Integrative Cancer Therapies
Volume 19: 1–9

DOI: 10.1177/1534735420924832
journals.sagepub.com/home/ict
SAGE

Application of Zizao Yangrong Granules for Treating Targeted Drugs–Related Skin Xerosis: A Randomized Double-Blinded Controlled Study

Yan Mei Peng, PhD, MD[1], Hua Duan, MD[2], Jingyi Zhang, MD[2], Chenyao Sun, MD[2], Xu Zhang, MD[2], Wen Shen, MD[2], Shuyue Zheng, MD[2], Kexin Tan, MD[2], Xuejiao Jiang, MD[2], Jia Li, MD[2], and Hui Juan Cui, PhD, MD[3]

Abstract

Background: Dermatologic toxicities are the most common side effects associated with the targeted drugs epidermal growth factor receptor inhibitors (EGFRIs), in which xerosis commonly complicated by pruritus severely disturbs the quality of life. The study has observed the curative effect of Zizao Yangrong granules (ZYG) from Chishui Xuanzhu in the treatment of EGFRIs-related xerosis and pruritus, as well as evaluating the safety of the prescription. **Methods:** Patients (n = 68) who had xerosis after using EGFRIs were enrolled and then randomly divided into the treatment group and control group, respectively, receiving ZYG and placebo granules combined with vitamin E ointment. The intervention lasted 4 weeks. Changes in xerosis and pruritus were observed, and blood routine examination as well as liver and kidney function *are observed as safety indexes. The water content of skin and qualify of life were observed*. **Results:** A total of 66 out of 68 patients finished the study with 34 patients *in each group*. The effective rates of xerosis among the treatment group and control group were 84.8% and 69.7% after 2 weeks' treatment ($P < .05$), while they were 84.8% and 75.8% after 4 weeks' treatment ($P < .05$). The patients in the experimental group had better quality of life than that in the control group ($P = .045$). **Conclusion:** ZYG can effectively improve the skin dryness associated with EGFRIs, and significantly improve the quality of life of patients with good safety; however, larger randomized controlled trials are needed to verify these findings.

Keywords

Zizao Yangrong granules, EGFRIs, xerosis, pruritus, clinical trial

Submitted September 27, 2019; revised March 7, 2020; accepted April 1, 2020

Introduction

The past years have witnessed rapid growth in the treatment of non–small cell lung cancer owing to targeted drugs. One class of agents includes the epidermal growth factor receptor inhibitors (EGFRIs), which have been shown to be efficacious in patients whose tumors harbor EGFR-activating mutations. Dermatologic toxicities are the most common side effects associated with the EGFRIs, in which xerosis commonly complicated by pruritus severely affects the quality of life.[1]

Xerosis is a problem in up to 33% of patients treated with EGFRIs with pruritus and pain. The patients suffer from xerosis after taking EGFRIs for approximately 30 to 60 days. This condition is usually followed or accompanied by acneiform eruption. The typical appearances present dry, scaly, and itchy skin on any part of body. Some patients report vaginal and perineal dryness. Patients with xerosis may develop chronic asteatotic eczema that predisposes to

[1]Fangshan Hospital, Beijing University of Chinese Medicine, Beijing, China
[2]Beijing University of Chinese Medicine, Beijing, China
[3]China-Japan Friendship Hospital, Beijing, China

Corresponding Author:
Hui Juan Cui, Department of Oncology, China-Japan Friendship Hospital, No. 2, Yinghua East Road, Chaoyang District, Beijing, China.
Email: chjzryhyy@sina.com

