



Original Article

Efficacy of compound traditional Chinese medicine oil in alleviating regorafenib-induced hand-foot skin reaction

Liyan Zhang^a, Jieyuan Cai^a, Hong Sun^{b,*}, Lin Shen^a^a The Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of GI Medical Oncology, Peking University School of Oncology, Beijing Cancer Hospital & Institute, Beijing, China^b Department of Integrative Medicine & Geriatric Oncology, Peking University School of Oncology, Beijing Cancer Hospital & Institute, Beijing, China

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ABSTRACT

Objective: Regorafenib is a novel, oral, anticancer target which greatly improves survival of patients with colorectal cancer. However, it causes 47%–71% patients occur hand-foot skin reaction (HFSR), which affects the quality of life (QOL) or prognosis of patients. However targeted and effective methods are rare. The study attempted to test the efficacy of the compound traditional Chinese medicine (CTCM) oil in relieving HFSR and improving the QOL. **Methods:** The present study was conducted in 85 patients with metastatic colorectal cancer presenting with HFSR from July 2019 to June 2020. These patients were divided into the control group ($n = 42$) and the intervention group ($n = 43$). The HFSR in the control group was managed using traditional methods, whereas that in the intervention group was treated with a CTCM oil comprising five selected herbs. This oil functions by regulating the vascular endothelial growth factor receptor, inflammatory factors, and immune status, and it was provided to the patients to apply externally twice a day. HFSR remission and QOL were evaluated in both groups after 2 weeks of intervention.

Results: The post-intervention HFSR remission rate was significantly higher in the intervention group than in the control group (65.1% vs. 16.7%) ($P < 0.01$). The overall QOL, physical function, social function, and emotional function of the patients in the intervention group were significantly improved ($P < 0.05$), whereas the pain symptoms were more significantly improved ($P < 0.01$).

Conclusions: The CTCM oil can effectively alleviate HFSR and improve the QOL of patients using regorafenib.

Introduction

Regorafenib is a novel, oral, small-molecule multi-kinase inhibitor¹, which targets kinases involved in tumor angiogenesis (VEGFR1, VEGFR2, VEGFR3, TIE2), oncogenesis (KIT, RET, RAF-1, BRAF, BRAFV600E), and tumor microenvironment (PDGFR, FGFR). Studies have reported that regorafenib can considerably improve overall and progression-free survival of patients with tumors such as colorectal cancer (CRC) and gastrointestinal stromal tumor (GIST).^{2–5} However, regorafenib often causes hand-foot skin reaction (HFSR) as an adverse effect in patients, with the total incidence ranging from 47% to 71%.^{2–7} HFSR significantly affects the quality of life (QOL) of patients.^{8,9} Additionally, approximately 20% of the patients with HFSR require dose reductions or treatment discontinuation, which affect their prognosis.

Therefore, reducing the incidence of regorafenib-induced HFSR is essential. Currently, the methods for managing HFSR include symptomatic

treatments such as moisturization, physical decompression, analgesia, or drug dose adjustment, although these treatments have limited efficacy.¹⁰ However, none of the studies have explored an effective targeted intervention for regorafenib-induced HFSR. Literature exhibits only a few small-scale trials with negative results. Barbara et al.¹¹ investigated the prophylactic effect of angiotensin-converting enzyme inhibitor, perindopril, on HFSR in 10 patients with CRC treated with regorafenib and exhibited that perindopril could not reduce the incidence and severity of HFSR. Therefore, randomized controlled trials are urgently required to identify more effective interventions for regorafenib-induced HFSR.

Traditional Chinese medicine is useful in chemotherapy-induced HFSR.^{12–15} However, it lacks applicability owing to differences in manifestations and mechanisms of HFSR between regorafenib and chemotherapy drugs.

The pathophysiology of HFSR induced by regorafenib is unclear. However, studies have exhibited^{11,16,17} that it may be caused by

* Corresponding author.

