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Efficacy and Safety of Modified Huang-Lian-Jie-Du Decoction Cream on Cancer Patients with Skin Side Effects Caused by EGFR Inhibition

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Abstract: (1) Background: The epidermal growth factor inhibitors (EGFRIs)/tyrosine kinase inhibitors (TKIs) are effective for cancer target therapy, but acneiform rashes or so-called inflammatory papulopustular exanthemas are common (50% to 90%). The conventional therapy for EGFRIs/TKIs-induced skin toxicity is steroids and antibacterial drugs, but it is still ineffective for some patients, and EGFRIs/TKIs dose reduction/interruption may be needed. In this study, a modified Chinese herbal medicine, Huang-Lian-Jie-Du decoction cream with Yin-Cold (YC) medicine characteristic, was investigated for the effect on patients suffering EGFRIs/TKIs-induced skin toxicity. (2) Methods: The modified Huang-Lian-Jie-Du (mHLJD) decoction cream was made from 10 herbal medicines, including 4 major medicines (Huanglian, Huangqin, Huangbo, and Zhizi) in traditional HLJD decoction. Patients with EGFRIs/TKIs-induced skin toxicity were enrolled. Patients were excluded if they also used other cream for skin toxicity. Skin conditions were monitored by follow up every 2 weeks. The patients' characteristics, the skin toxicities, treatment response, and adverse events were recorded and analyzed until skin problems resolved or the study ended. (3) Results: The mHLJD decoction cream and its sub-packages were stored at 4 °C before use. Thirty-four patients who had grade 1–3 skin toxicities after receiving EGFRIs/TKIs were enrolled. Seven patients withdrew or were excluded. Finally, data from 27 patients were analyzed. The mean grade of rash acneiform was significantly decreased from 2.19 (ranged 1 to 3) to 0.88 (ranged 0 to 2) after mHLJD decoction cream treatment for 4 weeks and to 0.55 (ranged 0 to 2) after mHLJD decoction cream treatment for 8 weeks. Additionally, the mean grade of dry skin was also significantly decreased from 1.57 (ranged 1 to 2) to 0.71 (ranged 0 to 1) after mHLJD decoction cream treatment for 4 weeks. The changes of skin toxicity were significant, with no obvious adverse events. (4) Conclusions: In summary, the mHLJD decoction cream provides benefits for alleviation of EGFRIs/TKIs-induced skin rash acneiform and dry skin. Additionally, no obvious side effects were found in patients using mHLJD decoction cream.

Keywords: EGFRIs/TKIs; skin rash; dry skin; Chinese herbal medicine

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1. Introduction

Epidermal growth factor receptor inhibitors (EGFRIs) and tyrosine kinase inhibitors (TKIs) are the commonly used anti-cancer drugs for EGFRI-targeting therapy. They can

be used in colon-rectal cancer, lung cancer, head and neck cancer, etc. EGFRIs/TKIs block EGFR tyrosine kinase, which regulates cellular activities, such as cell division. EGFRIs are monoclonal antibodies against EGFR, and TKIs are small molecules inhibiting tyrosine kinase activity. Though the drugs are effective for cancer therapy, acneiform rashes or so-called inflammatory papulopustular exanthemas are the most frequent (50% to 90%) adverse event [1]. The severe rashes occur more frequently in the former (10–17%) compared with the latter (5–9%) [2]. Since the rash reactions affect the quality of life, as they increase infection risk and decrease psychosocial activity, various treatments have been used to resolve the problems. Among these treatments, antibacterial drugs and steroids are the most prescribed regimens for the treatment and prevention of EGFRIs/TKIs-induced skin reactions [3]. According to a retrospective cohort study, integrating dermatologic care of evidence-based prophylaxis treatment may minimize skin toxicity-associated chemotherapy interruptions [4]. However, some patients still had skin toxicity after antibacterial treatment. Therefore, we tried a traditional Chinese medicine (TCM) by dermal application to evaluate the relief effect of EGFRIs/TKIs-induced skin toxicity.

EGFRIs/TKIs-induced skin reactions include papulopustular rash, pruritus, mucositis, xerosis, fissures, paronychia, scalp pustule, and scaring alopecia [5]. According to the TCM theory and the experiences of Chinese medicine doctors, skin rashes mostly belong to the Yang-heat (YH) type of TCM syndromes. The YH-type disease should be treated with Yin-Cold (YC) medicine to maintain the homeostasis of the whole body [6]. Because some TCMs are used for clearing heat, removing moisture, purging endogenous heat, and toxin excretion, they could be applied as YC herbal medicine, for example, Gan Lu Yin (GLY), Huang Lian Jie Du Tang (HLJDT), Pi Pa Qing Fei Yin (PPQFY), Tuo Li Xiao Du Yin (TLXDY), Wen Qing Yin (WQY), and Zhen Ren Huo Ming Yin (ZRHMY). They have shown some benefits for lung cancer patients with EGFR inhibitor-related dermatologic reactions [7].

