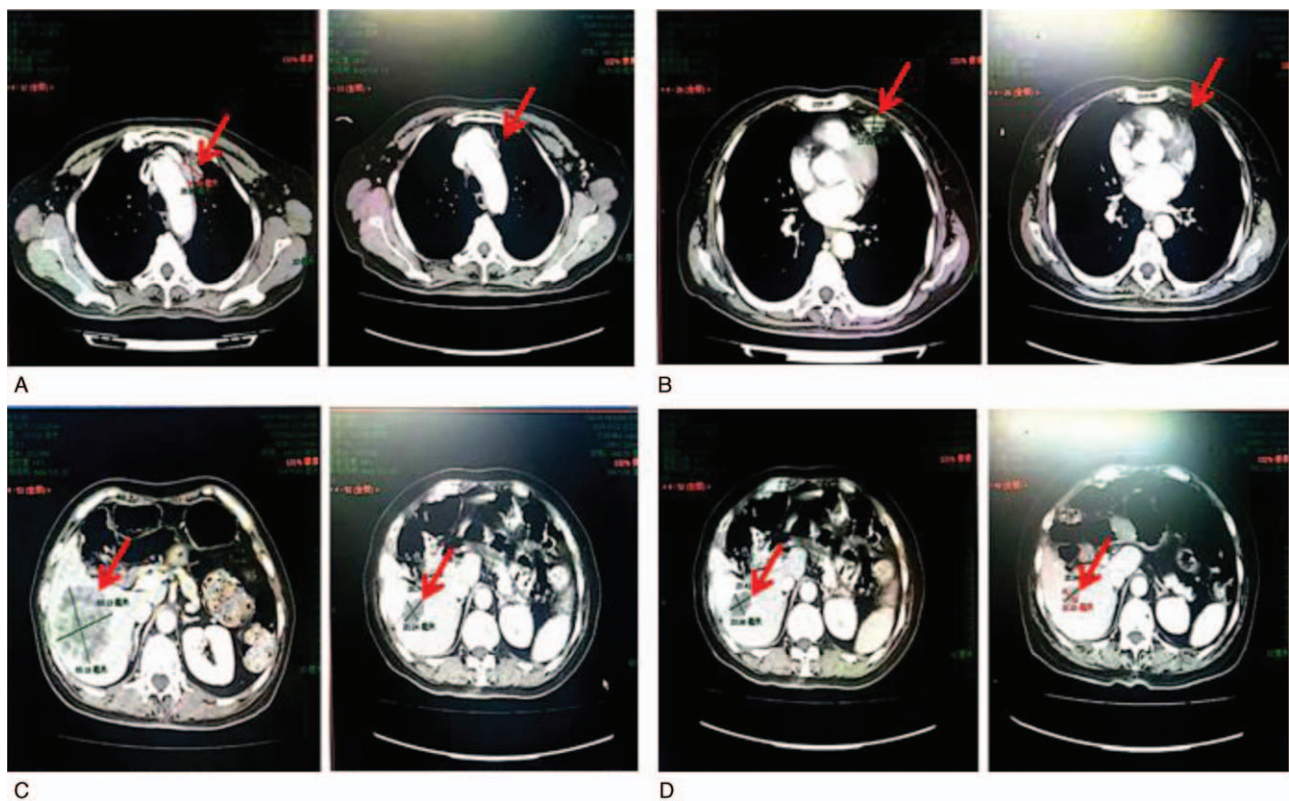


Figure 3. Compared the computed tomography scans on April 8, 2014 and that on November 22, 2014, the mediastinal lymph nodes shrank evidently (A and B). Also the metastasis in liver shrank from 63.13 cm × 69.16 cm to 28.74 cm × 20.24 cm (C). Up to August, 2015, the metastasis in liver still shrank (D).

For some time, the patient's condition was stable and rash never relapsed. After about 10 months, the patient was diagnosed with brain metastasis and treated with total brain radiotherapy. The patient gradually weakened and passed away due to dyscrasia in the terminal stage of cancer.