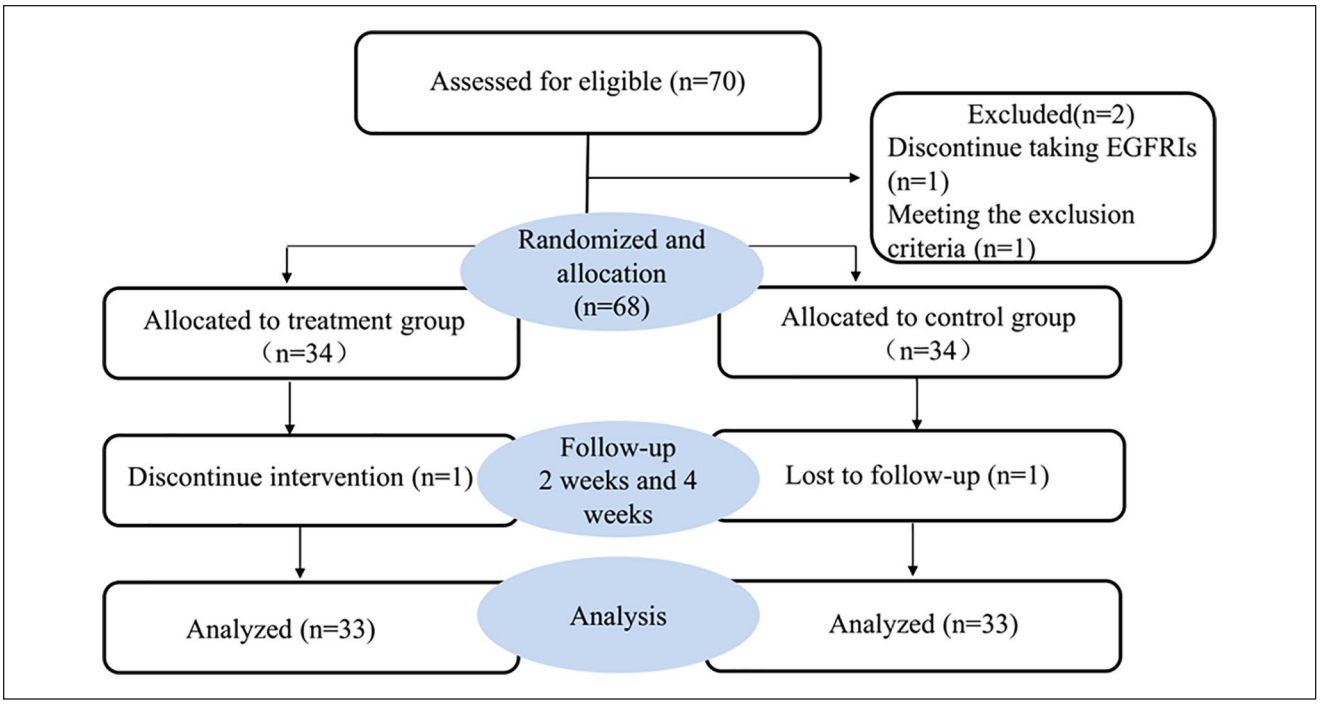

Figure 1. Flow diagram of enrollment.

secondary infections with *Staphylococcus aureus* or the herpes simplex virus.

The MASCC (Multinational Association of Supportive Care in Cancer) has recommended treatments for xerosis. The management mainly emphasizes prevention and external moisturizers, while the efficacy is far from satisfactory. Our goal as oncologists is to provide optimal patient care and improve quality of life with traditional Chinese medicine (TCM). It is expected that the implementation of such strategies will contribute to the optimization of EGFRIs therapies.

Methods

Design

This study was a double-blinded, randomized, placebo-controlled trial. The study was to observe the curative effect of Zizao Yangrong granules in the treatment of EGFRIs-related xerosis and evaluate the prescription's safety. The patients were enrolled from China-Japan Friendship Hospital.

Ethical Approval

The trial was performed with the approval of the Ethics Committee of China-Japan Friendship Hospital for Drug/Instrument Clinical Researches (2016-23). All patients signed an informed consent form before randomization and treatment.

Participants

A total of 68 patients were enrolled (Figure 1), which were randomized to receive Zizao Yangrong granules or placebo in an allocation ratio of 1:1.

Eligible patients had to meet the following inclusion criteria: (*a*) patients with malignant tumor confirmed by pathology or cytology; (*b*) patients with application of EGFRIs; (*c*) patients with EGFRIs-related skin xerosis; (*d*) no severe dysfunction of heart, liver, or kidney; (*e*) age from 18 to 85 years; (*f*) normal language ability and no mental disorders; (*g*) patients understand and agree to receive the treatment, and sign informed consent form; and (*h*) TCM syndrome: the syndrome of yin deficiency and blood dryness. The main symptoms include dry skin, itching, rare rash, desquamation, fatigue, dry mouth, red tongue with little fur, thready rapid pulse, or deep thready pulse.

Exclusion criteria were the following: (*a*) patients with EGFRI discontinuation; (*b*) patients with xerosis who did not meet the yin deficiency and blood dryness syndrome; (*c*) patients with allergic constitution; and (*d*) patients with poor compliance.

