

The Efficacy and Safety of the Shouzu Ning Decoction Treatment for Multi-Kinase Inhibitors-Associated Severe Hand–Foot Skin Reaction

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Background: Multi-kinase inhibitors (MKIs) treatment plays an important role in cancer therapy, but still suffers from a high incidence of hand–foot skin reaction (HFSR), leading to MKIs dose modification or termination. Thus, there is a high need for therapeutic strategy for HFSR.

Patients and Methods: This prospective analysis included twenty patients, who were continuously administered with MKIs treatment and presented with a grade 3 HFSR during January 2018 to December 2019. All the patients were treated with the Shouzu Ning Decoction (SND) twice a day, in addition to the MKIs treatment. Grading of HFSR was assessed by National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Pain intensity was evaluated using the numerical rating scale (NRS). Quality of life was assessed using the Hand–Foot Quality of Life Scale (HF-QoLS).

Results: The median time from MKIs initiation to onset of grade 3 HFSR was 26.2 days. Following the SND treatment, seventeen (17/20) patients displayed grade 2 HFSR with a median time of 5.1 days. Among whom, seven (7/17) finally transformed to grade 1 with a median time of 9.9 days. While all of the grade 1 patients (7/7) had local recurrence, and retreatment of the SND was effective. In addition, after the SND treatment, the score of NRS and HF-QoLS decreased to 1.60 ± 1.14 ($P < 0.01$) and 26.75 ± 11.76 ($P < 0.01$), respectively.

Conclusion: The SND treatment could alleviate symptoms, relieve pain and improve quality of life in HFSR patients. The SND treatment was proved to be an effective and well-tolerated treatment for MKIs-associated grade 3 HFSR patients for the first time. Indeed, further randomized controlled trials with large-scale, multi-center are required to fully determine the clinical application of the SND in MKIs-associated HFSR.

Keywords: hand-foot skin reaction, multi-kinase inhibitors, Shouzu Ning Decoction, efficacy, safety

Introduction

Multi-kinase inhibitors (MKIs) targeting specific tyrosine kinases have become one of the most promising classes of cancer-fighting agents.¹ Currently, more than twenty MKIs have been approved by the US Food and Drug Administration for the treatment of advanced solid tumors.² Some of them have been recommended as standard treatments for certain clinical indications^{3–5} [eg sorafenib in hepatocellular carcinoma, regorafenib in colorectal cancer, apatinib in gastric cancer, and anlotinib in non-small cell lung cancer].^{6–8} However, despite their clinical success, MKIs are prone to induce significant dermatologic adverse events.^{9,10}

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Hand-foot skin reaction (HFSR) is the most common dermatologic event developed in patients treated with MKIs.^{11,12} The incidence of HFSR ranges from 24.5% to 44.7% in various clinical trials.^{13–15} In all published Phase III trials, patients with grade ≥ 2 HFSR required dose modifications or treatment discontinuation.^{16,17} Although some drugs, such as topical urea-containing moisturizing cream, steroids, and celecoxib, have been suggested to reduce the incidence and severity of HFSR,^{18,19} their effectiveness were far from satisfactory. Dose modification or termination is a compromising strategy recommended in clinic treatment,² but usually lead to disease progression. There remains an urgent need for effective therapeutic options to treat HFSR.

Si-Miao-Yong-An decoction (SMYAD), a traditional Chinese medicine formula, was used for centuries to treat gangrene patients via eliminating heat and promoting blood circulation, according to the traditional Chinese medicine theory.^{20,21} Recently, the SMYAD were reported to be effective in relieving pressure ulcers, diabetic ulcers and venous stasis ulcers.^{22–24} These symptoms are some kind of similar to those of HFSR, which presenting with peeling, blister, bleeding, edema, or hyperkeratosis in the palms and soles.² We previously observed that the SMYAD could partially suppress the development of HFSR, but the results were still far from satisfactory.