3. Discussion

Crizotinib is a multi-target TKI with clinical activity as an ALK inhibitor, which is a selective ATP-competitive small-molecule inhibitor of receptor tyrosine kinases, targeting genes of ALK, MET, proto-oncogene tyrosine kinase c-ROS 1 (ROS1), and so on.^[12] In clinical practice, adverse events associated with crizotinib include vision disorders, gastrointestinal disturbances, cardiac and endocrine abnormalities, and most of them are grade 1 or 2 in severity. Reports about incidence rate of crizotinib-induced rash are rare, and we only obtained 2 articles. One reported the rash occurred in 8 patients (11%),^[13] and the other in 25 patients (10%),^[5] all cases with grade 1 or 2 cutaneous reaction. Thus, crizotinib-induced severe skin rash may be rare in the general population.

We report 2 patients with ALK-positive metastatic lung adenocarcinoma both of whom had a significant response to crizotinib therapy but had difficulty continuing due to severe skin toxicity. They were both qualified as grade III referring to NCI-CTCAE v4.0.^[7] But the manifestation of skin toxicity was different. The male was manifested by papules on chest and back, and pustules mainly on cheeks and head, while the female was manifested by multiple rash and erythema on the upper limbs, cheeks, neck, and auricle, and some of which were in escharosis

and exfoliation. The female patient also complained of the photosensitivity of rash and erythema, which would aggravate when exposed to sunshine. Both of them had severe pruritus affecting their sleep and daily activities. Neither of them took any other prescribed medicine except crizotinib. Moreover, neither had prior history of allergies nor had any clinical findings suggesting that the rash was associated with an infectious disease. So rash must be caused by crizotinib. Besides, the male patient had taken multiple kinds of antibiotics (amoxicillin, erythrocin, itraconazole) and anti-allergic medicine (antihistamine), but they did not help alleviate the symptoms.

Zhiyang Pingfu liquid has been proved effective for the treatment of rash caused by epidermal growth factor receptor inhibitors (EGFRIs) according to various randomized clinical trials,^[8–11] and has functions of anti-inflammation and regulating immunity. From the skin pathology of the female patient, we consider this type of skin toxicity be related to the immunity and inflammation. According to recent research, EGFR-induced rash originates from immune and inflammatory reactions of keratinocytes.^[14] We speculate the mechanism of crizotinib-induced rash may be similar to the EGFR-induced rash. Therefore, we applied Zhiyang Pingfu liquid for external application. The main phytochemical ingredients of Zhiyang Pingfu liquid are baicalin and baicalein from *S baicalensis*, sophocarpidine from *S flavescens*, dictamnine from *Cortex Dictamni*, extractive from *P oleracea*. Modern research has proved that baicalein can inhibit expression of interleukin (IL)-1 β , IL-6, tumor necrosis factor (TNF)- α , so it is evidently anti-inflammatory.^[15] Baicalin can absorb ultraviolet ray,^[16] which may be beneficial for photosensitive rash of the female patient, and has the function of anti-



Figure 4. (A–D) Multiple rashes and erythema were on upper limbs, cheeks, neck and auricle, some of which were in escharosis and exfoliation. The skin in exfoliation was sunken in light red. The skin of the patient was totally reddish, dry, and rough with itching. (E–H) Only after 5 days of treatment, rashes and erythema on upper limbs, cheeks, neck, and auricle declined in numbers and faded in color. Dryness and roughness of skin were relieved compared with before, and the skin gradually becomes radiant.

anaphylaxis.^[17] Sophocarpidine can evidently inhibit secretion and expression of IL-6.^[18,19] Monocase compounds of sophocarpidine can inhibit generation of TNF- α , interferon- γ , and IL-6.^[20] *P. oleracea* has rich *P. oleracea* which can promote growth of

epithelial cells and ulcer healing.^[21] Therefore, we think Chinese herbal compound Zhiyang Pingfu liquid has the functions of anti-inflammation, anti-anaphylaxis, and promoting repair of epidermal cells.