Outcomes and Endpoints

As for clinical outcomes, the primary endpoints were changes of xerosis and pruritus evaluated by MASCC[2] and NCI-CTCAE (National Cancer Institute-Common Terminology Criteria for Adverse Events)[3] grading systems,

respectively, every 2 weeks. The symptoms of dry mouth, eyes, and nose accompanying dry skin were also summarized. The secondary endpoints were water content of skin and the quality of life evaluated by Dermatology Life Quality Index.[4] The water content of skin was evaluated by the Soft Plus skin tester (Callegari, Italian) from limbs. The blood routine, liver, and kidney function were observed as safety indicators. According to the EGFRI Dermatologic Toxicity Forum, in 2006,[5] complete response (CR) was defined as dermatologic toxicities disappearing without subjective symptoms, sign of superinfection, and impact on activities of daily life; partial response (PR) was defined as the grade of dermatologic toxicities was lowered not <1 level; no response (NR) was defined as the grade of dermatologic toxicities had no changes or proceeded to the higher grades. Response included CR and PR.

Intervention

Patients in treatment group received oral Zizao Yangrong granules and control group received placebo granules. Both groups treated with external vitamin E ointment and were observed. The Zizao Yangrong granules mainly consisted of 5 TCM herbals, Radix Radix angelicae sinensis (当归), Rehmanniae Preparata (熟地黄), Scutellaria baicalensis Georgi (黄芩), Gentiana macrophylla Pall (秦艽), and Divaricate Saposhnikovia Root (防风), whose proportion was 3:3:3:2:2. The raw materials of the prescription in proportion are added to water and refluxed to extract twice, each time for 1.5 hours. The decoctions are combined, then filtered, concentrated, and 60% ethanol solution added to precipitate. The solution is allowed to stand, filtered, concentrated, and dried under reduced pressure. Dextrin was used as an excipient to make granules with the ratio of 3:1 between herbs and dextrin. The placebo was made of dextrin, starch syrup as adhesive, caramel pigment as colorant, and bitterant and aspartame as corrigent. They were packed with standardized packaging the same as Zizao Yangrong granules. The Zizao Yangrong granules or placebo were taken after dissolving in warm water twice a day for participants, while vitamin E ointment was applied externally. The intervention lasted 4 weeks.

Randomization and Blinding

The Zizao Yangrong granules and placebo granules were labeled with continuous codes, which represented randomization and intervention arms, and were pasted on the corresponding bags of granules. A form presented the code and the corresponding patients' randomization numbers. The randomization and codes were kept by an independent person blinded to the patients and researchers. The third party conducted coding and sealed blind codes. Researchers delivered drugs according to the corresponding form. The blind codes were uncovered twice. After verifying the blind situation, the research data were locked, and statisticians uncovered blind codes for the first time. The randomization was represented by A and B for statistical analysis. After the statistical analysis was over, the randomized group of A and B was published for the second time. If serious adverse events occurred, the emergency of breaking the blind was conducted; the responsible researchers decided whether to open the emergency letter. Once the emergency letter was opened, the case was considered as a case of shedding, not included in the efficacy analysis, but included in adverse reactions analysis.

Sample Size Calculations

The sample size calculations were based on our previous observation. It was considered that the effective rate of Zizao Yangrong granules was 70%, and that of placebo was 35%. For 90% power with α set at 0.05, we calculated that 31 participants would be needed in both groups by 1-tailed test. Considering 10% as the noncompletion rate, each group needed 34 participants.

Statistical Analysis

Statistical analyses were done using SPSS software version 20.0 and performed using 2-sided test. The statistical analysis of the differences for each experimental and control group was carried out using the Student's *t* tests for continuous variables with χ^2 for the comparison of rate. $P < .05$ were considered statistically significant.

Results

The study started on May 12, 2016, and was completed on January 24, 2018. There were 70 patients eligible for screening. Because of discontinuing taking EGFRIs and meeting the exclusion criteria, 2 patients were excluded. A total of 68 patients were randomized and allocated. A patient discontinued intervention in the treatment group and a patient was lost to follow-up in the control group, so 66 out of 68 patients completed the study. The overall mean age of the patients was 68 (range = 38-85) years. A total of 23 (33.8%) male patients and 45 (66.2%) female patients were enrolled. The median of xerosis occurrence after taking target drugs was 90 days. The population distribution had no difference between the 2 groups (Table 1).

Efficacy

Primary Endpoints. Of the 68 patients randomized to receive Zizao Yangrong granules and placebo combined with vitamin E ointment, 33 patients in each group were eligible for analysis. As for xerosis, the grade was significantly lowered

Table 1. Patients With EGFRIs-Related Dermatologic Toxicities in Treatment and Control Groups.