The formula of HLJDT (also called HLJD decoction) was first recorded in the book Wai-Tai-Mi-Yao in the Chinese Tang dynasty (618–907 A.D.). It consists of four traditional herbs, including Huanglian (Coptidis Rhizoma), Huangqin (Scutellariae Radix), Huangbo (Phellodendri Cortex), and Zhizi (Gardeniae Fructus) in a dry weight ratio of 3:2:2:3 [8]. HLJD decoction has been widely used in the treatment of inflammation. For example, it ameliorates type II collagen-induced rat arthritis by oral pathway [8] and reduces vascular cell adhesion molecule 1 protein expression and leukocyte-endothelial adhesion in rat lung venules after lipopolysaccharide (LPS) stimulation [9]. In spontaneous hypertensive rats, HLJD decoction also has an antihypertensive effect and alters gene expression profile, including the genes with immune function [10]. In dextran sulphate sodium-induced mice ulcerative colitis (UC), HLJD decoction alleviates the UC symptoms and decreases inflammatory cytokines in colons [11]. HLJD decoction mitigates mice atopic dermatitis induced by 2,4-dinitrochlorobenzene [12] and decreases nitric oxide and various cytokines release in LPS-stimulated RAW264.7 cells [13]. Taken together, HLJD decoction shows its effects in various inflammatory conditions.

In this study, we planned to treat EGFRIs/TKIs-induced adverse skin effects by HLJD decoction. In traditional use, the HLJD decoction was taken orally to affect the whole body. Here, we did not want to produce systemic reaction, because it might interfere with the anti-cancer effect of EGFRIs/TKIs. Therefore, we aimed to prepare the HLJD decoction as a cream formulation for a topical YC medicine. In addition to the 4 herbal medicines in original HLJD decoction, six other herbal medicines were also involved to make the modified HLJD (mHLJD) decoction: Sangbaipi (Mori Cortex), Longdan (Gentianae Radix et Rhizoma), Kushen (Sophorae flavescentis Radix), Tofulin (Smilacis Glabrae Rhizoma), Lianqiao (Forsythiae Fructus), and Shigao (Gypsum Fibrosum). The six additional herbal medicines were selected because they also have the efficacy of clearing heat and removing moisture. Therefore, the modified HLJD decoction cream in this study was a modified topical formula that is derived from the traditional oral HLJD decoction.

2. Materials and Methods

2.1. Modified HLJD (mHLJD) Decoction Preparation

All the herbal medicines were purchased from Fu-Xian herbal medicine store (Chiayi, Taiwan) and were identified by a professional pharmacist I-An Hung at Ditmanson Medical Foundation Chia-Yi Christian Hospital. The dry herbal medicine included Huanglian, Huangqin, Huangbo, and Zhizi, Sangbaipi, Longdan, Kushen, Tofulin, Lianqiao, and Shigao. The specimens of these 10 herbal medicines were deposited at Department of Chinese Medicine of Ditmanson Medical Foundation Chia-Yi Christian Hospital.

For decoction preparation, we weighed Huanglian (168.75 g), Huangqin (112.5 g), Huangbo (112.5 g), and Zhizi (168.75 g), Sangbaipi (75 g), Longdan (37.5 g), Kushen (112.5 g), Tofulin (112.5 g), Lianqiao (75 g), and Shigao (187.5 g), mixed them, and put them into a refined cotton bag. All the materials were soaked in 4500 mL water for 20 min at room temperature, then decocted by boiling water for 90 min. After removal from the cotton bag containing the materials, the remaining decoction was about 3000 mL. The mHLJD decoction was stored at 4 °C.

2.2. Production Process of Modified HLJD (mHLJD) Decoction Cream for Skin Use

There were 26 kinds of chemicals (Table 1) in the cream preparation, including the mHLJD decoction prepared as above. Figure 1 shows the procedure for making mHLJD decoction cream. The pH of mHLJD decoction cream was 5.00–5.20, and the viscosity of mHLJD decoction cream was 4500 cps. For oil-water separation analysis, the cream did not separate after centrifuging at 400× *g* for 30 min at 25 °C. Additionally, no oil-water separation happened after incubation at 45 °C or 5 °C for 20 days. The mHLJD decoction cream was stored at 4 °C before use.

Table 1. The 26 constituents of mHLDJ decoction cream.

No.	Ingredients	% (*w*/*w*)	Manufacturer	City	Country
1	Pure water	25.345	(not applicable)	(not applicable)	(not applicable)
2	Glycerin	2.00	P&G Chemicals	Cincinnati	USA
3	Butylene glycol	2.00	Oxea Chemical	Dallas	USA
4	Sodium alginate	1.00	Bright Moon Seaweed	Qingdao	China
5	Acetamidoethoxyethanol	2.00	Spiga Nord	Carasco	Italy
6	Methylparaben	0.20	Clariant Produkte GmbH	Frankfurt am Main	Germany
7	Sclerotium gum	0.60	Even Biochemical	Guangzhou	China
8	Polyglyceryl-3 stearate	3.00	Oleon	Evergem	Belgium
9	Glyceryl stearate citrate	2.00	Oleon	Evergem	Belgium
10	Potassium cetyl phosphate	1.00	DSM Fine Chemicals	Heerlen	Netherlands
11	Behenyl alcohol	2.00	Cognis Japan Ltd.	Tokyo	Japan
12	Stearyl alcohol	2.00	Cognis Oleochemicals (M) Sdn Bhd	Teluk Panglima Garang	Malaysia
13	Stearic acid	1.00	Pacific Oleochemicals	Pasir Gudang	Malaysia
14	Isopropyl isostearate	6.00	Oleon	Evergem	Belgium
15	Isostearic acid	3.00	Oleon	Evergem	Belgium
16	Octyldodecanol	1.00	BASF SE	Ludwigshafen	Germany
17	Caprylic/Capric triglyceride	2.00	Paim-OLEO/Selangor	Selangor	Malaysia
18	Jojoba oil	3.00	Eco Oil Argentina S.A.	Buenos Aires	Argentina
19	Macadamia nut oil	3.00	Arista	Wilton	USA
20	Vitamin E	0.50	DSM Nutritional Products	Kaiseraugst	Switzerland