E-mail address: sunhong2273@163.com (H. Sun).<https://doi.org/10.1016/j.ajon.2021.10.002>

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inhibition of the vascular endothelial growth factor receptor (VEGFR) target, which damages blood vessels and lowers their ability to repair. It may also be related to the inflammatory reaction at the lesion site, which affects wound healing.^{18,19}

Considering the high incidence of HFSR induced by regorafenib and significant adverse effects associated with it, a targeted and effective method is urgently required in clinical practice to alleviate symptoms, improve QOL, prolong time of drug use, and improve prognosis of patients.

Therefore, the present study attempted to evaluate the action of an oil comprising five traditional Chinese medicines that could activate VEGFR, produce anti-inflammatory effect, and regulate immune function on HFSR caused by regorafenib. The study attempted to test the efficacy of the compound traditional Chinese medicine (CTCM) oil in relieving HFSR and improving the QOL.

Methods

Study design

This present quasi-experiment study was conducted in 85 patients with metastatic colorectal cancer (mCRC) who presented with regorafenib-induced HFSR from July 2019 to June 2020 in the Peking University Cancer Hospital. To avoid confounding biases, 50 patients presenting with HFSR from July 2019 to November 2019 were assigned to the control group, whereas 47 patients presenting with HFSR from December 2019 to June 2020 were assigned to the intervention group. The patients in the control group were managed as per recommended guidelines, whereas the patients in the intervention group were managed using the traditional medicine oil twice a day. The rate of HFSR remission and QOL were evaluated in both groups after 2 weeks of intervention.

Patients

Patients meeting the following criteria were included in the study: having histologically confirmed mCRC; having an Eastern Cooperative Oncology Group performance status of 0 or 1 during 14 days prior to the initiation of experimental intervention; having a life expectancy of at least 6 months; on regorafenib treatment, 28 days/cycle, d1–d21 80–120 mg, d22–d28 interval; and presenting with HFSR symptoms according to the Common Terminology Criteria for Adverse Events 4.0 standard.²⁰ Patients treated simultaneously with other antitumor drugs that could cause HFSR, those who discontinued regorafenib during intervention, those exhibiting an uncontrolled medical disorder deemed significant by the treating physician, and those having mental diseases or psychiatric symptoms interfering with their daily life and communication were excluded from the study.

Initially, 50 patients presenting with HFSR from July 2019 to November 2019 were assigned to the control group, whereas 47 patients presenting with HFSR from December 2019 to June 2020 were assigned to the intervention group. Of these, 8 patients from the control group and 4 patients from the intervention group discontinued regorafenib because of severe HFSR symptoms during intervention and were therefore excluded from the study. Thus, 42 patients in the control group and 43 patients in the intervention group with complete follow-up data were finally enrolled in the study. The control group comprised 24 men and 18 women, aged between 23 and 78 years (average age: 58.05 ± 14.13 years), with colon cancer ($n = 15$) and rectal cancer ($n = 27$). The intervention group comprised 26 men and 17 women, aged between 25 and 79 years (average age: 59.19 ± 10.89 years), with colon cancer ($n = 13$) and rectal cancer ($n = 30$). The differences in gender, age, diagnosis, therapeutic regimen, and treatment cycles between the two groups were

Table 1
Demographic characteristics and clinical conditions at baseline.

Items	Control group (n = 41)	Intervention group (n = 43)	T/ χ^2 / Z	P
Age (years, Mean \pm SD)	58.05 \pm 14.03	59.19 \pm 10.89	1.151	0.250
Body mass index (kg/m ² , Mean \pm SD)	23.18 \pm 2.56	23.22 \pm 3.23	0.412	0.690
Gender				
Male	23	26	1.063	0.314
Female	18	17		
Primary tumor site				
Colon	15	13	1.432	0.188
Rectum	26	30		
Previous treatment				
Surgery	17	23	0.115	0.994
Chemotherapy	32	36		
Target therapy	18	16		
ECOG performance status				
0	34	33	1.272	0.866
1	7	10		
Liver function (AST/ALT/BIL)				
Normal	28	31	2.045	0.089
Abnormal (grade I)	13	12		
Regorafenib dose (mg)				
80	12	15	1.672	0.621
120	28	26		
160	1	2		
Median treatment cycles	5	6	0.897	1.261

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BIL, bilirubin; ECOG, Eastern Cooperative Oncology Group.

statistically nonsignificant ($P > 0.05$). Thus, demographic and clinical parameters were comparable between the two groups (Table 1).

