pISSN 1598-2998, eISSN 2005-9256

https://doi.org/10.4143/crt.2024.080 Cancer Res Treat. 2024;56(4):1050-1057

Original Article

Therapeutic Effect of Anti-inflammatory Tripeptide Cream in Hand-Foot Syndrome/Skin Reaction Related to Anticancer Drugs: A Randomized, Double-Blind, Placebo-Controlled Pilot Trial

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Purpose Hand-foot syndrome (HFS) and hand-foot skin reaction (HFSR) are relatively common toxicities that interfere with the quality of life (QoL) of patients with cancer. Anti-inflammatory tripeptide cream (ATPC) is a complex formulation of anti-inflammatory tripeptides, the CD99-agonist Binterin and the Wnt-antagonist Winhibin. The present study aimed to assess the therapeutic effects of ATPC in HFS/HFSR associated with anticancer drugs.

Materials and Methods This was a single-center, randomized, double-blind, placebo-controlled trial. Patients who developed grade 1 HFS/HFSR after systemic anticancer treatments were enrolled, and randomly assigned to receive either ATPC or placebo cream (PC) and followed up at 3-week intervals for up to 9 weeks. Primary endpoint was the development of grade ≥ 2 HFS/HFSR.

Results Between April 2019 and July 2022, 60 patients (31 in the ATPC and 29 in the PC group) completed the study. The incidence of grade ≥ 2 HFS/HFSR was significantly lower in the ATPC than in the PC group (25.8% vs. 51.7%, p=0.039). The ATPC showed trends towards a better QoL score, assessed by a HFSR and QoL questionnaire at 9 weeks (26.0 vs. 29.9, p=0.574), and a lower frequency of discontinuation, interruption, or dose reduction of anticancer drugs (51.6% vs. 58.6%, p=0.586) than the PC group over 9 weeks, though without statistical significance.

Conclusion Our results showed that ATPC significantly decreased the development of grade ≥ 2 HFS/HFSR in patients already with HFS/HFSR. Therefore, ATPC may be an effective treatment for HFS/HFSR associated with anticancer drugs.

Key words Hand-foot syndrome, Hand-foot skin reaction, Anticancer drug, Anti-inflammatory tripeptide cream

Introduction

Hand-foot syndrome (HFS) and hand-foot skin reaction (HFSR) are common dermatologic adverse events that are often associated with numerous cytotoxic chemotherapeutic agents and molecular-targeted multi-kinase inhibitors (MKIs) [1-4]. Although these dermatologic toxicities on hands and feet are not life-threatening, they are associated with compromised quality of life (QoL), increased possibility of dose reduction or discontinuation of anticancer drugs, and reduced efficacy of cancer treatments [1-4].

HFS, also known as palmar-plantar erythrodysesthesia, is associated with cytotoxic chemotherapeutic agents, such as fluoropyrimidines, pegylated liposomal doxorubicin, and taxanes [1-4]. HFSR is caused by MKIs, including sorafenib, sunitinib, axitinib, pazopanib, and regorafenib [1-3]. HFS is characterized by diffuse, symmetrical paresthesia, erythema, and desquamation of the palms and soles, whereas HFSR is characterized by more localized, well-demarcated yellow plaques in friction-prone areas, such as the interdigital web space and lateral aspect of the feet. The onset of symptoms on the hands and feet in HFS shows a dose-dependent pattern occurring several weeks to months after starting chemotherapy, whereas symptoms of HFSR show a dose-independent pattern occurring within days after starting MKI. However, the pathogenesis of HFS and HFS/HFSR still remains unclear. HFS is an inflammatory process caused by cyclooxygenase (COX)-2 activation due to the accumulation of chemotherapeutic agents and metabolites in sweat glands and keratinocytes. The main mechanisms of HFSR are considered to involve the disruption of the balance of vascular and epithelial trauma and repair in areas of pressure and friction through effects on a variety of molecular signaling pathways. Therefore, the treatment of HFS/HFSR

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Received January 22, 2024 **Accepted** June 4, 2024 **Published Online** June 5, 2024

is based on reducing local inflammation, decreasing hyperkeratosis, and preventing hyperplasia of epithelial cells. Several clinical trials have evaluated different drugs, including pyridoxines, topical urea creams, and COX-2 inhibitors, for the management of HFS/HFSR; however, the effectiveness of prevention and treatment strategies remains controversial.