Table 1. *Cont.*

No.	Ingredients	% (*w*/*w*)	Manufacturer	City	Country
21	Isododecane	1.00	LANXESS GmbH	Cologne	Germany
22	Dimethicone	1.00	Dow Corning	Midland	USA
23	Phenoxyethanol	0.25	Clariant Produkte GmbH	Frankfurt am Main	Germany
24	Octopirox	0.005	Hoechst Aktiengesellschaft	Frankfurt am Main	Germany
25	Proprylene paraben	0.10	Clariant Produkte GmbH	Frankfurt am Main	Germany
26	mHLJD decoction	35.0	(not applicable)	(not applicable)	(not applicable)
	Total	100			

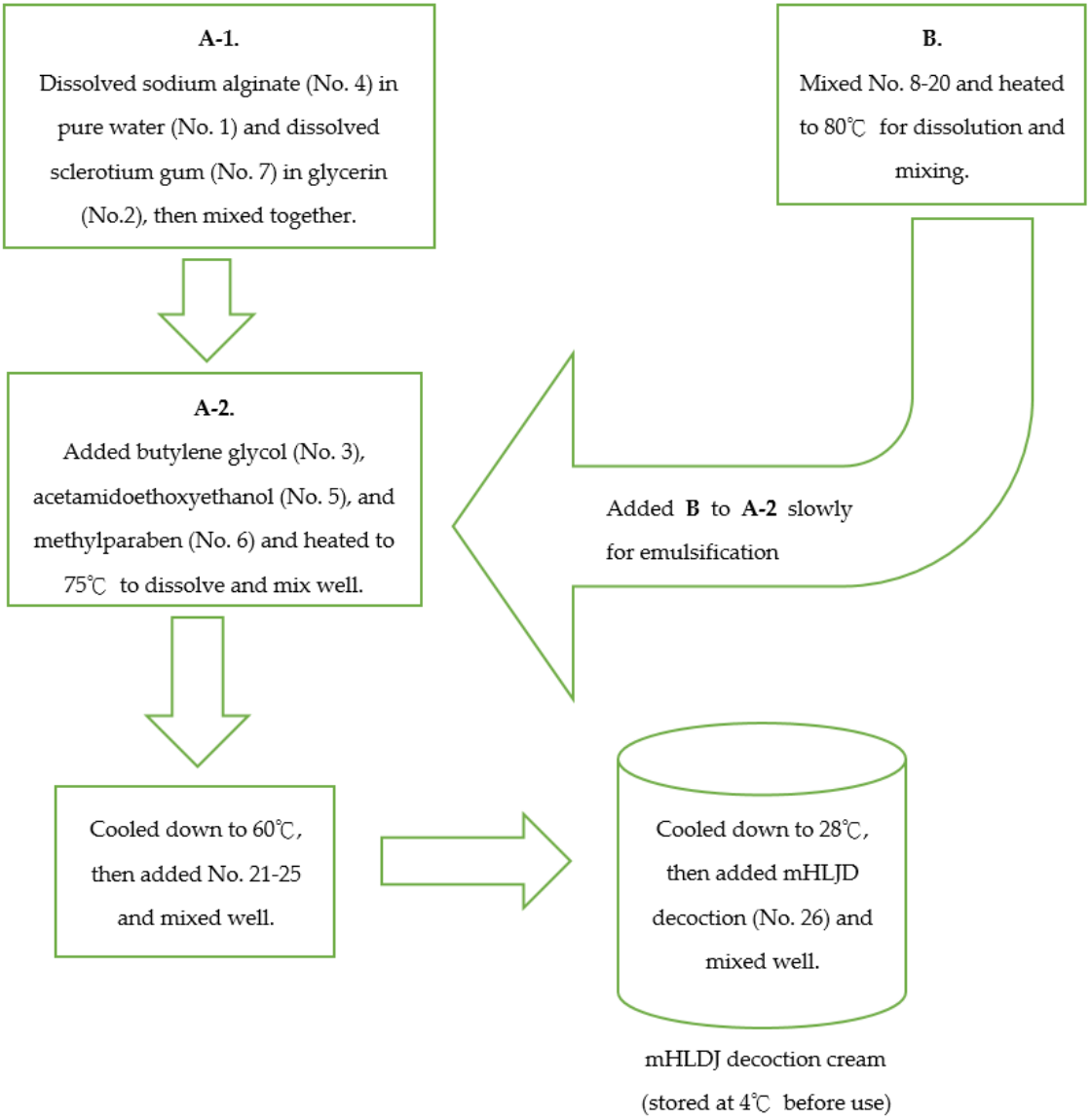


Figure 1. The procedure of mHLJD decoction cream preparation.

2.3. Patients

This is a phase II prospective and open trial. All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee (Institutional Review Board, IRB) of Ditmanson Medical Foundation Chia-Yi Christian

Hospital (IRB approval number: CYCH2019023). Patients who met the following inclusion and exclusion criteria were invited.

Inclusion criteria:

(1) Adult (over 20 years old) malignancy patients who received EGFRIs, such as monoclonal antibodies cetuximab or panitumumab, or who received TKIs, such as gefitinib, erlotinib, or afatinib, in Ditmanson Medical Foundation Chia-Yi Christian Hospital and were screened for this study.
(2) Patients with 1–3 grade of skin toxicities caused by above medications.
(3) If patients were using medications for treating the skin toxicities, they agreed to stop the medications for one week and, after one week, receive mHLJD decoction cream.