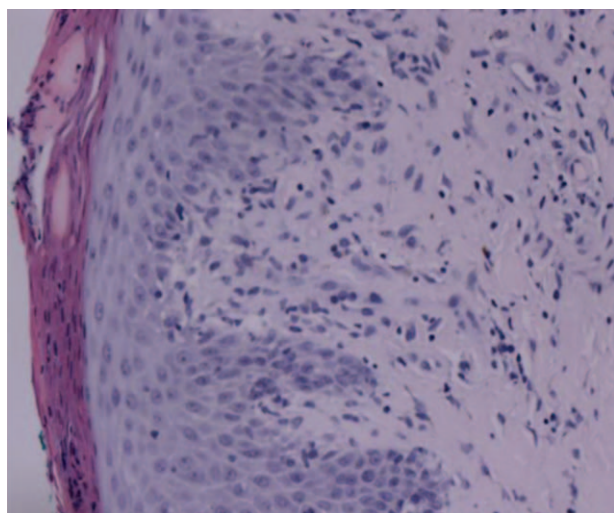


Figure 5. Pathology of the skin biopsy ($\times 200$, HE): The epidermis was hyperkeratosis or para-keratosis, with epithelial angle decurrent irregularly. Liquefactive degeneration was in the local basal layers. There were few lymphocytes infiltrating around small vessels in the shallow layer of dermis, with locally invading epidermis.

Simultaneously, we asked patients to take Minocycline hydrochloride tablets (Wyeth Pharmaceuticals Company; approval number: H10960010) and Aprepitant capsules (Merck Sharp & Dohme Australia Pty Ltd; approval number: H20130545). Minocycline has the function of anti-inflammation in the whole body. Antibiotics such as Minocycline were recommended for treating skin rash referring to NCI-CTCAE 4.^[7] But the male patient did not improve by taking multiple kinds of antibiotics (amoxicillin, erythrocin, itraconazole). Consequently, we suggest the simultaneous use of Minocycline and Zhiyang Pingfu liquid. Both patients had severe pruritus disturbing their sleep and daily activities, so we used Aprepitant which is anti-itching and has been used to treat Erlotinib-induced pruritus (NSCLC),^[22,23] and Nivolumab-induced pruritus (NSCLC).^[24] Rash and pruritus were evidently

relieved upon the 3- to 5-day treatment. The skin recovered to normal after 1 to 2 weeks. In addition, both patients took crizotinib regularly, without a withdrawal or reduction of the dose during the treatment. The follow-up yielded no relapse of their skin toxicity.

Databases such as PubMed, Web of Science, and Cochrane Library were searched to explore how other doctors in the world treated the crizotinib-induced severe skin rash. A total of 5 case reports^[14,25–28] were found up to April 2018 (Table 1). It is shown that women may be more likely to have crizotinib-induced severe skin toxicity (4/5); the appearance of skin toxicity after crizotinib administration is irregular; the clinical characteristics of skin toxicity are various such as erythematous rash with photosensitiveness, erythema multiforme, etc. Due to severe skin toxicity, all patients reported temporary reduction or withdrawal of crizotinib,^[13–16] or even gave up crizotinib treatment.^[13] Two patients were treated with diphenhydramine 1st and then the desensitization clinical protocol. Their skin toxicity never recurred, but neither of them received skin biopsy of rash for mechanism analysis. One patient took a rapid oral desensitization protocol and it worked well.^[16] The other patient took methylprednisolone, but it did not work.^[13] To our knowledge, this is the 1st report of treating crizotinib-induced severe rash successfully without withdrawing or reducing the dose. Dose reduction may cause tumor progression; therefore, combined treatment of Zhiyang Pingfu liquid and Western medicine deserves to be recommended.

Further studies and clinical experience are necessary to explore the mechanism of crizotinib-induced rash. Also, the combination of Zhiyang Pingfu liquid and Western medicine should be examined in a large number of patients to confirm their usefulness for treating ALK-TKI-induced skin toxicity. Alectinib, the 2nd generation of ALK inhibitors has come into the market, and in the AF-001 JP study, 1% of the patients developed a grade 3 rash.^[29] There was a case^[30] that reported the successful desensitization protocols therapy in treating alectinib-induced rash. It is hoped that this article would provide insights into methods of treating severe rash caused by crizotinib, even alectinib, and other targeted drugs, especially when antibiotics and anti-allergic medicine are ineffective.



Figure 6. Two months later, the skin of the patient gradually recovered to normal in color and was not dry and rough any more, only with sporadic scars (A and B).