Anti-inflammatory tripeptide cream (ATPC) is a combination formula of anti-inflammatory tripeptides (Palmitoyl sh-Tripeptide-4 Amide [Binterin] and Palmitoyl Tripeptide-53 Amide [Winhibin]), which have been used commercially as cosmetic ingredients in South Korea, United States, and other countries [5,6]. Binterin is a tripeptide composed of three amino acids derived from CD99, which is an anti-inflammatory protein that regulates the activation of nuclear factor kappa B and release of inflammatory cytokines, such as tumor necrosis factor-α and interleukin-1 in damaged skin [7]. It has anti-inflammatory, analgesic, and smoothing effect. Winhibin is a tripeptide derived from the secreted frizzled-related protein 5, which inhibits the Wnt signaling pathway and has anti-inflammatory and anti-pigmentation effects [8,9]. Both peptides have been shown to exert beneficial effects on skin barrier function. Also, these tripeptides are ultra-low-molecular-weight peptides of less than 500 Da that can be effectively absorbed into the skin [10].

The current pilot study aimed to investigate the therapeutic effects of ATPC on HFS/HFSR associated with anticancer drugs, and to determine the feasibility of a larger trial.

Materials and Methods

1. Study design and population

This single-center, randomized, double-blind, placebo-controlled trial was conducted at Chungbuk National University Hospital to assess whether ATPC could prevent the onset of grade 2 or higher HFS/HFSR (Fig. 1). Patients with advanced cancer who developed grade 1 HFS/HFSR, according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) ver. 5.0 [11], during treatment with chemotherapeutic agents or MKI were enrolled in the study. Patients were required to have a life expectancy of ≥ 3 months and adequate hematologic, hepatic, and renal function. Patients with pre-existing dermatologic conditions that could affect the hands or feet, and concurrent use of non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroid were excluded; however, use of antiemetic dexamethasone or prophylactic use of steroids for hypersensitivity reactions to chemotherapy were allowed.

The primary objective was to assess the efficacy of ATPC relative to that of a placebo cream (PC) in preventing HFS/HFSR of grade 2 or higher within a 9-week period. Secondary endpoints included QoL assessments, the percentage of patients with dose reductions/interruptions and discontinuation, and the relative dose intensity of anticancer drugs.

2. Treatment regimens

PC was a cream that only had a moisturizer, excluding the anti-inflammatory tripeptides (Binterin and Winhibin) of ATPC. ATPC and PC were applied twice a day, 1.0 to 1.5 g (approximately 1 teaspoon), to the hands and feet for 9 weeks. No other skin care product was allowed on the hands or feet during the study. If grade 2 or higher HFS/HFSR occurred, ATPC and PC were combined with the treatment recommended in the guidelines [1]. For grade 2 events, topical corticosteroids for painful blisters and topical analgesics could be applied twice daily. For grade 3 events, dose interruptions of anticancer drugs could be required in addition to oral analgesics, such as NSAIDs and opioids.

3. Toxicity and QoL assessments

HFS/HFSR grading and QoL assessment were performed at baseline and triweekly for 9 weeks (the visits numbered as 1, 2, and 3). HFS/HFSR was graded by investigators according to the NCI-CTCAE ver. 5.0 [11]. Grade 1 HFS/HFSR was defined as minimal changes in the skin or dermatitis without pain; grade 2 was defined as changes in the skin with pain, limiting instrumental activities of daily living (ADL); and grade 3 involved severe skin changes with pain, limiting self-care and ADL. Patients completed a validated Korean version of the hand-foot skin reaction and quality of life (HF-QoL) questionnaire, which consisted of 38 questions concerning 10 symptoms each for the hands and feet and 18 daily activities (S1 Table) [12,13].