Exclusion criteria:

(1) The patients' age less than 20 years old.
(2) Patients unable to achieve good compliance in using topical cream to skin lesions or with acute allergy reaction during first-time use.
(3) During mHLJD treatment period, patients were excluded if they also used other medications for the skin toxicity.

When the patients received mHLJD decoction cream treatment for the first time, the topical treatment was done by physicians. Skin condition was monitored for 30 min to check the acute allergy reaction. After passing the allergy test, the patients were enrolled in this trial after signing informed consent. They received mHLJD decoction cream topical treatment on the skin lesions three times per day by themselves. Skin conditions were followed up every 2 weeks for at least 4 weeks. The patients' characteristics, the skin toxicities, treatment response, and adverse events were recorded and analyzed. The evaluation of skin toxicities was according to Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

The managements of the skin side effects were in accordance with the recommendations of each drug's information from the drug company. The summary of the skin toxicity management is in Table 2.

Table 2. The summary of the skin toxicity management.

Grading of Skin Side Effect	EGFRI/TKI Drugs	mHLJD Decoction Cream
Grade 1	Original dose	Keep treatment
Grade 2	Original dose	Keep treatment
Grade 3, tolerable side effect	Original dose	Keep treatment, stop if no improvement within 7 days
Grade 3, intolerable side effect	Stop for one week or reduce dose	Keep treatment, stop if no improvement within 7 days
Grade 4	Stop treatment	Keep treatment, stop if no improvement within 3 days

2.4. Statistical Analysis

Demographic characteristics were expressed using means and standard deviations or medium and IQR for continuous variables, presented as numbers and percentages for categorical variables. The differences in continuous variables were estimated using Mann–Whitney U test, and differences between categorical variables were analyzed using the Fisher exact test. Wilcoxon signed-rank test were used to compare the treatment response at week 0 and week 2, week 0 and week 4, week 0 and week 6, week 0 and week 8, and week 0 and week 10. A two-tailed $p < 0.05$ was regarded as indicative of statistical significance. The SPSS for Windows version 21.0 (IBM, Armonk, NY, USA) was used for the statistical analysis.

3. Results

3.1. Patient Participation Status

From May 2019 to April 2020, 34 adult patients who had skin toxicities after receiving EGFRIs or TKIs were enrolled. The initial characterizes of skin toxicities were included as following: rash acneiform, dry skin, scalp pain, pruritus, pain of skin, palmar-plantar erythrodysesthesia, skin ulcer, skin hyperpigmentation, and paronychia.

Among the 34 patients, one case withdrew the study one week after enrolling due to uncomfortable, sticky sensation after smearing mHLJD decoction cream. Another one case withdrew the study due to refusal to regularly follow up in our out-patient clinic. In addition, three cases were also excluded in final analysis because two of them used other topical medicine cream by themselves, and another one case stopped TKI treatment due to cancer disease progression after entering the study. Furthermore, two cases had paronychia as an initial skin side-effect and did not have any improvement after using mHLJD decoction cream treatment for one week. These two cases changed to use other topical medications and withdrew from this study. The procedure is summarized in Figure 2. For the fine tuning, we then added paronychia as one of exclusion criteria after group discussion. Therefore, total 27 cases who successfully received mHLJD decoction cream treatment until skin problem resolved or end of study can be analyzed for the treatment response.

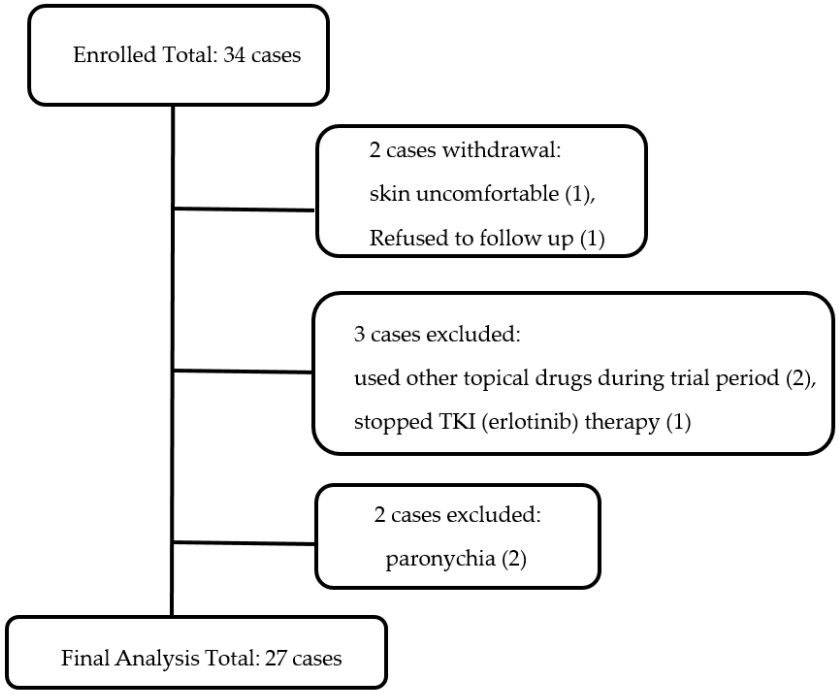


Figure 2. The exclusion procedure from 34 enrolled patients to 27 analyzed cases.