Characteristics	Cases (n = 68)		
	Treatment, n = 34	Placebo, n = 34	*P*
Age (years), Mean ± SD	68.9 ± 10.2	66.4 ± 11.1	.603
Sex, n			.798
Male	12	11	
Female	22	23	
Sites of xerosis, n			.947
Face and head	13	17	
Neck	8	14	
Breast	11	14	
Back	16	23	
Abdomen	12	16	
Left upper limb	23	29	
Right upper limb	24	29	
Left lower limb	34	32	
Right lower limb	33	33	
Hip	14	12	
The time to taking target drugs (day), median	90		
Xerosis grade			.851
Grade 1A	0	0	
Grade 1B	3	2	
Grade 2A	4	6	
Grade 2B	10	8	
Grade 3A	14	13	
Grade 3B	3	5	
Pruritus			
None	4	2	
Grade 1	13	9	
Grade 2	11	15	
Grade 3	5	7	
Responsible agent			.651
Icotinib	20	16	
Gefitinib	9	12	
Erlotinib	3	3	
Osimertinib	1	2	
Icotinib, osimertinib	1	0	
Gefitinib, osimertinib	0	1	

after 2-week and 4-week treatment both in treatment group and control group based on statistical analysis ($P < .05$). After the entire 4 weeks' treatment, 10 patients reported CR, and 18 patients reported PR with 5 patients NR in the treatment group, while 5 patients reported CR, and 20 patients reported PR with 8 patients NR in the control group. The overall curative effect of the treatment group (84.8%) was better than that of the control group (75.8%) in dry skin ($P = .027$; Table 2).

In terms of pruritus, 29 patients in treatment group and 31 patients in control group suffered from this symptom. Fifteen patients reported CR, and 8 patients reported PR with 6 patients NR in treatment group, while 7 patients reported CR, and 12 patients reported PR with 12 patients NR in control group. The curative effect of the treatment group (79.3%) and control group (61.3%) was comparable ($P = .269$; Table 3).

In addition, most patients included have the symptoms of dry mouth, eyes, and nose, while the analysis of symptom changes showed no significant difference.

Secondary Endpoints. After 2-week and 4-week treatment, the results of skin water content evaluation showed the water content of limbs increased ($P < .05$) except for the left lower limb in treatment group, while the water content of limbs increased ($P < .05$) except for the left lower limb

Table 2. Changes in Xerosis.

Xerosis	CR	PR	NR	RR (CR + PR)	*P*
Two weeks' treatment					
Treatment	4	24	5	84.80%	.000
Placebo	4	19	10	69.70%	
Four weeks' treatment					
Treatment	10	18	5	84.80%	.027
Placebo	5	20	8	75.80%	

Abbreviations: CR, complete response; PR, partial response; NR, no response; RR, response rate.

Table 3. Changes in Pruritus.

Pruritus	CR	PR	NR	RR (CR + PR)	*P*
Two weeks' treatment					
Treatment	13	8	8	72.40%	—
Placebo	4	14	13	58.10%	.000
Four weeks' treatment					
Treatment	15	8	6	79.30%	—
Placebo	7	12	12	61.30%	.269

Abbreviations: CR, complete response; PR, partial response; NR, no response; RR, response rate.

Table 4. Comparison of Skin Water Content Between 2 Groups.

Skin Water Content	Before Treatment	Two Weeks' Treatment	Four Weeks' Treatment
P	.45	.793	.504

in control group. No difference was observed in 2 groups after 2-week and 4-week treatment (Table 4).

The Dermatology Life Quality Index suggested that the quality of life significantly increased after 2-week and 4-week treatment both in treatment group and control group based on statistical analysis ($P < .05$). Encouragingly, the quality of life in the treatment group was highly improved compared with the control group ($P = .045$; Table 5).

Safety

The most common drug-related adverse events were mild gastrointestinal and respiratory symptoms, such as nausea, vomiting, abdominal pain, diarrhea, and cough. No fatal events were reported during the study. Four (12.1%) patients reported gastrointestinal symptoms and 2 (5.9%) patients reported respiratory symptoms in both the groups. In addition, 1 (3.0%) patient in the treatment group was observed to have abnormal liver function, which may have some relation to the targeted therapy. The adverse events could be well controlled with routine management. No important harm in either group were observed.

Table 5. Comparison of Dermatology Life Quality Index (DLQI) Score Between 2 Groups.