Shouzu Ning Decoction (SND) was empirically modified from the SMYAD, and was used to treat HFSR for the first time in clinical applications by our team. Our clinical observation showed that the remission rate for HFSR symptoms was significantly higher in the SND group compared to the SMYAD group (unpublished data). Meanwhile, no studies focused on the treatment of severe HFSR have been reported till now. In this study, 20 severe HFSR patients who previously received various treatments (steroids, celecoxib, and urea cream) were treated on a novel schedule by using the SND treatment. Our results showed that the SND treatment could alleviate symptoms, relieve pain and improve quality of life in the grade 3 HFSR patients.

Methods

Study Design

We prospectively collected data from all patients who received MKIs therapy at the First Affiliated Hospital of Zhejiang Chinese Medical University and developed grade 3 HFSR during January 2018 to December 2019. Patients

must meet all of the following criteria: i) at least 18 years old, ii) were continuously administered with MKIs treatment and presented with a grade 3 HFSR; iii) experienced failure of treatments such as topical urea-containing moisturizing cream, steroids, or NSAIDs. Patients were excluded if they had preexisting skin lesions, including peripheral neuropathy caused by diabetes or chemotherapy, hand and foot syndrome, hand and foot fungal infection, skin trauma. This study was approved by the Ethics Committee of the First Affiliated Hospital of Zhejiang Chinese Medical University and conducted in accordance with the principles of Helsinki Declaration. Written informed consent for both study participation and publication of identifying information/images was obtained from all patients.

Patient Characteristics

For included patients, charts were further reviewed for demographic characteristics, tumor histology and stage, prior history of HFSR or HFS, and types of MKIs in use. Demographic characteristics included age and sex. The histology consisted of hepatocellular carcinoma, lung cancer, gastrointestinal cancer, esophageal cancer, and renal cancers. The tumor stage was determined according to the American Joint Committee on Cancer's Cancer Staging Manual, 8th edition. Use of other chemotherapeutic agents that were reported to cause HFS was recorded (ie, capecitabine, epirubicin, or docetaxel).

HFSR

The degree of HFSR was graded from 1 to 3 in accordance with the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 5.0 (shown in Table 1). Relevant clinical data of HFSR, including skin changes, dermatitis, pain, and activities of daily living (ADL) were collected. Photos of palms and

Table 1 NCI-CTCAE Version 5.0 Grading of HFSR

Grade	Description
1	Minimal skin changes or dermatitis (eg, erythema, edema, hyperkeratosis) without pain
2	Skin changes (eg, peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain; limiting instrumental ADL
3	Severe skin changes (eg, peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain; limiting self care ADL

Abbreviations: ADL, activities of daily living; HFSR, hand-foot skin reaction; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

soles were recorded for clinical purposes. Pain intensity was evaluated using the numerical rating scale (NRS) from 0 (no pain) to 10 (most severe pain). Patients' HFS-related restrictions in daily activities were assessed using the Hand-Foot Quality of Life Scale (HF-QoLS).^{16,25} HF-QoLS consists of four subscales: physical (8 items), self-care (3 items), social (3 items), and psychological (4 items). Each item is scored on a scale of 0–4, with a higher score indicating greater difficulty in daily activities affecting HFSR-related quality of life. The timing of HFSR relative to MKIs treatment initiation was assessed. All patients had experienced treatment failure of topical urea-containing moisturizing cream, steroids, or NSAIDs.

Intervention

SND herbs (150 g) were consisted of 30 g *Lonicerae japonicae* Flos (Jin Yin Hua), 30 g *Angelicae sinensis* Radix (Dang Gui), 30 g *Lonicerae japonicae* Caulis (Ren Dong Teng), 30 g *Spatholobi* Caulis (Ji Xue Teng), and 30 g *Glycyrrhizae Radix et Rhizoma* (Gan Cao). All of them were purchased from the Zhejiang Chinese Medical University (Zhejiang, China), and were further authenticated by pharmacologist, Professor Jingxia Wang. A total of 150 g SND herbs were decocted twice with eightfold of water for 1 h. The extracts were combined, filtered, and then concentrated to a volume of 200 mL at 100 °C. The extracts were named as SND. SND used in this study were analyzed by a validated reversed-phase HPLC system (Thermo Dionex Ultimate 3000 HPLC system, Thermo Fisher Scientific, Waltham, MA, USA) using an Agilent Zorbax SB C18

column (4.6×150 mm, 5μm). A representative HPLC chromatogram of the SND was shown in Figure 1.