During the mHLJD decoction cream treatment, the EGFRIs and TKIs treatment were kept at the same dosage except for two severe cases with intolerable grade 3 skin toxicity. In these two cases, the TKI (erlotinib) was paused for one week, but mHLJD decoction cream treatment was continued. The basic information for EGFRIs or TKIs received by the 27 included patients is in Table 3. The 27 patients were divided into two groups. Period was the only one significant difference between the groups, because one group used EGFRI/TKI treatment for the first time and did not use systemic and/or topical medications for the skin side effects; the other group had used systemic and/or topical medications for controlling EGFRI/TKI-induced skin toxicity. We included the second group because their skin side effects did not completely resolve after use of the medications. The incidence percentage and the most severe grade of the skin toxicities in these 27 cases are summarized in Table 4.

Table 3. The basic information for EGFRIs or TKIs received by 27 patients. Period means the days from the first EGFRI/TKI use to the first mHLJD decoction cream use. SD, standard deviation; IQR, interquartile range.

Characteristic, *n* (%)	**Total Number (*n* = 27)**	**Previous Use of Medications for Skin Side Effects**		***p* Value**
		No (*n* = 16)	**Yes (*n* = 11)**	
Sex				
Male	12 (44.4%)	8 (50.0%)	4 (36.4%)	0.696
Female	15 (55.6%)	8 (50.0%)	7 (63.6%)	
Age, mean (SD)	59.1 (10.7)	58.4 (10.8)	60.1 (11.1)	0.716
<65	19	12 (75.0%)	7 (63.6%)	0.675
>/=65	8	4 (25.0%)	4 (36.4%)	
Period, medium (IQR)	71 (195)	18.5 (21.8)	222 (932)	**<0.001**
Drugs				
EGFRIs (cetuximab/panitumumab)	7 (25.9%) (6/1)	6 (37.5%)	1 (9.1%)	0.183
TKIs (gefitinib/erlotinib/afatinib)	20 (74.1%) (4/9/7)	10 (62.5%)	10 (90.9%)	

Table 4. The symptom percentage and the most severe grade of skin toxicities in the 27 patients.

	Rash Acneiform	**Dry Skin**	**Scalp Pain**	**Pain of Skin**	**Pruritus**	**Palmar-Plantar Erythrodysestheisa**	**Skin Hyperpig-mentation**
Number *	26	7	2	2	2	1	1
Percentage	96.30%	25.93%	7.41%	7.41%	7.41%	3.70%	3.70%
Most Severe Grade	3	2	3	2	2	1	1

* 27 patients who received mHLJD decoction cream until skin problem resolved or end of study were analyzed.

3.2. mHLJD Decoction Cream Significantly Decreased the Grades of Rash Acneiform

After mHLJD decoction cream treatment, the skin toxicities generally improved. The most common skin toxicity in our study is rash acneiform (n = 26, 96.30%). Calculating the most severe grade of every patient, the mean grade of rash acneiform was 2.19 (ranged 1 to 3). After treatment for four weeks, the mean grade of rash acneiform was 0.88 (ranged 0 to 2). The improvement was significant ($p < 0.001$). The consequent grade change of rash acneiform after mHLJD decoction cream treatment is presented as Table 5. The rash acneiform grades were also analyzed in the groups without or with previous use of medications for the skin side effects (Tables 6 and 7). In Tables 5–7, it is indicated that mHLJD decoction cream significantly decreased rash acneiform grade during two-week treatment. In Table 7, it is shown that grades decreased in 10 patients with previous medications for skin rash acneiform. This means that the effect of mHLJD decoction cream is significantly better than previous medications.

Table 5. The consequent grade change of rash acneiform after mHLJD decoction cream treatment in the 26 patients. The patients were monitored until skin problem resolved or end of study.

	Number	Mean	SD	Medium	IQR	*p* Value
Week 0	26	2.19	0.69	2.00	1.00	–
Week 2	26	1.27	0.83	1.00	1.00	**<0.001**
Week 4	26	0.88	0.65	1.00	1.00	**<0.001**
Week 6	22	0.68	0.65	1.00	1.00	**<0.001**
Week 8	20	0.55	0.69	0.00	1.00	**<0.001**
Week 10	19	0.37	0.50	0.00	1.00	**<0.001**

Table 6. The consequent grade change of rash acneiform after mHLJD decoction cream treatment in the 16 patients without previous use of medication for the skin side effects.

	Number	Mean	SD	Medium	IQR	*p* Value
Week 0	16	2.25	0.68	2.00	1.00	–
Week 2	16	1.31	0.79	1.00	1.00	**0.002**
Week 4	16	0.81	0.66	1.00	1.00	**<0.001**
Week 6	12	0.67	0.78	0.50	1.00	**0.002**
Week 8	11	0.55	0.82	0.00	1.00	**0.003**
Week 10	11	0.27	0.45	0.00	1.00	**0.002**

Table 7. The consequent grade change of rash acneiform after mHLJD decoction cream treatment in the 10 patients with previous use of medication for the skin side effects.

	Number	Mean	SD	Medium	IQR	*p* Value
Week 0	10	2.10	0.74	2.00	1.25	–
Week 2	10	1.20	0.92	1.00	1.25	**0.014**
Week 4	10	1.00	0.67	1.00	0.50	**0.005**
Week 6	10	0.70	0.48	1.00	1.00	**0.006**
Week 8	9	0.56	0.53	1.00	1.00	**0.006**
Week 10	8	0.50	0.54	0.50	1.00	**0.010**

3.3. mHLJD Decoction Cream Significantly Decreased the Grades of Dry Skin

The second common skin toxicity in our study is dry skin ($n = 7$, 25.93%). We recorded the most severe grade of every patient and calculated the mean grade of dry skin as 1.57 (ranged 1 to 2). After treatment for four weeks, the mean grade of dry skin was 0.71 (ranged 0 to 1). The improvement was also significant ($p = 0.034$). The consequent grade change of dry skin after mHLJD decoction cream treatment in each patient is presented as Table 8. The dry skin grades were also analyzed in the groups without or with previous use of medications for the skin side effects (Tables 9 and 10). In Table 8, mHLJD decoction cream is shown to have significantly decreased dry skin grade after four-week and six-week treatments.

