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Research Article

Stepwise Nursing Intervention for Hand-Foot Skin Reaction in Advanced Hepatocellular Carcinoma Patients Taking Sorafenib At Home: A Prospective Study

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1. Abstract

1.1. Background: The burden of therapy-related hand-foot skin reaction (HFSR) can reduce the benefit of treatment for patients. Evidence for the nursing management of sorafenib-related HFSR in nonclinical settings remains inadequate.

1.2. Aim: To establish Stepwise Nursing Intervention (SWNI) management to reduce the burden of therapy-related HFSR in patients with advanced Hepatocellular Carcinoma (HCC) who are taking sorafenib at home.

1.3. Methods: This study was a prospective, randomized controlled study involving informal caregivers of outpatients with advanced HCC and are receiving sorafenib. The participants were randomized into the SWNI management group (n=54) and the family caregiver group (FC, n=54). All patients with sorafenib-related HFSR were treated with 10% urea cream, which was applied to affected sites thrice a week under the SWNI or FC treatment. The primary endpoint was the incidence of grade 2 or 3 HFSR on the feet or hands.

1.4. Results: With a median follow-up time of 8.5 months, the median overall survival was 11.5 months in the SWNI group and 8.0 months in the FC group (p= 0.035). During nursing intervention management, grade 2 or higher HFSR was found in 33.3% of patients in the SWNI group, which was significantly lower than that in the FC group (57.4%) (p= 0.04). Compared with that in the FC group (31.6%), the percentage of patients discontinuing sorafenib in the SWNI group was significantly lowers (9.3%) (p=0.004), with a higher health-related quality of life.

1.5. Conclusion: SWNI management was an acceptable nursing intervention to prevent sorafenib-induced HFS from worsening and to provide the most therapeutic benefit at home.

2. Abbreviations: Hepatocellular Carcinoma: HCC; Adverse Events: AEs; Hand-Foot Skin Reaction: HFSR; Tyrosine Kinase Inhibitors: TKIs; Health-Related Quality of Life: HRQoL; Step-Wise Nursing Intervention: SWNI; Family Caregivers: FC; Institutional Review Board: IRB; Eastern Cooperative Oncology Group Performance Status: ECOG PS; Time to Progression: TTP; Overall Survival: OS.

3. Keywords: Stepwise nursing intervention; Family caregivers; Sorafenib; Hand-foot skin reaction; Hepatocellular carcinoma

4. Introduction

Hepatocellular Carcinoma (HCC) is the sixth most commonly occurring cancer, ranking fourth

as the leading cause of cancer-related mortality globally [1, 2] and second in China [3]. Most HCC patients have a poor prognosis because of the advanced stage of the disease at the time of initial diagnosis [1-4]. Small molecular tyrosine kinase inhibitors, such as sorafenib [5,6] and lenvatinib [7], can potentially improve the treatment of advanced HCC, thus prolonging life; moreover, these inhibitors have become the standard first-line systemic therapy for advanced HCC worldwide, including China [2,8].

However, dermatologic Adverse Events (AEs) occur, with Hand–Foot Skin Reaction (HFSR) being the most common AEs associated with sorafenib or lenvatinib [5-7]. HFSR comprises a group of non-life-threatening syndromes characterized by dysesthesia and tingling of the palms, fingers, and soles of the feet [9, 10]. Mild cases may continue for several days, leading to burning pain, diffuse erythema, and swelling. In severe cases, scaling, blistering, erosion, or ulcers on the skin may develop. The damage can be very painful and may interfere with even the simplest activities of daily life, such as walking or grabbing. The drugs most commonly associated with HFSR are the multi kinase inhibitors sorafenib [5, 6], sunitinib [11], regorafenib [12], and lenvatinib [7]. Frequently, the incidence of HFSR is considerably high in patients receiving these drugs, exceeding a 50% decline in health-related quality of life (HRQoL) [13]. Severe HFSR leads to poor compliance and/or discontinuation of cancer treatment [5-7, 14, 15]. Other studies demonstrated that the rate of all-grade HFSR was 65.5% and that of grade 3 HFSR was 15.5% during sorafenib treatment in patients with advanced HCC [16, 17]. Sorafenib prolongs survival in patients with advanced HCC, but its toxicity (including HFSR) reduces the advantage of sorafenib [18]. To treat these patients, topical urea cream therapy is commonly applied; regardless, evidence-based treatment strategies remain lacking [19]. Nurses are unable to identify and manage treatment-related AEs; thus, methods to communicate with patients need to be improved. However, the clinical and research focus of AE management for therapy-related HFRS has yet to be clarified, and available relevant data are rarely reported. Historical studies on nursing intervention to reduce HSFR burden related to targeted therapy remain unclear [20, 21]. Therefore, the establishment of proactive systematic nursing interventions to reduce the burden of HFSR related to targeted therapy is an urgent issue. It can ensure that patients with advanced HCC tolerate sorafenib dosage, improve their HRQoL, and prolong survival. This study describes a stepwise nursing intervention aimed at reducing the burden of sorafenib-related HFSR in outpatients.