Administration method: The patients were treated with the SND twice a day. For each treatments, 200 mL SND was diluted with water to a final volume of 1000 mL. Temperature was kept at 35 °C to 40 °C in a thermostatic bath. Then the hands and feet of the patients were soaked in the bath for 20 minutes.

Statistical Analysis

Standard descriptive and analytical methods were used to describe the baseline characteristics, symptom characteristics, and clinical outcomes of the patients. Data analyses were performed using SPSS 20.0 software (IBM Corporation, Armonk, NY, USA). A $p < 0.05$ (two-tailed) was considered as statistically significant.

Results

Patient Characteristics

Twenty-two patients who developed grade 3 HFSR during MKIs therapy were enrolled in this study. Two patients who had discontinued MKIs treatment after the disease progression dropped out. The remaining twenty patients were included in the analysis. The patient characteristics were shown in Table 2. Patient age ranged from 18 to 76 years, with a median age of 58 years. The male to female ratio was 15:5. Among these twenty patients, six patients were on stage III and fourteen patients were on stage IV. The most common types of cancers were hepatocellular carcinoma (50%), followed by lung cancer (20%) and gastric cancer (10%). The types of MKIs included sorafenib ($n = 8$

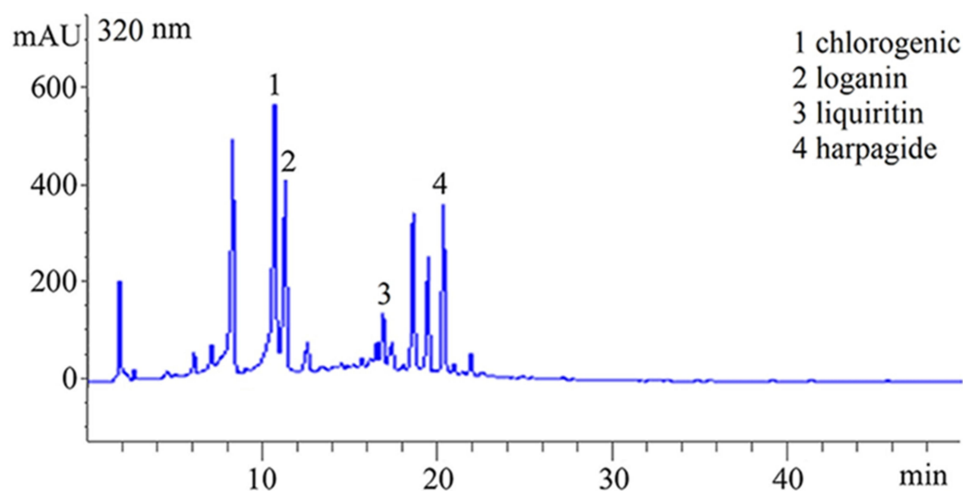


Figure 1 HPLC analysis of the Shouzu Ning Decoction (SND)

Table 2 Patient Characteristics (n=20)

Total	Number of Patient (n)	Percentage (%)
Sex		
Male	15	75
Female	5	25
Age (years)		
Median	58	–
Range	18–76	–
Cancer type		
Hepatocellular carcinoma	10	50
Lung cancer	4	20
Gastric cancer	2	10
Colorectal cancer	1	5
Rectal cancer	1	5
Esophageal cancer	1	5
Renal cancer	1	5
Cancer stage		
III	6	30
IV	14	70
MKIs type/Dose (mg/day)		
Apatinib/500/250	2/1	15
Sorafenib/800/600/400	4/2/2	40
Regorafenib/120	2	10
Anlotinib/12	4	20
Lenvatinib/8	3	15
Onset of grade 3 HFSR (day)		
Median	26.2	–
Range	8–60	–
History of grade ≥ 2 HFS induced by chemotherapy	2	10
History of grade ≥ 2 HFSR induced by MKIs	1	10

Abbreviations: MKIs, multi-kinase inhibitors; HFS, hand-foot syndrome.

patients), anlotinib (n = 4 patients), apatinib (n = 3 patients), lenvatinib (n = 3 patients), and regorafenib (n = 2 patients). Two patients and one patient had a history of grade ≥ 2 HFS/HFSR caused by capecitabine and sorafenib, respectively.