Table 8. The grade change of dry skin after mHLJD decoction cream treatment in the 7 patients. The patients were monitored until skin problem resolved or end of study.

	Number	Mean	SD	Medium	IQR	*p* Value
Week 0	7	1.57	0.54	2.00	1.00	–
Week 2	7	1.14	0.69	1.00	1.00	0.180
Week 4	7	0.71	0.49	1.00	1.00	**0.034**
Week 6	6	0.67	0.52	1.00	1.00	**0.034**
Week 8	5	0.80	0.45	1.00	0.50	0.059
Week 10	5	0.80	0.45	1.00	0.50	0.059

Table 9. The grade change of dry skin after mHLJD decoction cream treatment in the 4 patients without previous use of medication for the skin side effects.

	Number	Mean	SD	Medium	IQR	*p* Value
Week 0	4	1.57	0.50	2.00	0.75	–
Week 2	4	1.00	0.82	1.00	1.50	0.180
Week 4	4	0.75	0.50	1.00	0.75	0.102
Week 6	3	0.67	0.58	1.00	–	0.102
Week 8	3	0.67	0.58	1.00	–	0.102
Week 10	3	0.67	0.58	1.00	–	0.102

Table 10. The grade change of dry skin after mHLJD decoction cream treatment in the 3 patients with previous use of medication for the skin side effects.

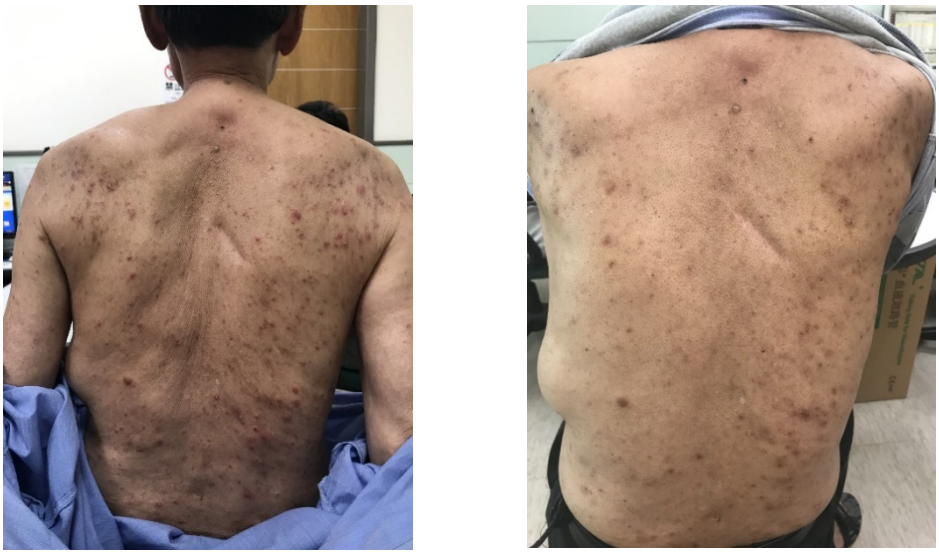
	Number	Mean	SD	Medium	IQR	*p* Value
Week 0	3	1.33	0.58	1.00	–	–
Week 2	3	1.33	0.58	1.00	–	>0.999
Week 4	3	0.67	0.58	1.00	–	0.157
Week 6	3	0.67	0.58	1.00	–	0.157
Week 8	2	1.00	0.00	1.00	–	0.317
Week 10	2	1.00	0.00	1.00	–	0.317

3.4. Safety of mHLJD Decoction Cream in This Trial

The adverse events of mHLJD decoction cream were also carefully observed in this trial. Only one patient complained about the uncomfortable, sticky sensation, and the case was excluded from the trial because he refused to use the cream. Although the skin became a little yellow after cream application, it could be washed off. No allergy, no pigmentation, no epilation, and no skin fading were observed in patients' skin after using the cream. In summary, there were no obvious side effects of mHLJD decoction cream except a sticky sensation; this suggests that mHLJD decoction cream is safe for skin application.

3.5. mHLJD Decoction Cream Significantly Decreased the Grades of Rash Acneiform in Three Cases