4. Statistical analysis

Data were reported as numbers and percentages for categorical variables and as means and standard deviations for numerical variables. The chi-square test was used to compare percentages, and the Student's t test was used to compare mean values. All statistical analyses were two-sided, and $p < 0.05$ was considered statistically significant. SPSS ver. 21 software was used for statistical analysis (IBM Corp., Armonk, NY).

Results

1. Patient characteristics

Between April 2019 and July 2022, 68 patients who developed grade 1 HFS/HFSR during treatment with chemotherapeutic agents or MKIs were randomized. Of these, eight were excluded from the analyses due to discontinuation of

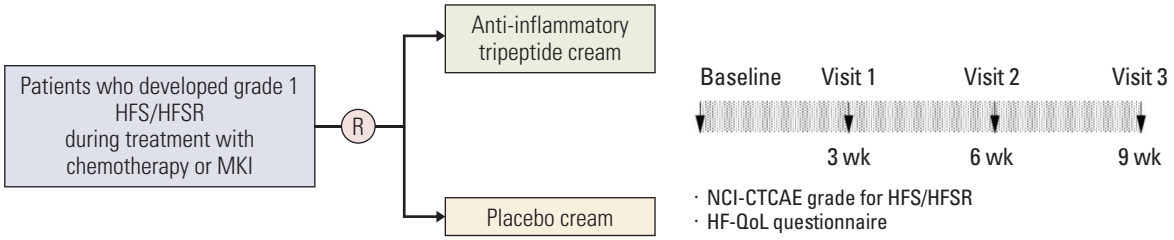


Fig. 1. Study design. HF-QoL, hand-foot skin reaction and quality of life; HFS, hand-foot syndrome; HFSR, hand-foot skin reaction; MKI, multikinase inhibitor; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

Table 1. Patient characteristics

	ATPC (n=31)	PC (n=29)	p-value
Age (yr), median (range)	65.0 (39.0-80.0)	57.0 (40.0-78.0)	0.468
Sex			
Male	17 (54.8)	17 (58.6)	0.768
Female	14 (45.2)	12 (41.4)	
ECOG PS			
0	4 (12.9)	3 (10.3)	0.871
1	24 (77.4)	24 (82.8)	
2	3 (9.7)	2 (6.9)	
Intent of systemic therapy			
Adjuvant	10 (32.3)	10 (34.5)	0.855
Palliative	21 (67.7)	19 (65.5)	
Anticancer drug			
Chemotherapeutic agent	28 (90.3)	25 (86.2)	0.500
MKI	3 (9.7)	4 (13.8)	
Regimen			
Monotherapy	13 (41.9)	15 (51.7)	0.119
Combination therapy	18 (58.1)	14 (48.3)	

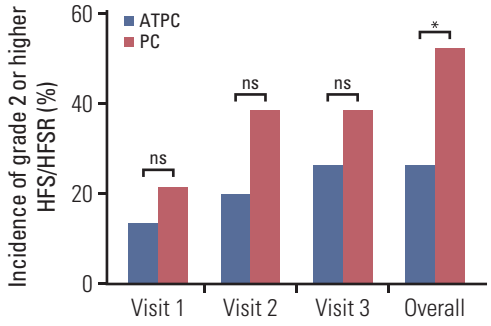
Values are presented as numbe (%) unless otherwise indicated. ATPC, anti-inflammatory tripeptide cream; ECOG PS, Eastern Cooperative Oncology Group performance status; MKI, multikinase inhibitor; PC, placebo cream.

the anticancer drugs that caused HFS within 9 weeks. Sixty patients (31 in the ATPC group and 29 in the PC group) completed the study and were included in the analysis.