Diagnosis, Management, and Evaluation of MKIs-associated Ind HFSR

The median time from MKIs initiation to onset of grade 3 HFSR was 26.2 days (range 8–60 days) (Table 3). The patients were initially diagnosed with HFSR and treated in accordance with the international recommendations, including topical urea-containing moisturizing cream,

steroids, or NSAIDs (Table 3), but had no clinical benefits which prompted the use of SND.

Prior to the SND treatment, all the patients presented with grade 3 HFSR according to NCI-CTCAE, version 5.0. The presenting symptoms of HFSR in patients: hyperkeratosis (17 of 20, 85%), erythema (13 of 20, 65%), edema (6 of 20, 30%), blisters (6 of 20, 30%), peeling (3 of 20, 15%), and bleeding (1 of 20, 5%), hand and foot pain (20 of 20, 100%), limiting instrumental ADL (20 of 20, 100%) (Table 3).

SND Treatment

The patients were continuously treated with the SND at a dose of 200 mL twice daily in addition to the treatment of MKIs until the clinical regression of grade 1 was observed. If the symptoms of HFSR were not relieved after two weeks of treatment, we also terminated the administration of both MKIs and SND. Meanwhile, MKIs dosage was not reduced during the combination treatment. Symptom remission was observed as early as 2 days after the treatment in patient NO. 18. Most of the patients (17/20) displayed grade 2. The median time from the starting of the SND treatment to HFSR symptom remission was 5.1 days (ranging from 3 days to 14 days). Among whom, seven patients (7/17) finally transformed to grade 1 with a median time of 9.9 days. As already known, patients who reach grade 1 HFSR could continue MKIs treatment at the same level as the initial dose, and those who reach grade 2 HFSR may need a dose reduction. While all of the grade 1 patients (7/7) had local recurrence. Retreatment of the SND was effective, which indicated that interruption of the SND treatment did not result in drug resistance.

Intriguingly, the results showed that the effect of the SND differed by symptoms of HFSR. Erythema and edema were completely remitted in all patients, whereas peeling, blister, and bleeding were partially reduced. Unfortunately, the symptoms of patient No. 3, 12, 14 characterized by severe hyper-keratinization in hands and feet were not alleviated after continuously treated with the SND for 2 weeks and the desired effect of the SND was not achieved. In addition, no side effects related to the SND treatment were observed (Table 3) except that the skin color changed to light brown. Skin discoloration disappeared within one week and did not need any treatment.

Numerical rating scale (NRS) of pain and HF-QoLS of daily activity subscale were taken in all patients before and after the SND treatment. Median NRS score and HF-QoLS