Methods

Routine nursing as per recommended guidelines was provided to the control group. This group was advised to avoid spicy food, eat food rich in protein and vitamins, and drink at least 2 L of water per day.²¹ Additionally, they were instructed to keep the skin on the hands and feet clean and implement basic moisturizing care. The patients in the control group were also advised to avoid using alkaline chemical detergent and to use petroleum jelly or VitE emulsion 10–20 g twice a day. All the patients were advised to wear soft and relaxed shoes and socks to avoid friction injury and avoid strenuous exercise.²² Additionally, they were advised to lift up the lower limbs when lying down to promote blood circulation.²³ In case of blisters appearing on the affected part, they were advised to follow doctor's advice and manage them based on symptoms. The intervention group was treated externally with the Chinese medicines oil. An HFSR management group, comprising one Chinese medicine oncologist and three senior nurses with an experience of 10 years, was set up. After evaluation of the HFSR situation in patients by nurses, the Chinese medicine oncologist prescribed a treatment plan consistent with the CTCM syndrome differentiation therapy. Five Chinese herbs, namely *Lithospermum erythrorhizon* (red gromwell; zicao), *Sophora flavescens* (kushen), *Carthamus tinctorius* L. (safflower), *Corydalis yanhusuo*, *Glycyrrhizae Radix et Rhizoma* (gancao), and *Borneolum syntheticum*, along with oily pharmaceutical excipients that could regulate VEGFR, inflammatory factors, and immune function were chosen. The dose of the elements was regulated based on patient symptoms. If the skin was severely dry and painful, the doses of *L. erythrorhizon* (red gromwell; zicao) and *C. yanhusuo* were increased. If patients exhibited thin skins and experienced pricking, the dose of *Borneolum syntheticum* was increased. The Chinese medicine oil was then decocted. The nurses packaged the Chinese herbs in gauze and put them into a dedicated casserole. An

appropriate amount of oily pharmaceutical excipients was then added, heated up to 350°C–380°C until boiling, and then gently heated for 7–13 min. It was then allowed to cool down, and the oil was separated from residues by sieving through a 100-particle size mesh before being transferred to another glass container. Thereafter, the mulling *B. syntheticum* was added to the oil, the mixture was stirred, and finally, the Chinese medicine oil was generated. This oil was applied to the hands and feet of the patients twice a day for 2 weeks concomitantly. The hands and feet were cleaned by immersing them into warm water for 20 min before applying the oil. Then, the hands and feet were wrapped with a plastic wrap for 20–30 min after the oil was absorbed into the skin to promote its absorption.²⁴ Patients applied the oil after being taught and used it correctly in the face of researchers at the first time, and all the health care providers applied the uniform dose protocols.

Measures

HFSR remission rate

The HFSR severity graded was evaluated by a prescribing health care provider according to the Common Terminology Criteria for Adverse Events, version 4.0, as follows²⁰—grade I: numbness, dysesthesia or paresthesia, tingling sensation, painless swelling or erythema of hands and feet, and discomfort that does not interfere with normal activities; grade II: painful erythema and swelling of hands and feet, and discomfort that affects normal activities; grade III: desquamation, ulceration, blistering, or severe pain in hands and feet and severe discomfort that disturbs normal activities.

The HFSR remission rate was calculated as follows: cases downgraded by more than one grade/total cases * 100%

Quality of life

Quality of Life c-30 (QLQ c-30), a tool designed by Aaronson et al. and reliably translated to Chinese by Wan Chonghua et al., was used to measure the QOL of the patients.^{18,25} QLQ c-30 has 30 items, which include 5 functional dimensions (physical, role, emotional, perception, and social functions), 9 symptom dimensions (fatigue, nausea and vomiting, pain, shortness of breath, insomnia, loss of appetite, astription, diarrhea, and economic difficulty), and 1 total health situation. The total health situation item is score from 1 to 7, whereas the other items are evaluated by Likert 4-grade score. Based on the scoring rules, every dimensional score was transferred to a standard score ranging from 0 to 100. The functional dimension score and total health situation score are positively correlated with the QOL of patients, whereas a high symptom dimension score represents severe manifestation.