5. Methods

5.1. Study Design and End Points

This prospective, single-set, randomized controlled study used mixed factorial design at four time points, which evaluated the efficacy of stepwise nursing intervention (SWNI) plus 10% urea cream treatment versus the Family Caregiver (FC) plus 10% urea cream treatment to reduce the burden of sorafenib-related HFSR in patients with advanced HCC who are taking sorafenib at home. The present study was conducted at the Fifth Medical Center of Chinese PLA General Hospital in China. Written informed consent was obtained from each patient. The study was conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. The primary endpoint was the incidence of grade 2 or 3 HFSR at week 12 after nursing intervention. The second endpoint included the duration of HFSR, HRQoL, percentages of patients with sorafenib dose reduction, interruption, termination, and time to progression (TTP) or overall survival (OS).

5.2. Sample Size

In a phase II trial, grade 2 or higher HFSR exhibited 68.8% incidence in patients with advanced HCC who received 10% urea cream monotherapy [22]. Owing to the potential synergistic effects, the rate of grade 2 or higher HFSR was estimated to be 53.3% after treatment with SWNI plus 10% urea cream. To achieve a power of 0.80 and a significance level of 0.05 between the two groups after nursing intervention for 12 weeks, 45 cases would be needed in each group, as determined using SAS ver. 9.4 (SAS Institute Inc., Cary, NC, USA). With a drop-out rate of approximately 15%-20%, each group would need 59 cases (i.e., a total of 108 cases).

5.3. Patients

Patients who met the following inclusion criteria participated and were enrolled in the study:

- Male or female patients with advanced HCC who developed grade 1 acute HFSR (appearing at ~0 to 1 month) who received sorafenib (400 mg b.i.d.) [19];
- Eastern Cooperative Oncology Group Performance Status (ECOGPS) ≤ 2;
- Child-Pugh class ≤ B7, total serum bilirubin level < 51.3 μmol/L, alanine amino transferase and aspartate amino transferase levels< five times the normal upper limit, adequate hematologic function (platelet count > 50×10^9/L) and hemoglobin level > 80 g/L), and adequate renal function (serum creatinine level < 1.5 times the normal upper limit);
- Life expectancy of at least 12 weeks. Patients were excluded

if they were treated with other drugs designed for specific molecular targets and had systemic skin disease and had ≥ grade 2 HFSR or other AEs ≥ grade 3 or delayed-onset HFSR (appearing at 1–3 months).

5.4. Study Process

After enrollment, patients were randomized into the SWNI group or the FC group at a 1:1 ratio. During Week 12, all patients received treatment for sorafenib-related HFSR, with 10% urea cream (Eucerin, Beiersdorf, Inc, Hamburg, Germany) applied to the affected area t.i.d., working thrice a week with the SWNI treatment (for the SWNI group) or FC treatment (for the FC group). A team of multidisciplinary health professionals (1 oncologist, 1 general practitioner, 3 nurses, 3 home care nurses, and 1 psychologist) completed the SWNI intervention, which included the following steps: assessing cases, setting objectives, selecting options and measures, and evaluating nursing interventions. (Table 1) presents the flowchart of SWNI treatment for sorafenib-related HFSR and their specific objectives. The management of Sorafenib-related HFSR is summarized in (Table 2). Management of sorafenib dose adjustment strategy for HFSR is as follows:

- For grade 1 HFSR, the dose of the targeted agent is maintained;
- If the HFSR progresses to grade 2, the dose is reduced by 50% for 7–28 d, 2 weeks after the nursing intervention;
- If HFSR progresses to grade 3, treatment dose is interrupted for 7 d until the condition improves to grades 0–1;
- In severe or persistent cases of HFSR, treatment is to be permanently discontinued after the nursing intervention.