Table 3 MKIs-associated HFSR Characteristics and the SND Treatment

Patients	Onset of Grade 3 HFSR (Day)	Previous HFSR Treatment	HFSR Clinical Presentation	SND Treatment		Remission (Day)		Recurrence (Day)	Side Effects
				Dosing (mL)	Times (Day)	Grade 3 to Grade 2	Grade 2 to Grade 1		
1	11	Moisturizing cream, steroids	Erythema, peeling, hyperkeratosis	200 twice daily	13	5	8	4	No
2	26	Moisturizing cream, NSAIDs, and steroids	Erythema, edema, blisters, hyperkeratosis	200 twice daily	14	6	–	–	No
3	34	Steroids	Hyperkeratosis, erythema, peeling	200 twice daily	14	–	–	–	No
4	17	Moisturizing cream	Edema, blisters, hyperkeratosis, peeling	200 twice daily	14	6	–	–	No
5	60	Moisturizing cream, NSAIDs	Erythema, blisters, hyperkeratosis	200 twice daily	10	3	7	10	No
6	28	Moisturizing cream, NSAIDs, and steroids	Erythema, blisters, hyperkeratosis	200 twice daily	14	6	8	5	No
7	20	Moisturizing cream, NSAIDs	Erythema, hyperkeratosis	200 twice daily	14	8	–	–	No
8	40	Moisturizing cream, NSAIDs	Bleeding, hyperkeratosis	200 twice daily	14	6	–	–	No
9	28	Moisturizing cream, NSAIDs	Hyperkeratosis	200 twice daily	14	7	–	–	No
10	28	Moisturizing cream, NSAIDs	Erythema, hyperkeratosis	200 twice daily	14	5	–	–	No
11	55	Moisturizing cream, NSAIDs, and steroids	Erythema, edema	200 twice daily	7	3	4	7	No
12	20	Moisturizing cream, NSAIDs	Hyperkeratosis, erythema, blisters	200 twice daily	14	–	–	–	No
13	8	Moisturizing cream	Peeling, hyperkeratosis	200 twice daily	14	3	–	–	No

(Continued)

Table 3 (Continued).

Patients	Onset of Grade 3 HFSR (Day)	Previous HFSR Treatment	HFSR Clinical Presentation	SND Treatment		Remission (Day)		Recurrence (Day)	Side Effects
				Dosing (mL)	Times (Day)	Grade 3 to Grade 2	Grade 2 to Grade 1		
14	25	Moisturizing cream, steroids	Hyperkeratosis, erythema, bleeding,	200 twice daily	14	–	–	–	No
15	13	Moisturizing cream, steroids	Erythema, edema, hyperkeratosis	200 twice daily	9	5	4	3	No
16	45	Moisturizing cream, NSAIDs, and steroids	Peeling, hyperkeratosis	200 twice daily	14	8	–	–	No
17	22	Moisturizing cream, NSAIDs	Blisters, peeling, hyperkeratosis	200 twice daily	10	4	6	5	No
18	15	Moisturizing cream, NSAIDs, and steroids	Blisters, erythema	200 twice daily	14	2	–	–	No
19	13	Moisturizing cream, NSAIDs	Edema, blisters	200 twice daily	6	3	3	3	No
20	16	Moisturizing cream, NSAIDs, and steroids	Erythema, edema, hyperkeratosis	200 twice daily	14	6	–	–	No

Abbreviation: NSAIDs, Non-Steroidal Anti-inflammatory Drugs.

score were 4.30 ± 1.26 and 53.80 ± 4.16 at the onset of grade 3 HFSR, respectively. After the SND treatment, the score of NRS and HF-QoLS decreased to 1.60 ± 1.14 ($P < 0.01$) and 26.75 ± 11.76 ($P < 0.01$), respectively (Figure 2). Our results indicated that the SND treatment could decrease pain and improve quality of life in patients with HFSR. We also compared baseline characteristics between the 15% of patients who did not respond to the SND to the 85% of patients who were treated effectively. No significant difference were observed between groups (Table 4).

Discussion

MKIs are a promising cancer therapeutic strategy, but usually lead to a high incidence of HFSR, which limits their clinical application.² To date, only prevention measures have been reported to reduce the severity of HFSR.²⁶ Once severe HFSR occurs, dose modification or

termination are taken for a comprising therapy, which may lead to tumor progression. At present, evidence from clinical trials and real-world experience determines the interventions to manage HFSR. In a randomized, open-label trial, advanced hepatocellular carcinoma (HCC) patients with initial sorafenib treatment were co-treated with 10% urea-based cream (UBC) plus best supportive care (BSC) or BSC alone. The results showed that the prophylactic use of UBC could reduce the incidence of HFSR and prolong the time of first onset.²⁷ In addition, there was another similar trial using combined oral nutritional supplement and sorafenib in patients with HCC, the results suggested that prophylactic HMB, L-arginine and L-glutamine supplementation effectively prevented sorafenib-associated HFSR in patients with advanced HCC.²⁸ However, these studies only provided some prophylaxis strategies but not the treatment strategy of HFSR.