DLQI Score	Before Treatment	Two Weeks' Treatment	Four weeks' Treatment
P	.058	.016	.045

Discussion

Xerosis, one of the common dermatological adverse events, occurred in 10% to 49% (moderate-and-severe grade 0% to 7%) patients with the use of EGFRIs.[6] For the review of large randomized controlled trials, erlotinib accounted for the highest incidence of xerosis, followed by gefitinib and afatinib, while xerosis was rarely reported with icotinib. Xerosis was not observed in cetuximab and panitumumab[7] (Table 6). However, the patients enrolled in this study mostly took icotinib, since it was developed and approved in China and recommended to more Chinese as anti-EGFR therapy. The site of xerosis has lacked systematic observation. In our study, limbs, head, and face tended to more susceptible.

The mechanism of xerosis is not well explained. It is possible that abnormal keratinocyte differentiation caused by EGFRIs can impair the epidermal barrier, decreasing loricrin, the main protein forming the scaffold for the epidermis. Ultimately, xerosis is caused by an unwoven epidermal layer that loses moisture.[30] Previous study showed that patients who are taking gefitinib experienced cutaneous side effects including xerosis cutis, acneiform eruptions, and paronychia, and had mean transepidermal water loss values higher than normal.[31] In our study, we evaluated the skin water content by the skin testing instrument to illustrate the efficacy of Zizao Yangrong granules.

Topical moisturizers are encouraged for patients suffering from EGFRIs-related skin xerosis; however, the most water retention in the skin and general xerosis is hard to improve. Until now, no systematic study designed to observe TCM for EGFRIs-related skin xerosis has been published. This Zizao Yangrong prescription seems to be more effective than moisturizer in treating xerosis. Although there was only narrow difference with efficiency, the general xerosis was obviously relieved. The quality of life was also improved. As for pruritus, the Zizao Yangrong granules and vitamin E ointment have comparable effect. This result may be affected by the limited number of cases. Twenty-nine cases with pruritus were in the treatment group and 31 cases in the control group. The skin water content may be influenced by the external environment in our observation.

Zizao Yangrong formula consisted of Danggui, Shudi, Huangqin, Qinjiao, and Fangfeng. In the theory of treatment based on syndrome differentiation of TCM, the Zizao Yangrong prescription has the function of nourishing yin and blood, moistening dryness, and eliminating itch. Danggui is the root of *Angelica sinensis*. Its main chemical

Table 6. Incidence of EGFRIs Xerosis in RCTs.

Lead Author	Study	Patients (n)	EGFRIs Treatment	Xerosis	
				All (%)	≥Grade 3 (%)
Crinò et al[8]	INVITE	196	Gefitinib	6.4	0
Kim et al[9]	INTEREST	1466	Gefitinib	15.2	0
Mok et al[10]	IPASS	1217	Gefitinib	23.9	0
Mitsudomi et al[11]	WJTOG3405	177	Gefitinib	54	0
Lee et al[12]	ISTANA	161	Gefitinib	14.8	0
Ciuleanu et al[13]	TITAN	2590	Erlotinib	4	0
Zhang et al[14]	INFORM/C-TONG 0804	296	Gefitinib	6	0
Ramalingam et al[15]	A7471028	188	Dacomitinib	23.7	1.1
			Erlotinib	14.9	2.1
Sequist et al[16]	LUX-Lung 3	1269	Afatinib	29.3	0.4
Seto et al[17]	JO25567	154	Erlotinib	75	3
Price et al[18]	ASPECCT	999	Panitumumab	25	0.4
			Cetuximab	24	0.6
Ellis et al[19]	NCIC CTG BR.26	720	Dacomitinib	29	<1
Ramalingam et al[20]	ARCHER 1009	878	Dacomitinib	19	<1
			Erlotinib	18	0
Soria et al[21]	LUX-Lung 8	795	Afatinib	9	<1
			Erlotinib	11	0
Wu et al[22]	ENSURE	217	Erlotinib	9.1	0
Schuler et al[23]	LUX-Lung 5	202	Afatinib	4.5	0
Mok et al[24]	AURA3	419	Osimertinib	23	0
Wu et al[25]	ARCHER 1050	452	Dacomitinib	27	1
			Gefitinib	17	0
Yang et al[26]	CTONG 0901	256	Gefitinib	11	0
			Erlotinib	13	0
Paz-Ares et al[27]	LUX-Lung 7	319	Afatinib	32.5	0
			Gefitinib	37.1	0
Scagliotti et al[28]	MARQUEE	1048	Erlotinib	15.1	0
Soria et al[29]	FLAURA	556	Osimertinib	33	1
			Gefitinib	33	3