Adverse events due to the application of Chinese herbal oil

We observed and interviewed allergic refection (itching, redness or rash), which were common adverse events of externally applied agents. And there was no patients report such adverse events.

Data analysis

All data were input by two nurses, and the SPSS 20.0 software (SPSS Inc., Chicago, IL, USA) was used to perform the statistical analyses. Descriptive statistics were used to describe the demographics, HFSR grades, and QOL of patients. Qualitative data are presented as frequency and percentage, whereas quantitative data are presented as mean and standard deviation. Independent sample t test was used to compare differences in the percentage, HFSR remission rate, and QOL between the groups. A *P* value of <0.05 was considered statistically significant.

Ethical considerations

This study was approved by the hospital's ethics committee (Approval No. 2020KT08). All of the participants were asked to sign a written consent form before participating in the study.

Results

HFSR remission rate

The differences in the demographic and clinical parameters between the two groups at baseline were statistically nonsignificant. After intervention, HFSR degraded by at least 1 grade in 28 patients in the intervention group but in only 7 patients in the control group. The intervention group exhibited an HFSR remission rate of 65.1% (28/43), which was significantly higher than that in the control group (16.7%; 7/43). The number of patients in the intervention group exhibiting grade I HFSR was higher than that in the control group. Additionally, the number of patients in the intervention group exhibiting grade II or III HFSR was lower than that in the control group (*P* < 0.01) (Table 2).

Quality of life

At baseline, every functional and symptom dimension of the QOL-c30 questionnaire was comparable between the two groups (*P* > 0.05). The postoperative scores of the total health situation (66.18 vs. 53.73), physical function (74.23 vs. 69.12), social function (61.58 vs. 58.35), emotional function (73.40 vs. 69.80), and pain (45.30 vs. 58.32) in the intervention group were higher than those in the control group, and these differences were statistically significant (*P* < 0.01; Table 3).

Discussion

Chinese medicine oil can effectively reduce HFSR severity

Regorafenib exhibits direct toxicity on the skin and affects the recovery of hands and feet skin injury by targeting VEGFR.¹¹ This effect caused by regorafenib causes a high rate of HFSR, resulting in dose reductions or treatment discontinuation, which in turn significantly influences the QOL of patients.^{8–10} Unfortunately, pertinent measurements to handle this adverse effect are unclear. The present study exhibited that Chinese medicine oil effectively decreased HFSR severity. The HFSR remission rate in the intervention group was significantly higher than that in the control group (65.1% vs. 16.7%). Both the grade and frequency of HFSR in the intervention group were significantly lower than those in the control group (*P* < 0.001; Table 2). This may be due to VEGFR targeting by the oil agent, which is blocked by regorafenib and inflammation. Five Chinese herbs capable of activating VEGFR, decreasing inflammation, and regulating immune function were selected. *L. erythrorhizon* (red gromwell; zicao) extract in this oil can regulate the expression of VEGF121, VEGF165, and VEGF189¹⁹ to promote angiogenesis. Simultaneously, it can increase interleukin (IL)-10 expression through inhibition of tumor necrosis factor (TNF)- α , nuclear factor (NF)- κ B, caspase-1, IL-1 β , IL-6, and TGF- β 1 expression,²⁶ which promotes the proliferation of target cells such as natural killer cells²⁷ to inhibit the inflammatory reaction, contributing to cellular proliferation and skin recovery. *Glycyrrhizae Radix et Rhizoma* extract can positively regulate VEGF expression to enhance the repair function of VEGF and inhibit IL-1, IL-6, IL-8, NF- κ B, and TNF- α expression to ensure the ratio balance of proinflammatory and anti-inflammatory factors and assist in the anti-inflammatory process.²⁸ *C. tinctorius* L. increases VEGF expression to

Table 2
Grades of HFSR before and after intervention.