Table 1: Flow Chart of Stepwise of Nursing Intervention for Hand-foot Skin Reaction

Stepwise	When	Where	What	Why	How
Step 1	start of treatment	Hospital	first nurse counselling session	Preparing patients to deal (adequately) with side effect at home: Preventing Side effects Monitoring Side effects Reporting and discussion Side effects Managing/relieving side effects Getting to know the patient and estimating his/her symptom self-management prolife	In-person Family caregiver present (if possible) New patient brochure symptom diary Estimate duration: 30~60 minutes
Step 2	First days at home	Home	second nurse counselling session contact	Evaluating HFSR burden and reviewing self-management strategies providing or planning professional symptom Reviewing and reinforcing adequate self-management strategies Estimating his/her self-management profile	Telephone Symptom diary Estimate duration: 10~20 minutes
Step 3	At every later hospital appointment or patient contact	Hospital	Evaluation of the need for further intervention	Reviewing file reports on the patient self-management prolife and actual symptom burden and/or consultation with clinical nu rse Planning and delivering of additional counselling sessions in hospital or at home	Assessment of patient file and/or consultation with clinical nurse Planning and delivering of further coaching intervention if necessary
Step 4	Throughout treatment	Home	Patient brochure: dealing with HFRS from Sorafenib at home	Offering information and self-care advice on possible HFRS from professionals and fellow patients Describing professionals support or resources Formulating alarm signals for contacting health care professionals	Symptom diary
Step 5	Throughout treatment	Home	Access to an on-call or online nursing serve	Offering continuous professionals supports via an approachable nursing service to discussion symptom burden. Describing professionals support or resources Formulating alarm signals for contacting health care professionals	cellphone, WeChat or email working twice a week

Table 2: Hand-Food Symptom Reaction Management: Nurse Intervention from Clinical Practice

Questionnaire items	Answer	Recommendations nurse intervention
Symptoms		
Pain from HFSR		
Moderately painful	Yes/[no]	a. 10% urea cream
Very painful	Yes/[no]	b. 10% urea cream in combination with 5% fluorouracil cream twice daily
Severity	Yes/[no]	c. temporary dose interruption or reduction of sorafenib by 50% plus analgesic (Ibuprofen) plus b.
Sensitive to pressure	Yes/[no]	Wear slippers, Avoid exercise or physical labour
Feel numbness or tingling	Yes/[no]	Vitamin B6, Give analgesics (Ibuprofen) when necessary
Burning or “hot” sensation	Yes/[no]	Reduce hand-Food contact with hot water, Soak in cold water or wear ice gloves or socks 4 times once day
Have peeling skin	Yes/[no]	10% urea cream
Have thickened or calloused skin	Yes/[no]	Soak your hand-food in warm water and wipe dry, and apply 40% urea cream twice once day
Feel swollen	Yes/[no]	Raise your hand or food at rest
Have blisters or sores	Yes/[no]	temporary dose interruption or reduction of sorafenib by 50% for 2 weeks
Daily activities Physical		
Hard to turn the door knob	Yes/[no]	Prevent skin damage on hands and feet
Difficulty performing everyday activities Mild	Yes/[no]	Avoid heavy physical labor and strenuous exercise
From time to time (unable to work)	Yes/[no]	temporary dose interruption or reduction of sorafenib by 50% for 2 weeks
Hard to drive my car	Yes/[no]	Avoid to drive car, Give analgesics (Ibuprofen) when necessary
Difficulty walking, even short distances	Yes/[no]	Wear soft insoles or Apply a nicotine patch with vasoconstriction or Give analgesics (Ibuprofen) when necessary
Self-care		
Difficulty washing myself or putting on makeup (or shaving)	Yes/[no]	Need family caregiver
Hard to put on stockings/tights (or socks)	Yes/[no]	Wear slacks and long clothes
I take longer than usual to get dressed	Yes/[no]	Need family caregiver
Difficulty putting shoes on Unable to self-care	Yes/[no]	temporary dose interruption or reduction of sorafenib by 50% for 2 weeks
Social		
My relationships with others are less amicable	Yes/[no]	Psychological help
Psychological		
Hard to fall asleep	Yes/[no]	Psychological help, Give depressant (estazolam) when necessary
Work is suffering	Yes/[no]	Psychological help
Feel helpless	Yes/[no]	Wake up the hope :HFSR is nonlife-threatening symptoms, predicts efficacy to sorafenib

5.5. Assessment

Assessment of the severity of sorafenib-related HFSR under in accordance with the Common Terminology Criteria for Adverse Events v4.0 published by the National Cancer Institute [10]. We evaluated HRQoL, including physical functioning, role limitation due to physical health, bodily pain, general health, vitality, social function, role limitation due to emotional health, and mental health associated with HFSR by using a questionnaire with visual analog scales [23]. The maximum score for each dimension was 100, and higher scores indicated better health conditions. All questionnaires were self-administered in different time (Week 0, 4, 8, and 12) via WeChat.