Abbreviations: EGFRIs, epidermal growth factor receptor inhibitors; RCTs, randomized controlled trials.

compounds are neutral oil components such as β-pinene, α-pinene, and terpenes. Its acidic oil component contains compounds such as p-methylbenzyl alcohol or 5-methoxy-2,3-xylenol, an organic acid, a saccharide, a vitamin, an amino acid, and others. It has the functions of promoting blood circulation, anti-inflammatory, antitumor, and analgesia.[32] Shudi is the root of *Dioscorea zingiberensis*, containing emodin, mannitol, vitamin A, sugar, and amino acids. It has the functions of promoting hematopoiesis, antioxidation, antiaging, anti-fatigue, antitumor, and immune enhancement.[33] Huangqin is the dried root of *Astragalus membranaceus*, which contains baicalin, wogonin, baicalein, acetophenone, and β-sitosterol. It has anti-inflammatory activity related to its inhibition of NO, cytokine, chemokine, and growth factor production in macrophages.[34] Qinjiao is the dried root of *Gentiana macrophylla, Gentiana straminea*, or *Rhizoma chinensis*. It contains prostrate A, B, C, gentiopicrin, angelica, montanic acid, methyl montanate, α-romatic alcohol, β-sitosterol, and has the functions of anti-inflammatory, immunosuppressive, liver-protecting, antiviral, calming, and analgesic effects.[35] Fangfeng is the root of a plant in the Umbelliferae family, which contains volatile oil, mannitol, β-sitosterol, picric acid, phenols, polysaccharides, and organic acids. It has anti-inflammatory, anti-allergic, antipyretic and analgesic effects, and regulates immunity.[36]

It is critical for oncologists and dermatologists to recognize target therapy–induced xerosis, understand its mechanisms and choose optimum treatments for patients. TCM may provide us a new treatment decision, improving therapy compliance, and the quality of life. This study was the first randomized, double-blind, placebo-controlled study of TCM for EGFRIs-related xerosis. Some limitations of the study provide implications for future studies. We collected the symptoms of dry mouth, eyes, and nose, for which the analysis of symptom changes showed no

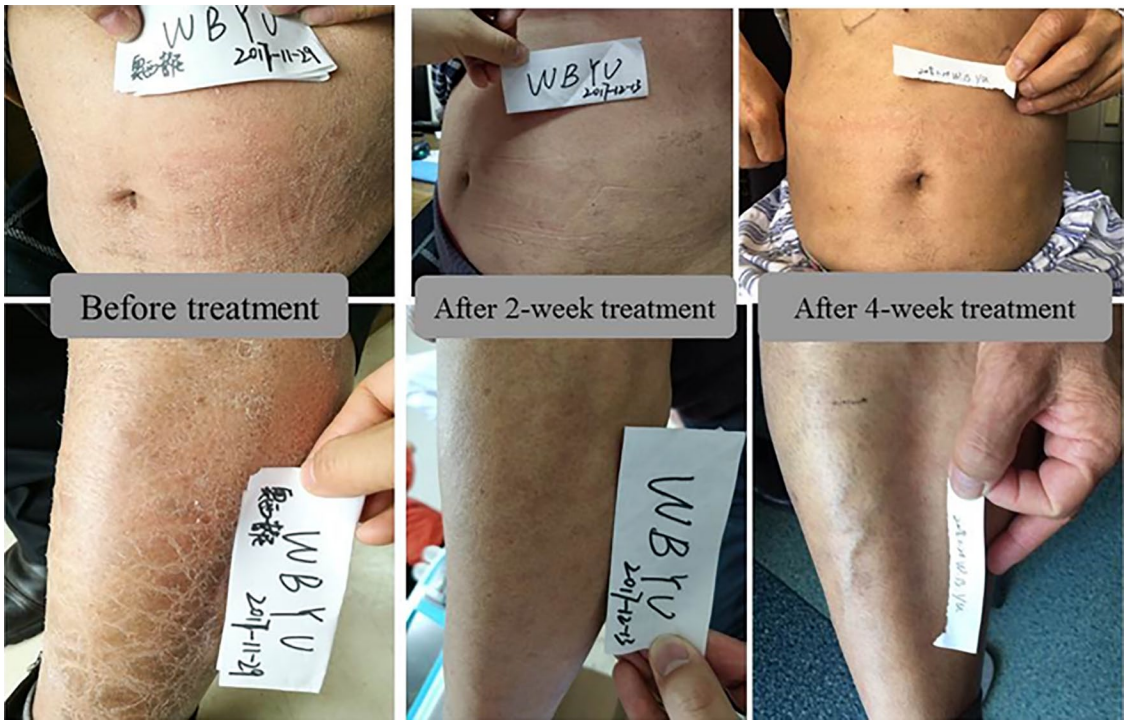

Figure 2. The effect comparison of xerosis before and after using Zizao Yangrong granules in the treatment group.