Table 1**Case reports of crizotinib-induced severe skin toxicity.**

Case	Year	Age/sex	DP	PLL	TAR	GST	TST (V/I)	WWC
Matthew G. Oser ^[22]	2014	71/male	Biopsy of a bony lesion with metastatic lung adenocarcinoma	Left hilum	2 mo	An erythematous rash with	photosensitiveness	Methylprednisolone (I)
Discontinue Mark M. Awad ^[23]	2014	77/female	Endobronchial biopsy of a subcarinal lymph node	Left lower lobe	3rd dose of crizotinib	Pruritic urticarial lesions	First diphenhydramine and then a 12-step oral desensitization clinical protocol (V)	Discontinue during skin toxicity treatment
Mark M. Awad ^[14]	2014	45/female	Unspecified	Unspecified	15 d	An erythematous maculopapular rash	First diphenhydramine and then the desensitization clinical protocol (V)	Discontinue during skin toxicity treatment
Soichiro Sawamura ^[24]	2015	63/female	Unspecified	Right upper lobe	1 wk	Erythema multiforme	Topical clobetasol ointment (V)	Discontinue during skin toxicity treatment, then unspecified
Sánchez-López J ^[25]	2015	78/female	Unspecified	Unspecified	40 d	Itchy hives with associated facial edema	A rapid oral desensitization protocol (V)	Discontinue during skin toxicity treatment

GST = clinical characteristics of skin toxicity, DP = diagnostic procedure, PLL = primary lung location, TA = time of alleviating, TAR = time of skin toxicity appearance after taking crizotinib, TST (V/I) = treatment of the skin toxicity (valid/invalid), WWC = whether to continue crizotinib.

4. Conclusion

Combination of Zhiyang Pingfu liquid and Western medicine could be a recommendation for ALK-rearranged patients with NSCLC with severe crizotinib-induced skin toxicity. To date, this is the 1st report of treating crizotinib-induced severe rash without withdrawing or reducing the dose. However, further studies and clinical experience are needed to explore the mechanism and the therapeutic efficacy.

Acknowledgment

The authors thank Professor Qing Wu (English Department, School of Humanities, Beijing University of Chinese Medicine, Beijing, China) to review the manuscript for improving language quality. The authors also express their gratitude to the 2 patients and their family.

Author contributions

SZ, WS, HC, YP, HD, and YQ were responsible for collection and assembly of the patients' data. SZ, HD, YP, QL, JZ, CS, and XZ performed data analysis and literature searching. All authors contributed toward data analysis, drafting, and revising the paper and agree to be accountable for all aspects of the work.