5.6. Ethical Aspects

The study was approved by the Institutional Review Board or the Ethics Committee of the Fifth Medical Center of Chinese PLA General Hospital (decree number: 2015017N). Informed consent was obtained from each study subject. Confidentiality was ensured, as was the ability of the participants to withdraw from the study at any time with no negative influence on their care.

5.7. Statistical Analysis

Data were analyzed using SAS v 9.4 (SAS Institute Inc., Cary, NC, USA). Categorical data were expressed as numbers (percentages) and continuous variables as either mean or median. Comparisons between groups were conducted using Student's t-test (variance homogeneity) or Satterthwaite's test (variance non-homogeneity) or the Wilcoxon rank–sum test for continuous variables and the chi-squared test for categorical variables. For the evaluation of efficacy based on the categorical variables, the Cochran–Mantel–Haenszel test was applied for the determination of the central effect. When the Breslow–Day test showed no significant central effect ($P>0.05$), the chi-squared test was directly used on the classification data. Statistical significance was assessed at the 0.05 level and defined as a two-sided $P < 0.05$.

6. Results

6.1. Patient Characteristics

From 16 January 2015 to 31 May 2018, 272 advanced HCC patients who developed grade 1 acute HFSR in taking sorafenib (400 mg b.i.d.) treatment were enrolled and screened. Of this number, 108 patients were randomized into the SWNI group (n=54) and the FC group (n=54) and received the assigned nursing intervention at least once. A total of 164 patients were excluded from the study for the following reasons: 56 ECOG > 2, 33 Child-Pugh ≥ 8, 28 ≥ grade 2 HFSR, 22 HFSR delayed onset (appears at 1~3months), 11 grade 3 AEs other than HFSR and 14 consent withdrawn (Figure 1).