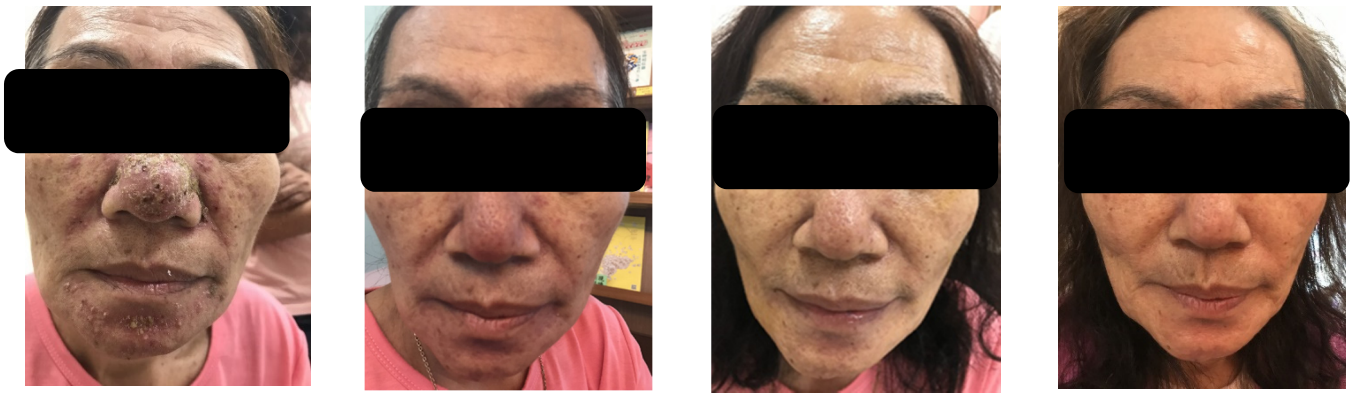
Three cases that had skin toxicity on different areas of the body are described as follows. Figure 3 shows the photos for a patient with rash acneiform on his back. He was enrolled after 400 mg cetuximab treatment for about one month. The rash acneiform was grade 3 before mHLJD decoction cream treatment (Figure 3a). After smearing mHLJD decoction cream every day for four weeks, the grade decreased to 0 with only scars on his back (Figure 3b).



(**a**) (**b**)

Figure 3. One case of cetuximab-induced rash acneiform. (**a**) The rash acneiform before mHLJD decoction cream treatment. (**b**) The rash acneiform after mHLJD decoction cream treatment for 4 weeks.

The photos in Figure 4 are from a patient who received 40 mg afatinib treatment. She was enrolled after afatinib treatment for two weeks. At that time, the rash acneiform on her face was grade 3 (Figure 4a). After mHLJD decoction cream treatment for about four weeks, the grade decreased to 1 (Figure 4b), and it decreased to 0 after an eight-week treatment (Figure 4c). Though the skin condition was completely evaluated for 10 weeks in this trial, the patient wanted to continue to use the cream. Her skin condition became better after mHLJD decoction cream treatment for 20 weeks (Figure 4d) without stopping or decreasing afatinib dosage.

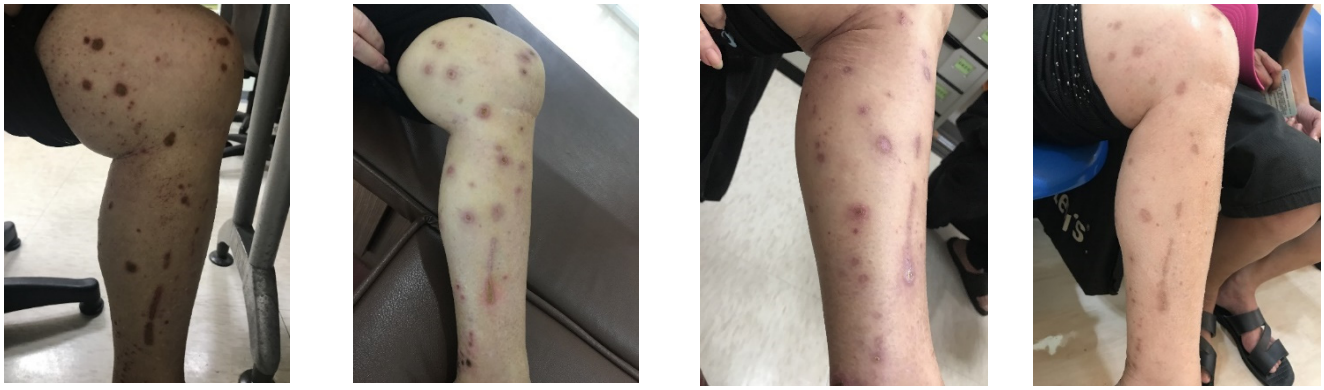


(**a**) (**b**) (**c**) (**d**)

Figure 4. One case of afatinib-induced rash acneiform. (**a**) The rash acneiform before mHLJD decoction cream treatment. (**b**) The rash acneiform after mHLJD decoction cream treatment for 4 weeks. (**c**) The rash acneiform after mHLJD decoction cream treatment for about 8 weeks. (**d**) The rash acneiform after mHLJD decoction cream treatment for 20 weeks.

Another special case is in Figure 5: a patient with rash acneiform on her legs. She was enrolled after receiving 150 mg erlotinib treatment for about 12 weeks. After mHLJD decoction cream treatment for four and eight weeks, the rash acneiform was decreased from grade 2 (Figure 5a) to grade 1 (Figure 5b,c). Actually, after 28-week treatment (Figure 5d), the skin condition was getting better without anti-cancer regimen change. In this case, the

grade evaluation was completed after mHLJD decoction cream treatment for 10 weeks, but the skin condition continued to improve day after day under the use of the cream.



(**a**) (**b**) (**c**) (**d**)

Figure 5. One case of erlotinib-induced rash acneiform. (**a**) The rash acneiform before mHLJD decoction cream treatment. (**b**) The rash acneiform after mHLJD decoction cream treatment for about 4 weeks. (**c**) The rash acneiform after mHLJD decoction cream treatment for about 8 weeks. (**d**) The rash acneiform after mHLJD decoction cream treatment for 28 weeks.