significant difference. In addition, the tongue and pulse were observed, but we failed to find obvious differences before and after TCM treatment (Figure 2). We think these results may be related to the course of treatment, which may not have been long enough to change the patients' constitution. Further study will pay more attention to the changes of syndrome.

Conclusion

Zizao Yangrong granules have a significant curative effect on EGFRIs-related skin xerosis and improve the quality of life without serious adverse reactions. Moreover, Chinese medicine has broad prospects in the treatment of targeted drugs–related dermatologic adverse reactions. A larger study is needed to verify this finding.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This trial was supported by Beijing Municipal Science and Technology Commission (Grant No.: Z151100004015168).

Trial Registration

This trial was registered at www.chictr.org.cn as ChiCTR-IOR -17013498.

ORCID iDs

Yan Mei Peng https://orcid.org/0000-0001-5739-5566
Wen Shen https://orcid.org/0000-0003-0095-0068

References

1. Clabbers JMK, Boers-Doets CB, Gelderblom H, et al. Xerosis and pruritus as major EGFRI-associated adverse events. *Support Care Cancer*. 2016;24:513-521.
2. Lacouture ME, Maitland ML, Segaert S, et al. A proposed EGFR inhibitor dermatologic adverse event-specific grading scale from the MASCC skin toxicity study group. *Support Care Cancer*. 2010;18:509-522.
3. Chen AP, Setser A, Anadkat MJ, et al. Grading dermatologic adverse events of cancer treatments: the Common Terminology Criteria for Adverse Events Version 4.0. *J Am Acad Dermatol*. 2012;67:1025-1039.
4. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)—a simple practical measure for routine clinical use. *Clin Exp Dermatol*. 1994;19:210-216.