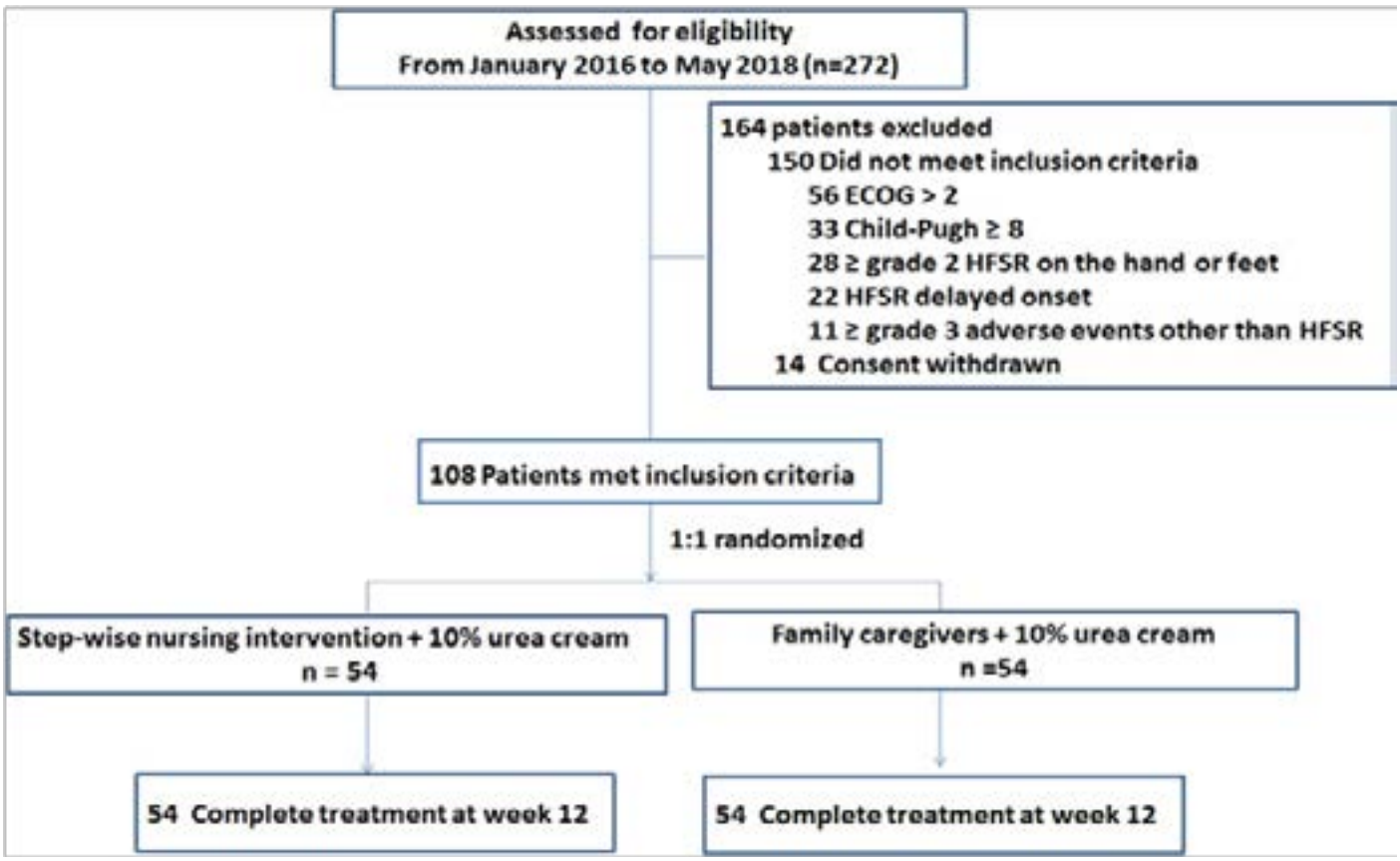

Figure 1: Flow chart of the study population

6.2. Efficacy Outcome Measures

Overall, 108 patients with advanced HCC and were receiving sorafenib were included in the final analysis. At baseline, the two groups were generally well matched demographically and clinically (Table 3).

Table 3: Baseline Demographics and Clinical Characteristics of the Studied Patients

Characteristic	Stepwise nursing intervention + 10% UC （n= 54）	Family caregivers + 10% UC （n= 54）	*p* value
Age (mean ±SD)	51.2±11.6	52.6±9.8	0.735
Male / Female, no. (%)	43 (79.6) / 11 (20.4)	44 (81.5) /10 (18.5)	0.808
Child-Pugh class, no. (%)			0.968
A5	17 (31.5)	16 (29.6)	
A6	23 (42.6)	23 (42.6)	
B7	14 (25.9)	15 (27.8)	
Platatet count (×10 9/L)	101 ± 48.7	116 ± 53.3	0.682
Total bilirubin (umoL /L)	21.6 ± 18.3	23.3 ± 11.8	0.481
Prothrombin Time (s)	10.3 ± 7.3	11.1 ± 6.9	0.672
ECOG PS, no (%)			0.972
0	12 (22.2)	11 (20.4)	
1	36 (66.7)	37 (68.5)	
2	6 (11.1)	6 (11.1)	
Hand-food symptom reaction, no (%)			0.773
feet	51 (94.4)	49 (90.7)	
hand or fingers	45 (83.3)	47 (87.0)	
Note: UC, urea cream			

All 108 enrolled patients were included in the intention-to-treat analysis. The median follow-up time was 8.5 months (range: 3.0–28.0 months), the advanced HCC patients receiving sorafenib (400 mg b.i.d.) and who developed grade 1 acute HFSR and received SWNI plus 10% urea cream had a median OS of 11.5 months (95 % CI: 6.5–14.5 months), whereas those receiving FC plus 10% urea cream had a median of 8.0 months (95%CI: 5.5–11.5 months) (log-rank test, P = 0.0353; (Figure 2A). Moreover, the median post-nursing intervention TTPs were 6.0 months (95%CI: 5.0–7.0 months) in the SWNI group and 5.5 months (95%CI: 3.6–7.4 months) in the FC group (Figure 2B). No significant difference was found between the groups (p = 0.5441, log-rank test). The data were also analyzed for between-group comparisons of the efficacy evaluation of all endpoints and are listed in (Table 4). The incidence of the FC group with grade 2 or higher HFSR was significantly higher than that of the SWNI group [FC: 31/54 (57.4%) vs. SWNI: 18/54 (33.3%); p = 0.04]. Compared with the patients receiving FC plus 10% urea cream, those treated with SWNI plus 10% urea cream had a low proportion of advanced HFSR on their feet (33.3% vs. 57.4%, p = 0.04). Moreover, the frequencies of grade ≥2 HFSR on the hands were 38.9% and 53.7% (p = 0.38), respectively. The median time to onset of grade 2 or higher HFSR was 29 d (95%CI: 15–36 d) in the SWNI group, which was significantly longer than the median time to onset of grade 2 or higher HFSR (21 d) (95%CI: 11–29 d) in the FC group (p = 0.04, log-rank test). After SWNI or FC treatment for 12 weeks, 5/54 (9.3%) patients in the SWNI group received a reduced dose of sorafenib; meanwhile, 10/54 (18.6%) patients received a reduced dose of sorafenib, 5/54 (9.3%) patients received a dose interruption, and 2/54 (3.7%) patients (1 case with persistent grade 3 HFSR on the soles of the feet accompanied by severe anxiety and another case with severe grade 3 HFSR on the hands and the soles of the feet) terminated treatment. Compared with the FC group, the SWNI group showed a significantly lower rate of discontinued sorafenib (p=0.004, (Table 4). The median duration of sorafenib treatment was 80 d (range: 10-94 d) in the SWNI group and 69 d (range: 6-84 d) in the FC group; no significant difference was indicated (p = 0.16).