Baseline characteristics of the patients are presented in Table 1. There was no significant difference in age, sex, Eastern Cooperative Oncology Group performance status, intent of anticancer treatments, or type of anticancer drugs (chemotherapeutic agent vs. MKI, monotherapy vs. combination therapy) between the ATPC and PC groups. Of all the patients analyzed, 88.3% were treated with chemotherapeutic agents and 53.3% were treated with combination chemotherapy. All patients receiving chemotherapeutic agents were treated with fluoropyrimidine-based regimens: 28 in the ATPC group with capecitabine, and in the PC group, 20 with capecitabine, two with 5-fluorouracil, and two with S-1. Combination therapy included platinum combinations for all 18 patients in the ATPC group and 11 in the PC group, while the remaining three patients in the PC group received capecitabine and lapatinib. There were no significant differences in regimens between the two groups (p=0.119).

2. Prevention of HFS/HFSR of grade 2 or higher

Twenty-three patients (38.3%) developed grade 2 or higher HFS/HFSR. Only one patient in the PC group who was treated with capecitabine developed grade 3 HFS. Following the baseline evaluation after grade 1 HFS/HFSR occurred, the incidence of grade 2 or higher HFS/HFSR was lower in the ATPC group than in the PC group at visit 1 (12.9% vs. 20.7%), visit 2 (19.4% vs. 37.9%), and visit 3 (25.8% vs. 37.9%) (Fig. 2). The overall incidence of grade 2 or higher HFS/HFSR within a 9-week period was significantly lower in the ATPC group than in the PC group (25.8% vs. 51.7%, p=0.039) (Fig. 2).



Incidence of grade 2 or higher HFS/HFSR	No. of patients (%)		p-value
	ATPC (n=31)	PC (n=29)	
Visit 1 (after 3 wk)	4 (12.9)	6 (20.7)	0.419
Visit 2 (after 6 wk)	6 (19.4)	11 (37.9)	0.111
Visit 3 (after 9 wk)	8 (25.8)	11 (37.9)	0.313
Overall	8 (25.8)	15 (51.7)	0.039

Fig. 2. Incidence of grade 2 or higher HFS/HFSR. ATPC, anti-inflammatory tripeptide cream; HFS, hand-foot syndrome; HFSR, hand-foot skin reaction; ns, not significant; PC, placebo cream. *p < 0.05.

3. HF-QoL and dose modification of anticancer drugs

QoL scores of hands, feet, and daily activities, and the overall score in the ATPC group tended to be lower than those in the PC group, indicating a better HF-QoL (Fig. 3, S2 Table). The ATPC group tended to have better overall HF-QoL scores than the PC group at visit 3, although the difference was not statistically significant (26.0 vs. 29.9, p=0.574) (Fig. 3D, S2 Table). While the HF-QoL scores in the ATPC group tended to be lower than those in the PC group from baseline before the application of ATPC or PC, the HF-QoL scores persisted for the whole of 9 weeks (Fig. 3, S2 Table, S3 Fig.).

The ATPC group showed a lower overall frequency of discontinuation, interruption, and dose reduction of anticancer drugs than the PC group; however, the difference was not statistically significant (51.6% vs. 58.6%, p=0.586). There were no significant differences between the two groups in the proportions of patients undergoing discontinuation, interruption, or dose reduction of anticancer drugs, as well as in dose intensity (Table 2).