4. Discussion

In Taiwan, Chinese medicine clinics are very popular in each city and are essential in larger hospitals. In the Ditmanson Medical Foundation Chia-Yi Christian Hospital, Chinese medicine clinics have their own patients; they also provide consultations for other departments, for example, cancer treatment in hematology and oncology. Recently, the cancer patients accepting molecular-targeting drug therapy have gradually increased, especially EGFRIs/TKIs. As the skin toxicity induced by EGFRIs/TKIs is getting more serious, and some patients fail to have positive responses to steroids and antibacterial treatment, the alternative therapy by Chinese medicine was introduced and attained significant improvement for patients in this study.

According to the Chinese therapy theory, HLJD decoction might have the ability to relieve the EGFRIs/TKIs-induced skin toxicity. In this study, mHLJD decoction cream shows a significant effect in relieving EGFRIs/TKIs-induced rash acneiform (Tables 5–7) and dry skin (Table 8). In addition to the Chinese theory, some chemicals in the herbal medicine have been reported to have biological functions related to anti-skin inflammation. The four major herbal medicines of the HLJD decoction and their ingredients are summarized in Table 11. The major chemical in Huanglian and Huangbo is berberine. Berberine has been reported to produce anti-inflammatory effects in human keratinocytes, for example, it inhibits 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced matrix metalloproteinase-9 activity and interleukin-6 expression, which are indicators of aging and inflammation [14]. It also inhibits heat-killed *Propionibacterium acnes*-induced nitric oxide and proinflammatory cytokine production in HaCaT keratinocytic cells via inhibiting mitogen-activated protein kinase and NF-κB signaling pathways [15].

Table 11. The major herbal medicine of HLJD decoction and their major ingredients.

Chinese Name	Latin Name	Major Ingredients
Huanglian	Coptidis Rhizoma	berberine
Huangbo	Phellodendri chinensis Cortex	berberine
Huangqin	Scutellariae Radix	baicalin, baicalein, wogonin
Zhizi	Gardenia jasminoides Ellis	geniposide

The major chemicals in Huangqin are baicalin, baicalein, and wogonin. In a mice study, it suggests that baicalin can be metabolized to baicalein and oroxylin A by intestinal microflora. All these compounds inhibit LPS-stimulated peritoneal cytokine production and NF-kB activation in mice [16]. Baicalein also inhibits TPA-induced skin infiltration of polymorphonuclear leukocytes in mice dermis [17]. Wogonin, a derivative of baicalein, also inhibits IL-1beta or TNF-induced cyclooxygenase-2 expression in skin fibroblast NIH/3T3 cells [18].

The major compound in Zhizi is geniposide. It has been reported that geniposide has anti-inflammation effects in LPS-activated rat fibroblast-like synoviocytes [19]. It also has anti-inflammation effects in LPS-induced mice mastitis [20]. Furthermore, geniposide was proven to be absorbed by skin and accumulated in subcutaneous tissue within 1 h in a mice study [21]. In addition to anti-inflammation effect of berberine, baicalin, and geniposide, berberine also has anti-bacterial activity [22,23]. Therefore, the potential anti-inflammatory and anti-bacterial effects of these compounds in the mHLJD decoction cream might constitute the therapeutic effect in this trial.

The evidence-based recommendations for EGFRIs/TKIs-induced papulopustular eruption are systemic antibacterial drugs for the first 6–8 weeks and sunscreen [24]. The management concept is prevention. A prophylactic study shows that topical 4% doxycycline foam has a statistical benefit for EGFRIs/TKIs-induced skin toxicity on the Global Severity Score scale by paired-difference analysis [25]. On the other hand, clindamycin phosphate and benzoyl peroxide (duac® gel) are effective for the treatment of cetuximab-associated acneiform eruption without placebo control [26]. Just like the duac® gel study, the design of our study was for treatment and not for prophylactics. Though we did not compare mHLJD decoction cream with a placebo, we enrolled 40.7% of patients (11/27) with previous medical management for skin toxicity. Many of them were not satisfied with the antibacterial and/or steroid treatment. Comparing the effect of previous drugs and mHLJD decoction cream in the 10 patients with rash acneiform, a significant reduction effect is also evident (Table 7). There was even a special patient who refused EGFRIs treatment because of the resulting skin toxicity but saw obvious improvement on EGFRIs-induced rash acneiform after using mHLJD decoction cream. According to the data analysis results of 27 patients in this study, mHLJD decoction cream showed a statistical improvement for patients with EGFRIs/TKIs-induced rash acneiform (Tables 5–7) and dry skin (Table 8).

There was no effect of mHLJD decoction cream on paronychia in this study. The mechanism was unknown, but maybe the bacterial spectrum of paronychia could not be inhibited by mHLJD. In previous studies, the pathophysiology of EGFRIs/TKIs-induced paronychia included disruption of the protective barrier between the nail and the nail fold and secondary bacterial and fungal infections [27,28]. The majority of the compounds in mHLJD decoction cream, such as berberine, have an anti-bacterial effect but focus on Staphylococcus [29]. However, the bacterial spectrum of paronychia can be both aerobic bacteria (for example, *Staphylococcus aureus*) and anaerobic bacteria [30,31]. There was no report about the effect of HLJD decoction on anaerobic bacteria; thus, in our study, it may be the reason that mHLJD decoction cream did not result in a positive therapeutic effect for paronychia lesions.

5. Conclusions

In this phase II trial, we conclude that the mHLJD decoction cream provides benefits for EGFRIs/TKIs-induced skin rash acneiform and dry skin. Though it is a phase II trial, a further phase III study will be needed to confirm the results. The aim of this study is to provide an alternative treatment for skin side effects in patients using EGFRIs/TKIs that will allow them to keep up an effective dosage of EGFRIs/TKIs therapy, which is very important for cancer therapy.

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