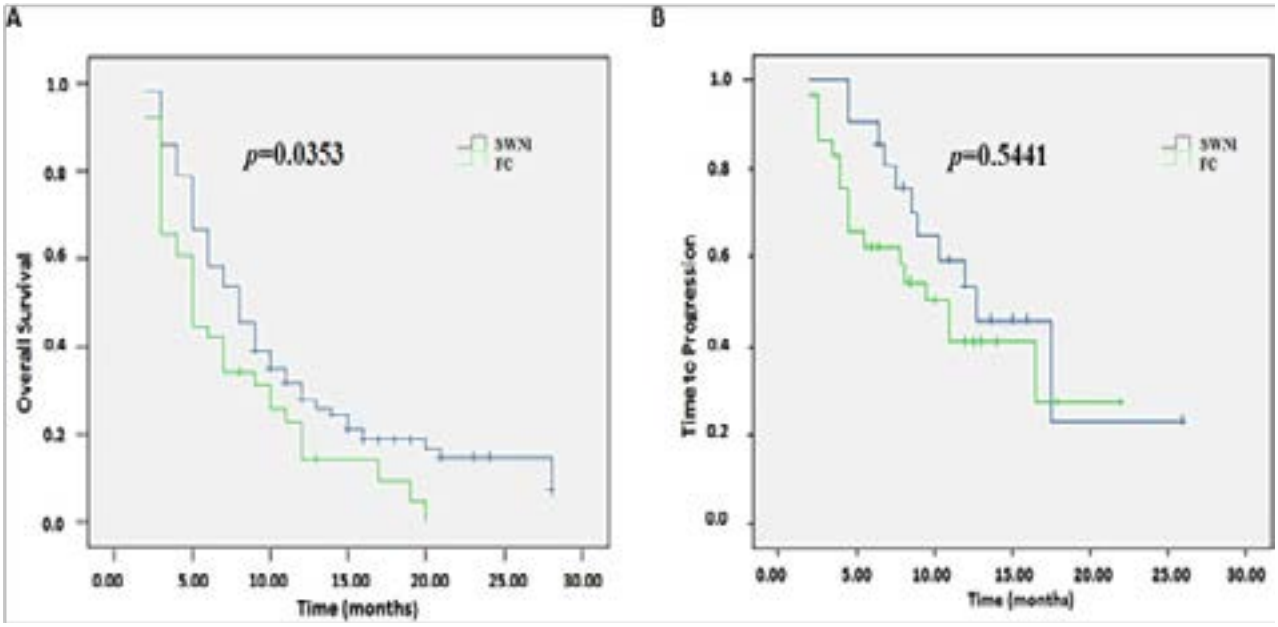

Figure 2: Kaplan–Meier estimates of OS and TTP. A. Kaplan–Meier survival curves are shown for 54 patients treated with stepwise nursing intervention plus 10% urea cream (SWNI) and 54 patients with family caregivers plus 10% urea cream (FC) in patients with advanced HCC who are receiving sorafenib. Median OS is significantly longer (p = 0.0353) in the SWNI group than in the FC group; B. Kaplan–Meier survival curves show no significant difference in TTP between the two groups (p= 0.5441). OS, overall survival; TTP, time to progression.