Groups	Baseline			After intervention			
	I	II	III	0	I	II	III
Control group (n = 42)	10	20	12	3	10	16	13
Intervention group (n = 43)	12	18	13	8	24	8	3
χ^2	0.315			16.945			
<i>P</i>	0.854			0.000			

HFSR, hand-foot skin reaction.

Table 3
QOL between two groups before and after intervention (Mean ± SD).

Dimensions	Intervention group (n = 43)		Control group (n = 42)		T1	T2
	Before	After	Before	After		
Total situation	51.25 ± 12.73	66.18 ± 10.24	50.69 ± 15.76	53.73 ± 12.09	0.832	12.266**
Physical function	69.58 ± 18.26	74.23 ± 15.98	70.56 ± 13.38	69.12 ± 11.24	-0.682	4.299**
Role function	68.72 ± 18.12	67.98 ± 20.11	69.07 ± 21.31	66.96 ± 14.09	-0.327	0.132
Social function	56.78 ± 11.31	61.58 ± 13.21	55.88 ± 11.35	58.35 ± 11.27	0.872	2.357*
Emotional function	69.57 ± 18.22	73.40 ± 12.11	70.37 ± 19.39	69.80 ± 17.33	-0.714	3.213*
Perception function	70.28 ± 13.01	69.72 ± 18.43	69.88 ± 14.03	69.41 ± 15.88	0.543	0.173
Fatigue	48.79 ± 18.37	46.74 ± 12.32	49.32 ± 14.14	48.26 ± 11.93	0.475	-1.108
Nausea and vomiting	33.33 ± 10.59	31.96 ± 9.51	32.85 ± 11.71	29.98 ± 5.90	0.325	1.728
Pain	66.57 ± 14.16	45.30 ± 8.79	67.95 ± 14.86	58.32 ± 8.86	-0.512	-12.058**
Shortness of breath	22.92 ± 7.14	20.51 ± 3.91	23.46 ± 9.08	21.28 ± 1.87	-0.463	-0.877
Insomnia	46.08 ± 13.29	45.32 ± 5.61	45.79 ± 16.45	45.08 ± 9.60	0.418	1.864
Loss of appetite	45.89 ± 19.48	46.67 ± 7.37	46.15 ± 15.35	45.98 ± 8.36	-0.566	0.508
Astriction	33.17 ± 9.33	31.68 ± 9.90	32.89 ± 10.53	31.94 ± 11.35	0.628	-0.355
Diarrhea	22.98 ± 6.24	21.78 ± 7.37	23.06 ± 9.41	21.71 ± 5.66	-0.095	0.086
Economic difficult	46.72 ± 16.44	48.02 ± 15.67	47.15 ± 17.22	50.67 ± 18.34	-1.257	-1.688

T1, comparison of the two groups before intervention; T2, comparison of the two groups after intervention; *, $P < 0.05$; **, $P < 0.01$. QOL, quality of life.

promote angiogenesis²⁹ for skin healing and inhibits IL-2, IL-6, and NF- κ B expression to facilitate the anti-inflammatory process.³⁰ *S. flavescens* extract inhibits the inflammatory process by inhibiting NF- κ B, IL-1, IL-6, and TNF- α expression.³¹ Simultaneously, it can regulate the immune function and improve the barrier function of the skin.³² The synergistic effect of all these herbs enhances the vessel repair, anti-inflammatory process, and skin barrier function, contributing to skin healing and a better QOL of the patient.