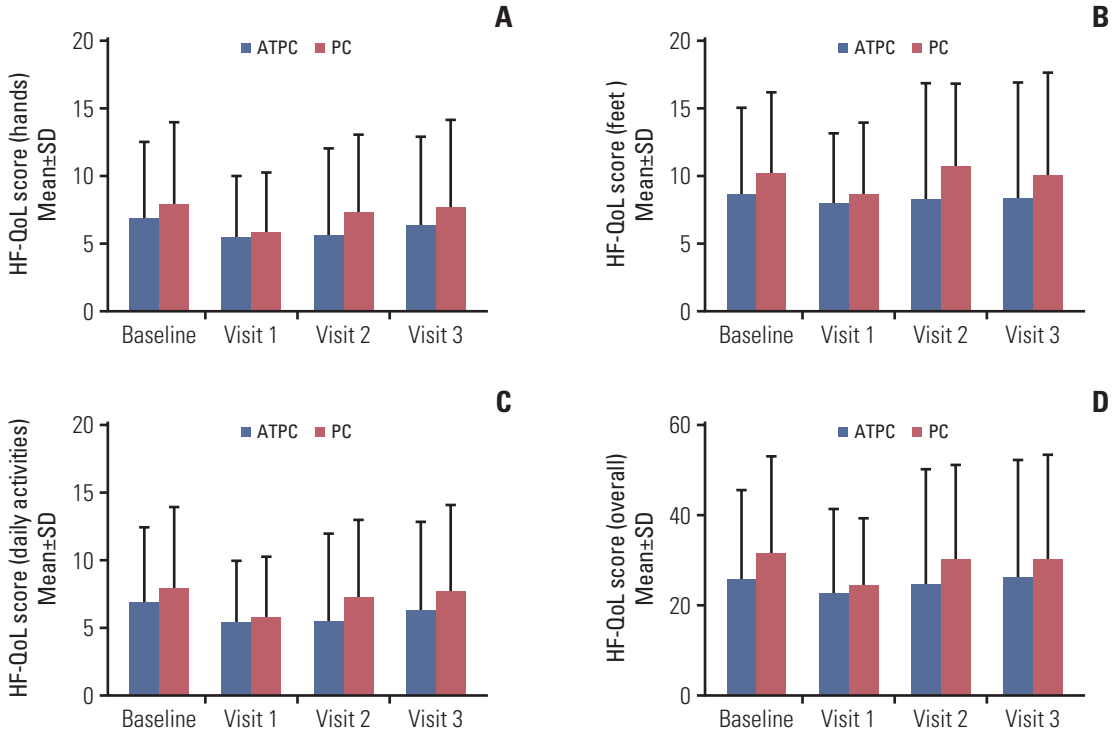


Fig. 3. HF-QoL score of hands (A), feet (B), daily activities (C), and overall by treatment group (D). ATPC, anti-inflammatory tripeptide cream; HF-QoL, hand-foot skin reaction and quality of life; PC, placebo cream; SD, standard deviation.

Table 2. Dose modification of anticancer drug by treatment group

	ATPC (n=31)	PC (n=29)	p-value
Dose modification	16 (51.6)	17 (58.6)	0.586
Discontinuation	0	1 (3.4)	NA
Interruption	3 (9.7)	3 (10.3)	0.931
Dose reduction	15 (48.4)	16 (55.2)	0.599
Dose intensity (%)	87.3±15.3	85.7±15.8	0.698

Values are presented as number (%) or mean±SD. ATPC, anti-inflammatory tripeptide cream; NA, not applicable; PC, placebo cream; SD, standard deviation.

Discussion

This study was the first to demonstrate the efficacy of ATPC in the treatment of HFS/HFSR related to chemotherapeutic agent or MKI. Development of moderate-to-severe HFS/HFSR in the patients was significantly lower in the ATPC group than in the PC group. The ATPC group showed a better HF-QoL than the PC group, and the proportion of patients who reduced, interrupted, or discontinued their anticancer drugs tended to be lower in the ATPC group than in the PC group, although this difference was not statistically significant.