Table 4: Comparison of Efficacy Evaluation of All Endpoints

Endpoints	**SWIN + 10% UC （n= 54）**	**FC + 10% UC （n= 54）**	**χ^2**	***p* value**
HFSR on the hand or fingers			3.078	0.38
Grade 0, no. (%)	5 (9.3)	3 (5.5)		
Grade 1, no. (%)	28 (51.9)	22 (40.8)		
Grade 2, no. (%)	11 (20.3)	12 (22.2)		
Grade 3, no. (%)	10 (18.5)	17 (31.5)		
Mild HFSR, no. (%)	33 (61.1)	25 (46.3)	2.383	0.12
Advanced HFSR, no. (%)	21 (38.9)	29 (53.7)		
HFSR on the feet			8.337	0.04
Grade 0, no. (%)	2 (3.7)	2 (3.7)		
Grade 1, no. (%)	34 (62.9)	21 (38.9)		
Grade 2, no. (%)	14 (25.9)	18 (33.3)		
Grade 3, no. (%)	4 (7.5)	13 (24.1)		
Mild HFSR, no. (%)	36 (66.7)	23 (42.6)	6.313	0.01
Advanced HFSR, no. (%)	18 (33.3)	31 (57.4)		
Onset of grade 2 or 3 HFSR, median (range)	29 (95% CI 15-36)	21 (95% CI 11-29)		0.04
Sorafenib treatment				
Duration, median (range)	80 (95% CI 10-84)	69 (95% CI 6-84)		0.16
Dose reduction, no. (%)	5 (9.3)	10 (18.6)	8.22	0.004
Interruption, no. (%)	0 (0)	5 (9.3)		
Termination, no. (%)	0 (0)	2 (3.7)		

Note: SWNI, stepwise nursing intervention; FC, family caregivers; UC, urea cream; HFSR, hand-food symptom reaction; Mild HFSR was defined as a HFSR grade 0 or HFSR grade 1; advanced HFSR as a HFSR grade 2 or HFSR grade 3.

6.3. Assessments Health-Related Quality of Life

Of the 108 patients available for efficacy analysis, 51 (94%) patients submitted their responses to questionnaires assessing HRQoL after nursing intervention for 4 weeks in the SWNI group and 49 (90.7%) patients in the FC group. Questionnaires assessing HRQoL at Week 12 after the start of SWNI mostly for physical disorders, social disorders, and pain associated with HFSR in HRQoL assessment were significantly different between the two groups ($p< 0.05$, (Table 5). The SWNI group showed potential for improvement in the physical and social quality of life.

Table 5: Time-point Comparison of Changes in HRQOL Domain Scores in the Two Groups

SF-36 domain score	SWNI + 10% urea cream mean ± SD	FC + 10% urea cream mean ± SD	p value
PF			
At entry	66.4±24.7	67.1±30.4	0.6189
Week 4	65.8±20.3	63.4±19.2	0.4264
Week 8	64.6±25.3	59.7±24.3	0.0638
Week 12	65.1±19.6	56.2±23.3	0.0416
RP			
At entry	77.1±26.3	76.8±21.7	0.5892
Week 4	75.6±21.3	77.1±23.4	0.3714
Week 8	72.9±19.1	67.1±19.1	0.0812
Week 12	72.1±21.6	59.1±22.3	0.0329
BP			
At entry	73.1±29.1	74.2±21.7	0.6723
Week 4	68.9±22.5	60.1±16.8	0.0387
Week 8	65.4±19.3	57.8±19.3	0.0219
Week 12	66.2±23.6	55.3±22.7	0.0025
GV			
At entry	53.2±12.1	54.1±15.7	0.4728
Week 4	52.7±10.3	52.4±17.3	0.7631
Week 8	50.9±16.5	50.4±13.8	0.5729
Week 12	51.8±14.1	51.1±13.7	0.6291
VT			
At entry	46.7±17.3	47.1±16.3	0.6391
Week 4	45.3±14.1	45.6±11.5	0.4819
Week 8	44.7±12.7	43.1±10.6	0.2897
Week 12	44.5±10.7	40.1±9.8	0.0661
SF			
At entry	74.2±22.1	72.6±18.5	0.3168
Week 4	73.6±17.4	72.1±14.3	0.4163
Week 8	72.8±15.6	71.8±20.1	0.3367
Week 12	72.2±12.6	70.4±13.2	0.1935
RE			
At entry	70.1±18.2	69.3±20.4	0.4926
Week 4	71.4±16.8	68.6±17.3	0.2658
Week 8	70.8±15.3	65.8±14.8	0.0411
Week 12	69.5±13.7	60.6±17.2	0.0405
MH			
At entry	60.7±12.3	61.4±14.7	0.6219
Week 4	61.3±13.4	60.6±15.3	0.2892
Week 8	60.8±15.1	58.7±12.7	0.1726
Week 12	60.5±14.8	54.7±16.1	0.0411

Note: HRQOL, health-related quality of life; SF-36, Short Form 36; SWNI, step-wise nursing intervention; FC, family caregivers; PF, physical functioning; RP, physical role functioning; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, emotional role; MH, mental health.