Additionally, the formula is appropriate in composition.³³ As per the “monarch, minister, assistant, and guide” system in CTCM prescription, *L. erythrorhizon* is the monarch in the formula that can cool the blood, promote circulation, and eliminate toxicities. *C. tinctorius* L. and *S. flavescens* are the ministers; *C. tinctorius* L. promotes circulation and dissolves the clot to reduce pain, whereas *S. flavescens* clears heat, eliminates dampness, dispels wind, and arrests itching. *C. yanhusuo* plays the role of an assistant and activates blood and relieves the pain, whereas *B. syntheticum* reduces the local pain. *Glycyrrhizae Radix et Rhizoma* is the guide that relieves spasm and pain, moderates the herbal property, and decreases toxicities. The whole formula is capable of removing pathogenic heat from blood, dispelling wind, arresting itching, and invigorating blood circulation to alleviate pain. This formula can promote the resolution of inflammation and accelerate healing, particularly in patients with swollen, painful, itchy, and cracked hands and feet.

All the herbs in the oil formula are documented in pharmacopoeia³⁴ and could be used externally to treat skin diseases. These herbs can ease itching and alleviate carbuncles, eczema, and emphyosis. *L. erythrorhizon*, *C. tinctorius* L., *C. yanhusuo*, and *Glycyrrhizae Radix et Rhizoma* are used to alleviate skin and external diseases, eczema, swelling, pain, skin injury, and bruises. *S. flavescens* relieves eczema and itching.

Furthermore, studies have exhibited that *L. erythrorhizon* contains alkannin, which possesses anti-inflammatory and antimicrobial properties, inhibits capillary hyperpermeability, promotes granulation tissue proliferation, and significantly facilitates wound healing by improving immune function.^{26,27} *C. tinctorius* L. has anti-inflammatory, analgesic, antitumor, antibacterial, and antifatigue properties, and it exerts significantly enhanced effects on nonspecific and cellular immune functions.³⁵ The formula containing these two drugs can effectively reduce the symptoms of inflammation, pain, and cracked skin to enhance the self-protective function of the skin, eventually promoting skin repair and wound healing.

The oil agent can be directly applied to the skin surface, which is more convenient to use than soaking to improve patient compliance and operability. Alkannin, the therapeutic agent in *L. erythrorhizon*, is a class of naphthoquinone pigments³⁶ with strong fat-soluble properties, and thus, it can be more effective in fatty solvents. Additionally, the oil agent

forms a protective film on the skin surface, which increases the drug absorption rate and improves the moisturizing effect compared with a water agent.

Chinese medicine oil can effectively improve QOL in patients with HFSR

Regorafenib-related HFSR manifests as hand and foot paresthesia, cracks, swelling, and even skin peeling, which affect basic activities of patients such as walking and grabbing stuffs. The symptoms of HFSR affect the QOL of patients, causing pessimism and depression.^{8,9} The present study exhibited better QOL, physical function, social function, emotional function, and pain score ($P < 0.05$, Table 3) in the intervention group two weeks after treatment. This improvement may be explained by the fact that the oil agent targets the mechanism of HFSR and directly affects the wound, thereby alleviating pain and swelling. By promoting the local circulation and skin barrier, the Chinese medicine oil contributes to skin repair and benefits patients by improving their QOL and physical function. A better physical function is related to a better social function, resulting in a better psychological state of the patient. Thus, the oil agent holistically benefits the patients.

Limitations

This study has several limitations. First, the relatively small sample size and the single-center design of the study prevent the generalization of the findings. A multicenter study with a larger sample size and different patient populations is thus required to generalize the results. Additionally, the quasi-experimental design necessitates the validation of test results in large-sample, randomized controlled studies.

Conclusions

Although regorafenib has significant therapeutic effects, HFSR is a commonly associated adverse effect. HFSR reduces the QOL of patients and is the main cause of dose reduction or discontinuation in patients treated with regorafenib. Our Chinese medicine oil comprising five herbs activates VEGFR expression, promotes anti-inflammatory action, and regulates immune function, thereby targeting the mechanism through which regorafenib causes HFSR. The use of this oil relieves HFSR and improves the QOL in patients.

Author contribution statement

Hong Sun contributed to the conceptualization and supervision; as

the first author, Liyan Zhang contributed to conceptualization, data curation, formal analysis, investigation, methodology, and original drafting of the manuscript; Lin Shen is the project administrator and provided resources; Jieyuan Cai contributed to the translation.

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Declaration of competing interest

None declared.

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