5. Lynch TJ Jr, Kim ES, Eaby B, Garey J, West DP, Lacouture ME. Epidermal growth factor receptor inhibitor-associated cutaneous toxicities: an evolving paradigm in clinical management. *Oncologist*. 2007;12:610-621.
6. Tischer B, Huber R, Kraemer M, Lacouture ME. Dermatologic events from EGFR inhibitors: the issue of the missing patient voice. *Support Care Cancer*. 2017;25:651-660.
7. Petrelli F, Ardito R, Ghidini A, et al. Different toxicity of cetuximab and panitumumab in metastatic colorectal cancer treatment: a systematic review and meta-analysis. *Oncology*. 2018;94:191-199.
8. Crinò L, Cappuzzo F, Zatloukal P, et al. Gefitinib versus vinorelbine in chemotherapy-naive elderly patients with advanced non-small-cell lung cancer (INVITE): a randomized, phase II study. *J Clin Oncol*. 2008;26:4253-4260.
9. Kim ES, Hirsh V, Mok T, et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. *Lancet*. 2008;372:1809-1818.
10. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med*. 2009;361:947-957.
11. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol*. 2010;11:121-128.
12. Lee DH, Park K, Kim JH, et al. Randomized phase III trial of gefitinib versus docetaxel in non-small cell lung cancer patients who have previously received platinum-based chemotherapy. *Clin Cancer Res*. 2010;16:1307-1314.
13. Ciuleanu T, Stelmakh L, Cicenas S, et al. Efficacy and safety of erlotinib versus chemotherapy in second-line treatment of patients with advanced, non-small-cell lung cancer with poor prognosis (TITAN): a randomised multicentre, open-label, phase 3 study. *Lancet Oncol*. 2012;13:300-308.
14. Zhang L, Ma S, Song X, et al. Gefitinib versus placebo as maintenance therapy in patients with locally advanced or metastatic non-small-cell lung cancer (INFORM; C-TONG 0804): a multicentre, double-blind randomised phase 3 trial. *Lancet Oncol*. 2012;13:466-475.
15. Ramalingam SS, Blackhall F, Krzakowski M, et al. Randomized phase II study of dacomitinib (PF-00299804), an irreversible pan-human epidermal growth factor receptor inhibitor, versus erlotinib in patients with advanced non-small-cell lung cancer. *J Clin Oncol*. 2012;30:3337-3344.
16. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol*. 2013;31:3327-3334.
17. Seto T, Kato T, Nishio M, et al. Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring EGFR mutations (JO25567): an open-label, randomised, multicentre, phase 2 study. *Lancet Oncol*. 2014;15:1236-1244.
18. Price TJ, Peeters M, Kim TW, et al. Panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (ASPECCT): a randomised, multicentre, open-label, non-inferiority phase 3 study. *Lancet Oncol*. 2014;15:569-579.
19. Ellis PM, Shepherd FA, Millward M, et al. Dacomitinib compared with placebo in pretreated patients with advanced or metastatic non-small-cell lung cancer (NCIC CTG BR.26): a double-blind, randomised, phase 3 trial. *Lancet Oncol*. 2014; 15:1379-1388.
20. Ramalingam SS, Jänne PA, Mok T, et al. Dacomitinib versus erlotinib in patients with advanced-stage, previously treated non-small-cell lung cancer (ARCHER 1009): a randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2014;15: 1369-1378.
21. Soria JC, Felip E, Cobo M, et al. Afatinib versus erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung (LUX-Lung 8): an open-label randomised controlled phase 3 trial. *Lancet Oncol*. 2015;16:897-907.
22. Wu YL, Zhou C, Liam CK, et al. First-line erlotinib versus gemcitabine/cisplatin in patients with advanced EGFR mutation-positive non-small-cell lung cancer: analyses from the phase III, randomized, open-label, ENSURE study. *Ann Oncol*. 2015;26:1883-1889.
23. Schuler M, Yang JC, Park K, et al. Afatinib beyond progression in patients with non-small-cell lung cancer following chemotherapy, erlotinib/gefitinib and afatinib: phase III randomized LUX-Lung 5 trial. *Ann Oncol*. 2016;27: 417-423.
24. Mok TS, Wu YL, Ahn MJ, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *N Engl J Med*. 2017;376:629-640.
25. Wu YL, Cheng Y, Zhou X, et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2017;18:1454-1466.
26. Yang JJ, Zhou Q, Yan HH, et al. A phase III randomised controlled trial of erlotinib vs gefitinib in advanced non-small cell lung cancer with EGFR mutations. *Br J Cancer*. 2017;116:568-574.
27. Paz-Ares L, Tan EH, O'Byrne K, et al. Afatinib versus gefitinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: overall survival data from the phase IIb LUX-Lung 7 trial. *Ann Oncol*. 2017;28:270-277.
28. Scagliotti GV, Shuster D, Orlov S, et al. Tivantinib in combination with erlotinib versus erlotinib alone for EGFR-mutant NSCLC: an exploratory analysis of the phase 3 MARQUEE study. *J Thorac Oncol*. 2018;13:849-854.
29. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med*. 2018;378:113-125.
30. Han SS, Lee M, Park GH, et al. Investigation of papulopustular eruptions caused by cetuximab treatment shows altered differentiation markers and increases in inflammatory cytokines. *Br J Dermatol*. 2010;162:371-379.
31. Chandra F, Sandiono D, Sugiri U, Suwarsa O, Gunawan H. cutaneous side effects and transepidermal water loss to gefitinib: a study of 11 patients. *Dermatol Ther (Heidelb)*. 2017;7:133-141.

32. Jin Y, Qu C, Tang Y, et al. Herb pairs containing *Angelicae Sinensis* Radix (Danggui): a review of bio-active constituents and compatibility effects. *J Ethnopharmacol*. 2016;181: 158-171.
33. Li NQ. Advances in pharmacological studies of active constituents of *Rehmannia glutinosa* [in Chinese]. *J China Prescription Drug*. 2017;15:15.
34. Yoon SB, Lee YJ, Park SK, et al. Anti-inflammatory effects of *Scutellaria baicalensis* water extract on LPS-activated RAW 264.7 macrophages. *J Ethnopharmacol*. 2009;125: 286-290.
35. Nie AZ, Lin ZJ, Wang Y, Zhang B. Advance in studies on chemical constituents of *Gentianae macrophyllae* Radix and their pharmacologica [in Chinese]. *Chin Tradit Herbal Drugs*. 2017;48:597-608.
36. Xin G, Li X, Huang XW. Research progress on chemical constituents and pharmacological action of radix sileris [in Chinese]. *Jilin J Chin Med*. 2018;38:1323-1325.