References

- Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatinpaclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009;361:947–57.
- Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med* 2010;363:1693–703.
- Bergeth K, Shaw AT, Ou SH, et al. ROS1 rearrangements define a unique molecular class of lung cancers. *J Clin Oncol* 2012;30:863–70.
- Yasuda H, de Figueiredo-Pontes LL, Kobayashi S, et al. Preclinical rationale for use of the clinically available multi-targeted tyrosine kinase inhibitor crizotinib in ROS1-translocated lung cancer. *J Thorac Oncol* 2012;7:1086–90.
- Dikopf A, Wood K, Salgia R. A safety assessment of crizotinib in the treatment of ALK-positive NSCLC patients. *Expert Opin Drug Saf* 2015;14:485–93.
- Edge S, Byrd DR, Compton CC, et al. *AJCC cancer staging manual*. 7th ed. Springer, New York:2010.
- Lacouture ME, Maitland ML, Segal S, et al. A proposed EGFR inhibitor dermatologic adverse event-specific grading scale from the MASCC skin toxicity study group. *Support Care Cancer* 2010;18:509–22.
- Peng YM, Cui HJ, Liu Z, et al. Treatment of EGFRs-related skin adverse reactions by Zhiyang Pingfu liquid. *Chin J Integr Med* 2017;149–54.
- Wang HY, Zou C, Cui HJ, et al. Treatment of epidermal growth factor receptor inhibitors associated adverse skin reactions by Zhiyang Pingfu liquid: a clinical study. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 2015;35:820–2.
- Wang HY, Zou C, Cui HJ, et al. EGFRs-related rash treated with external Chinese medicinal with actions of clearing heat and draining dampness in 120 cases. *J Beijing Univ Trad Chin Med* 2013;14–7.
- Cui HJ, Wang HY, Bai YP, et al. EGFRs-related rash treated with Zhiyang Pingfu liquid in 20 cases. *J Chin Jap Friend Hosp* 2012;97:98+102.
- Chen X, Zhou JY, Zhao J, et al. Crizotinib overcomes hepatocyte growth factor-mediated resistance to gefitinib in EGFR-mutant non-small-cell lung cancer cells. *Anticancer Drugs* 2013;24:1039–46.
- Cui S, Zhao Y, Gu A, et al. Efficacy and tolerability of crizotinib in the treatment of ALK-positive, advanced non-small cell lung cancer in Chinese patients. *Med Oncol* 2015;32:626.
- Pastore S, Lulli D, Girolomoni G. Epidermal growth factor receptor signalling in keratinocyte biology: implications for skin toxicity of tyrosine kinase inhibitors. *Arch Toxicol* 2014;88:1189–203.
- Yun BY, Zhou L, Xie KP, et al. Antibacterial activity and mechanism of baicalin. *Acta Pharmaceutica Sinica* 2012;47:1587–92.
- Min W, Luo D, Lin XF. Experimental study on the photo-protection of Baikal skullcap root of human skin cells from ultraviolet radiation damage. *Acta Academiae Medicinae Xuzhou* 2004;24:167–70.
- Zheng G, Liang QH, You WH, et al. The effect of baicalin on the proliferation and activation of the mouse T lymphocytes. *Pharmacol Clin Chin Mat Med* 2007;23:20–2.
- Zhang L, Zhang H, Zhu Z, et al. Matrine regulates immune functions to inhibit the proliferation of leukemic cells. *Int J Clin Exp Med* 2015;8:5591–600.
- Chen SF, Zhang ZY, Zhang JL. Matrine increases the inhibitory effects of afatinib on H1975 cells via the IL-6/JAK1/STAT3 signaling pathway. *Mol Med Rep* 2017;16:2733–9.
- Zhou XY, Chen J, Jin L, et al. Pharmacologic action and anti-inflammatory compounds of root of Cortex Dictamnii. *J Changzhou Univ* 2018;30:82–6.
- Wang TN, Liu YT, Xiao FQ, et al. *Chin J Exp Trad Med Form* 2018;24:224–34.
- Vincenzi B, Tonini G, Santini D. Aprepitant for erlotinib-induced pruritus. *N Engl J Med* 2010;363:397–8.

- [23] Mir O, Blanchet B, Goldwasser F. More on aprepitant for erlotinib-induced pruritus. *N Engl J Med* 2011;364:487.
- [24] Ito J, Fujimoto D, Nakamura A, et al. Aprepitant for refractory nivolumab-induced pruritus. *Lung Cancer* 2017;109:58–61.
- [25] Oser MG, Janne PA. A severe photosensitivity dermatitis caused by crizotinib. *J Thorac Oncol* 2014;9:51–3.
- [26] Awad MM, Lax TP, Slawski BR, et al. Successful desensitization of two patients with ALK-positive lung cancer and hypersensitivity to crizotinib. *J Thorac Oncol* 2014;9:1726–8.
- [27] Sawamura S, Kajihara I, Ichihara A, et al. Crizotinib-associated erythema multiforme in a lung cancer patient. *Drug Discov Ther* 2015;9:142.
- [28] Sánchez-López J, Viñolas N, Muñoz-Cano R, et al. Successful oral desensitization in a patient with hypersensitivity reaction to crizotinib. *J Investig Allergol Clin Immunol* 2015;25:307–8.
- [29] Seto T, Kiura K, Nishio M, et al. CH5424802 (RO5424802) for patients with ALK-rearranged advanced non-small-cell lung cancer (AF-001JP study): a single-arm, open-label, phase 1-2 study. *Lancet Oncol* 2013;14:590–8.
- [30] Shirasawa M, Kubotaa M, Harada S, et al. Successful oral desensitization against skin rash induced by alectinib in a patient with anaplastic lymphoma kinase-positive lung adenocarcinoma: a case report. *Lung Cancer* 2016;99:66–8.