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

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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 quality 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

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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 aceneiform 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
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 EGFR 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 MASCC² 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. 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, 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 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 3:3:2:2:2. 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 responses 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 \( \alpha \) 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 \( \chi^2 \) 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...
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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 \((P = .027; \text{Table 2})\).

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

| Characteristics                    | 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                  |                     | .851  |
| Xerosis grade                      |                        |                     |       |
| 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                            |                        |                     | .651  |
| None                               | 4                      | 2                   |       |
| Grade 1                            | 13                     | 9                   |       |
| Grade 2                            | 11                     | 15                  |       |
| Grade 3                            | 5                      | 7                   |       |
| Responsible agent                   |                        |                     |       |
| Icotinib                           | 20                     | 16                  |       |
| Gefitinib                          | 9                      | 12                  |       |
| Erlotinib                          | 3                      | 3                   |       |
| Osimertinib                        | 1                      | 2                   |       |
| Icotinib, osimertinib              | 1                      | 0                   |       |
| Gefitinib, osimertinib             | 0                      | 1                   |       |
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 \((P = .045; \text{Table 5})\).

**Table 2. Changes in Xerosis.**

| Xerosis | CR | PR | NR | RR (CR + PR) | \(P\) |
|---------|----|----|----|--------------|------|
| Two weeks’ treatment | 4  | 24 | 5  | 84.80%  | .000 |
| Treatment          |     |    |    |            |      |
| Placebo           | 4  | 19 | 10 | 69.70%    |      |
| Four weeks’ treatment | 10 | 18 | 5  | 84.80%  | .027 |
| Treatment          |     |    |    |            |      |
| 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 | 13 | 8  | 8  | 72.40%  | —    |
| Treatment          |     |    |    |            |      |
| Placebo           | 4  | 14 | 13 | 58.10%    | .000 |
| Four weeks’ treatment | 15 | 8  | 6  | 79.30%  | —    |
| Treatment          |     |    |    |            |      |
| 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                 |

**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, acniform 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
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, anti-inflammation, 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, gentiopicroin, angelica, montanic acid, methyl montanate, α-romantic 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

Table 6. Incidence of EGFRIs Xerosis in RCTs.

| Lead Author | Study | Patients (n) | EGFRIs Treatment | Xerosis |
|-------------|-------|-------------|------------------|--------|
| Crinò et al8 | INVITE | 196 | Gefitinib | All (%) |
| Kim et al10 | INTEREST | 1466 | Gefitinib | ≥ Grade 3 (%) |
| Mok et al10 | IPASS | 1217 | Gefitinib | 6.4 |
| Mitsudomi et al11 | WJTOG3405 | 177 | Gefitinib | 15.2 |
| Lee et al12 | ISTANA | 161 | Gefitinib | 23.9 |
| Ciuleanu et al13 | TITAN | 2590 | Gefitinib | 54 |
| Zhang et al14 | INFORM/C-TONG 0804 | 296 | Gefitinib | 14.8 |
| Ramalingam et al15 | A7471028 | 188 | Gefitinib | 4 |
| Sequist et al16 | LUX-Lung 3 | 1269 | Gefitinib | 6 |
| Seto et al17 | JO25567 | 154 | Gefitinib | 14.8 |
| Price et al18 | ASPECCT | 999 | Gefitinib | 23.9 |
| Ellis et al19 | NCIC CTG BR.26 | 720 | Gefitinib | 54 |
| Ramalingam et al10 | ARCHER 1009 | 878 | Gefitinib | 14.9 |
| Soria et al21 | LUX-Lung 8 | 795 | Gefitinib | 14.9 |
| Wu et al22 | ENSURE | 217 | Gefitinib | 29 |
| Schuler et al23 | LUX-Lung 5 | 202 | Gefitinib | 75 |
| Mok et al24 | AURA3 | 419 | Gefitinib | 25 |
| Wu et al25 | ARCHER 1050 | 452 | Gefitinib | 24 |
| Yang et al26 | CTONG 0901 | 256 | Gefitinib | 24 |
| Paz-Ares et al27 | LUX-Lung 7 | 319 | Gefitinib | 24 |
| Scagliotti et al28 | MARQUEE | 1048 | Gefitinib | 24 |
| Soria et al29 | FLAURA | 556 | Gefitinib | 24 |

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

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Trial Registration

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

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