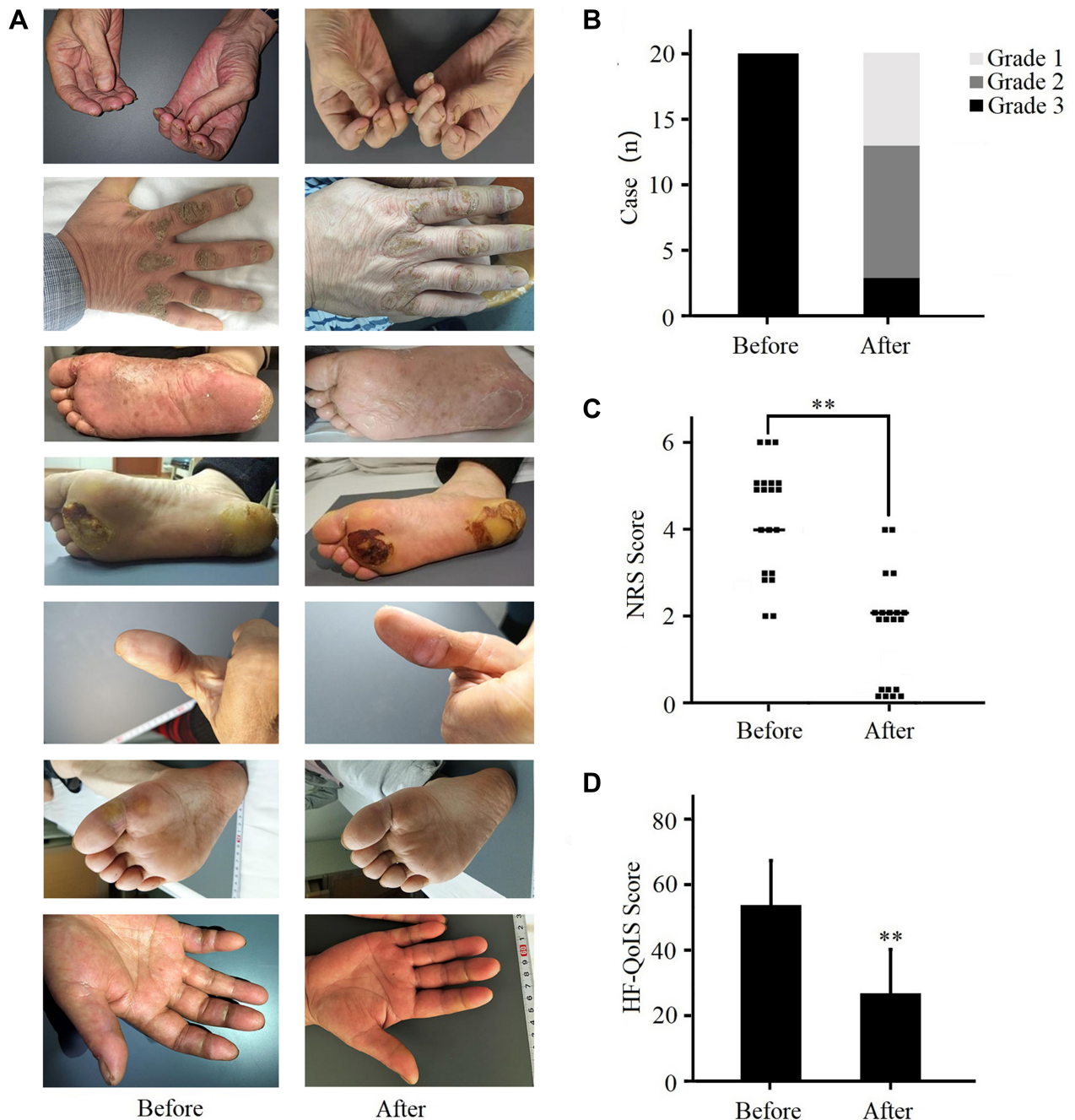


Figure 2 Evaluation of MKIs-associated HFSR through NCI (National Cancer Institute) grades, NRS score, and HF-QoLS score, respectively. **(A)** Representative photos of hands and feet of the twenty patients. Before the SND treatment: shown in the left panels; after the SND treatment: shown in the right panels. **(B)** Grading of HFSR before and after the SND treatment. **(C)** NRS score before and after the SND treatment. **(D)** HF-QoLS score before and after the SND treatment. $^{**}p < 0.01$.