Several agents have been investigated for the management of HFS/HFSR, based on the pathogenesis of COX inflammatory-type reactions, impairment of wound repair mechanisms, and histopathological findings, such as hyperkeratosis, epidermal necrosis, and dermal inflammation [1-4]. Pyridoxine, celecoxib, and urea-based creams are the most widely studied treatment strategies for HFS and HFSR. Pyridoxine is a relatively non-toxic and inexpensive treatment, and its metabolite, pyridoxal, accelerates skin barrier repair and prevents epithelial hyperplasia [14-17]. Celecoxib is a non-steroidal anti-inflammatory COX-2 inhibitor that has been widely investigated in the management of HFS/HFSR, since HFS is a type of inflammation caused by COX-2 overexpression [18-21]. Urea cream is a topical agent that has no systemic effects and is readily available and inexpensive. It has keratolytic properties, softens hyperkeratotic areas, and reduces epidermal proliferation [22-25]. A recent meta-analysis reported that celecoxib and urea cream were both effective in preventing HFS/HFSR in patients receiving chemotherapeutic agents or MKIs, while pyridoxine failed to show significant benefits [26]. In particular, celecoxib was found to be more effective in preventing capecitabine-induced HFS while urea cream was more beneficial in preventing moderate-to-severe sorafenib-induced HFSR. Considering the pathogenesis of HFS/HFSR, COX-2 inhibitors are effective for HFS, which is mainly caused by COX-2 inflammatory reaction, and urea cream is effective for HFSR, which is mainly caused by hyperkeratosis due to the impairment of the skin barrier mechanism. However, considering the several causative mechanisms of HFS/HFSR and the side effects associated with long-term use of current treatments, novel preventive and therapeutic measures are still required. Celecoxib is associated with long-term cardiovascular or upper gastrointestinal side effects upon long-term use [27,28], and does not have topical keratolytic and moisturizing effects. Urea cream does not have anti-inflammatory effects. For moderate-to-severe HFS/HFSR, the use of topical corticosteroids is recommended in order to directly reduce inflammation and irritation. However, long-term use of topical corticosteroids over weeks to months may cause local side effects, such as skin thinning, easy bruising, prominent capillaries, or pustular psoriasis [29]. Therefore, conventionally applied drugs, such as celecoxib, urea cream, or topical corticosteroids, have limitations for long-term use and for preventive strategies or treatment of mild HFS/HFSR.

ATPC is a combination of the anti-inflammatory tripeptides Binterin and Winhibin. It has anti-inflammatory, analgesic, smoothing and skin barrier function and is a topical agent with no systemic effect that can control the various pathogenic and histopathological findings of HFS/HFSR. Most previous studies on HFS/HFSR had focused on prophylactic strategies [14-26], and very few focused on therapeutic strategies for HFS/HFSR [30]. When ATPC was applied to mild HFS/HFSR that occurred during systemic cancer treatment with chemotherapeutic agents or tyrosine kinase inhibitor, it not only lowered the frequency of moderate or severe development but also showed improvement in mild HFS/HFSR while continuing the anticancer treatment (S4 Fig.). Therefore, ATPC is expected to be an effective prophylactic strategy for HFS/HFSR and for the treatment of mild HFS/HFSR.

The final goal of HFS/HFSR management is to improve the patient's QoL as well as anticancer effects through appropriate anticancer drug administration without decreasing the dose density or discontinuation. In our study, the HF-QoL questionnaire specific to HFS/HFSR was used to meas-

ure QoL. The HF-QoL questionnaire was developed to measure HFS/HFSR symptoms associated with anticancer drugs and their effect on daily activities [10,11]. The ATPC group showed better HF-QoL than the PC group, which remained consistent over 9 weeks. However, the baseline HF-QoL tended to be lower in the ATPC group and showed no statistically significant improvement over 9 weeks. Furthermore, the grading of HFS/HFSR was assessed by the investigator at the clinic, and HF-QoL questionnaires were completed by the patients at the clinic during each visit. The recall period for adverse events or QoL encompassed the entire period from the last clinic visit. In many cases, patients may not be able to fully reflect on their experiences of HFS/HFSR and QoL over a 3-week period. Therefore, a daily self-reported diary would be more accurate for the assessment of HFS/HFSR and QoL. In terms of maintaining an appropriate dose of anticancer drugs, which is the final goal of HFS/HFSR management, the ATPC group had a lower rate of dose reduction, interruption, or discontinuation of anticancer drugs, and the dose intensity was higher than that in the PC group; however, statistical significance was not observed. Dose reduction of anticancer drug was recommended for patients who developed grade 3 HFS/HFSR or recurrent grade 2 HFS/HFSR. However, there was only one patient who developed grade 3 HFS/HFSR, and the study period was relatively short to determine the recurrence of grade 2 or higher HFS/HFSR. Therefore, there was no significant difference in dose modification of anticancer drug between the ATPC and PC groups. Prospective clinical trials with a large number of patients and long-term follow-up would be required in future to determine whether active prophylaxis and treatment for HFS/HFSR could improve the efficacy of anticancer treatment by maintaining appropriate anticancer drugs.