7. Discussion

HFSR is one of the most common AEs in patients with advanced HCC who are treated with sorafenib or lenvatinib. HFSR is also the most common cause of reductions in sorafenib or lenvatinib dose. However, most management strategies for sorafenib-related HFSR discussed in the literature were based on experience rather than evidence [19], and only two small clinical studies investigated HFSR management and identified techniques [14, 21]. The reason for the current lack of evidence for HFSR management strategies may be that placebo-controlled clinical trials for treated cancer patients with AEs are not generally approved by the ethics committee. To the best of our knowledge, no previous studies have systematically evaluated the ability of the nursing intervention to prevent and/or reduce the burden of sorafenib-related HFSR in outpatients. In this study, we developed a nursing intervention, referred to as SWNI, which was aimed at reducing the burden of therapy-related HFSR in advanced HCC patients taking sorafenib at home. SWNI included in-person evaluation and guidance, telephone counseling, and WeChat access to nursing support. The results of the present study demonstrate that SWNI management can effectively prevent the progression of HFSR from grade 1 to grade 2 or higher, compared with FC treatment in patients with advanced HCC undergoing sorafenib therapy. In addition, HFSR progression from grade 1 to grade 2 or higher was longer in the SWNI group than in the FC group. The use of SWNI in the management of sorafenib-related HFSR can also effectively reduce pain caused by HFSR and improve the quality of life of patients. Notably, SWNI can significantly reduce the number of sorafenib dose reductions or discontinued cases. For sorafenib-related HFSR, the greatest advantage of SWNI management over FC treatment is that the former is based on clinical practice, such as personalized management of HFSR with various ointments (mild analgesia, local anti-inflammatory) for unbroken skin, emollients, and oatmeal baths. This prospective study suggests that the SWNI management of patients with advanced HCC who are receiving sorafenib employ We Chat to assist individuals better understand their illness, enhance their self-management behaviors, as well as ultimately improve their HRQoL (Table 5), thereby reducing the burden of illness at home. Thus, for patients with advanced HCC who are being treated with sorafenib, early SWNI management is critical in order to extend the time before HFSR progresses from grade 1 to grade 2 or higher to reduce its risk through Week 12; such management also improves the survival of patients with advanced HCC who are under sorafenib therapy. As indicated in this study, the SWNI management of sorafenib-related HFSR significantly improved the survival of patients with advanced HCC under sorafenib therapy because of multiple factors. The most important factor could be SWNI management, which ensures that patients have access to communication and a high standard of care; moreover, the treatment provides a warm environment for patients under sorafenib therapy to express any fear and anxiety. Second, SWNI management can eliminate the fear of advanced HCC in patients, implying that most patients with advanced HCC adhere to active treatment to survive regardless of the presence of serious AEs. Over adherence may increase the severity of certain AEs and/or lead to untruthful reporting of treatment-related AEs induced by excessive fear of therapy-related HFSR. By contrast, some patients may also adhere poorly, consequently compromising efficacy. Thus, without scientific and effective nursing intervention management, patients may not realize the most therapeutic benefit. Finally, the clinical benefits of SWNI management may largely decrease the chance of sorafenib dose reduction caused by HFSR during treatment. The present study extends our current knowledge that SWNI management uses a personalized approach of encouragement, rather than broad guidance, to deliver programmatic interventions and recommendations to patients, unlike those currently used in traditional care. This study also a great opportunity to rethink nursing interventions that target the burden of sorafenib-related symptoms at home. The distinct values of the results generated in the present study imply the importance of developing SWNI management aimed at reducing the burden of sorafenib-related HFSR outside the clinical setting. These encouraging results indicate that SWNI management can improve the burden of HFSR in advanced HCC patients receiving sorafenib, thus providing the most therapeutic benefit.

Undoubtedly, our SWNI management also has several limitations. First, the limitation of a single-center study may mask the effect of SWNI in these areas. Second, the observation was conducted within a short duration. Last, the present study did not investigate the underlying mechanisms of how to reduce the burden of therapy-related HFSR and possible SWNI management as a personalized approach of encouragement based on the self-management records of the patient. To validate SWNI, multicenter randomized controlled trials would be necessary for further research.

8. Conclusion

In conclusion, SWNI management prevented the aggravation of HSFR induced by sorafenib treatment in advanced HCC patients, improved HRQoL, and provided the most therapeutic benefit. SWNI management may thus be considered as a standard of nursing intervention in patients with advanced HCC who are receiving sorafenib at home.

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