Previous studies showed that modified Taohongsiwu decoction and Compound Danxiong Granules (CDG) could effectively attenuate MKIs-associated HFSR.^{29,30} However, previous topical use of Chinese herbal was applicable to all-grade HFSR especially grade 1 and 2.³¹ In this study, we reported the effectiveness of our strategy for grade 3 HFSR. Topical urea-containing moisturizing

cream, steroids, and NSAIDs were applied in accordance with the international recommendations, which were not feasible in these patients. Whereas MKIs therapy was a long-term treatment to control the disease, and these patients thus represented a group of difficult-to-treat cases. We found that administration of two weeks of SND was sufficient to achieve the remission. The median

Table 4 Comparison of Patient Characteristics in Effective and Non-effective Samples

Characteristics	Effective Treatment	Non-Effective Treatment	P-value
Sex			0.718
Male	12 (70.6%)	3 (100.0%)	
Female	5 (29.4%)	0 (0.0%)	
Age (years)	56.59 ± 12.74	64.00 ± 9.17	0.352
Cancer type			0.955
Hepatocellular carcinom	8 (47.1%)	2 (66.7%)	
Lung cancer	3 (17.6%)	1 (33.3%)	
Gastric cancer	2 (11.8%)	0 (0%)	
Colorectal cancer	1 (5.9%)	0 (0%)	
Rectal cancer	1 (5.9%)	0 (0%)	
Esophageal cancer	1 (5.9%)	0 (0%)	
Renal cancer	1 (5.9%)	0 (0%)	
MKIs type			0.504
Apatinib	3 (17.6%)	0 (0%)	
Sorafenib	7 (41.2%)	1 (33.3%)	
Regorafenib	3 (17.6%)	1 (33.3%)	
Anlotinib	3 (17.6%)	1 (33.3%)	
Lenvatinib	1 (5.9%)	0 (0%)	
Onset of grade 3 HFSR (day)	26.18 ± 15.42	26.33 ± 7.10	0.987

duration of response was less than 5 days from initiation of the SND treatment. It is less likely that the severe HFSR could be eliminated without additional novel therapeutic strategies. Alternatively, SND could be chosen to suppress MKIs-associated HFSR and extend the therapeutic window of SND.

In this study, erythema and edema in hands and feet almost disappeared in the patients, hyper-keratinization were partially relieved. As illustrated by patient No. 3, 12, 14, with severe hyper-keratinization, the SND treatment was failed to release the symptoms, indicating the SND treatment might not suitable for patients with hyper-keratinization. It has been reported that HFSR-related hand and foot symptom significantly restricted patients' daily activities, including barriers to social participation, lack of willingness to work and continue treatment.^{16,25} In addition to alleviating the symptoms, the SND treatment led to a significant lower NRS score and improved quality of life of patients. We believed that the SND treatment was an appropriate choice for most of the patients with MKIs-associated HFSR. Another situation where prophylactic treatment with the SND could be suggested.

Despite the strengths, there were several limitations of this study. First, the lack of a control group limited the ability to separate the effect of SND. Second, the sample size in this study was small. Therefore, the concept of the SND treatment in patients with HFSR should be explored in further larger scale studies. Last, the lack of biomarkers of HFSR makes the mechanistic inside remains to be explored.

Conclusions

This is a study to suggest that the SND treatment was an effective and well-tolerated treatment for MKIs-associated grade 3 HFSR patients for the first time. The results of this study showed that the SND treatment could alleviate symptoms, relieve pain and improve quality of life in HFSR patients. In addition, randomized controlled trails with large-scale, multi-center would fully determine the clinical application of the SND in MKIs-associated HFSR.

Acknowledgment

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Disclosure

The authors report no conflicts of interest in this work.

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