This pilot study was conducted at a single institution to estimate the efficacy of ATPC for HFS/HFSR. It had some limitations. First, our study was based on a relatively small sample size, which limited the analysis to secondary endpoints and subgroups. In particular, patients with MKI-induced HFSR accounted for only 11.7% (n=7) of all patients analyzed. Therefore, caution should be exercised when interpreting the efficacy of ATPC for HFSR. Second, since HFS and HFSR differ in terms of the causative agents, pathogenesis, histopathology, symptomatology, and treatment, independent studies on the efficacy of ATPC in HFS and HFSR are recommended. Third, clinical factors that may influence HFS/HFSR were not stratified during randomization in this pilot study. Stratification factors that might affect HFS/HFSR include age, sex, dose or regimen of anticancer drugs, and intent to undergo cancer therapy. Although stratification was not performed in this study, there was no significant difference in the proportions of these major clinical factors between the two groups. Fourth, two-thirds of the patients received chemotherapy for palliative intent, and because the treatment goal was to maintain the patient's quality of life during the treatment, the proportion of dose reduction according to the investigators' decision dose was high (51.7%). Clarification of dose reduction guidelines in protocols could lead to clear benefits in the dose intensity of chemotherapy with interventions for HFS/HFSR.

Our pilot study showed that ATPC significantly decreased the development of moderate-to-severe HFS/HFSR in patients with basal HFS/HFSR related to anticancer drugs. Therefore, ATPC could be effective for the prophylaxis or treatment of HFS/HFSR associated with anticancer drugs. Further prospective, large-scale, randomized controlled trials would be required to confirm the efficacy of ATPC in cancer patients treated with anticancer drugs associated with HFS/HFSR.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (https://www.e-crt.org).

Ethical Statement

All the patients provided written informed consent to participate in the study. This study was reviewed and approved by the Institutional Review Board of Chungbuk National University Hospital (IRB approval number: 2018-08-010-016).

Author Contributions

Conceived and designed the analysis: Hahn JH, Kim MS, Han HS.
Collected the data: Yang Y, Han HS.
Contributed data or analysis tools: Yang Y, Jo M, Lee YP, Kim H, Kim HK, Kwon J, Lee KH, Han HS.
Performed the analysis: Yang Y, Han HS.
Wrote the paper: Yang Y, Hahn JH, Kim MS, Jo M, Lee YP, Kim H, Kim HK, Kwon J, Lee KH, Han HS.
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Conflicts of Interest

Dr. Jang-Hee Hahn, a co-author, is the CEO and a stock holder of SupadElixir Co. Ltd., in which Binterin and Winhibin have been developed. Min Seo Kim, a co-author, is an employee of SupadElixir Co. Ltd. All the other authors declared no conflict of interest.

Acknowledgments

This research was supported by the Korean Society of Medical Oncology (KSMO) and the Basic Science Research Program through the National Research Foundation of Korea (NRF), funded by the Ministry of Education, Science, and Technology [grant number 2017R1A5A2015541]. Anti-inflammatory tripeptide creams and placebo creams were provided by SupadElixir Co., Ltd., Chuncheon, South Korea.

References

1. Chen J, Wang Z. How to conduct integrated pharmaceutical care for patients with hand-foot syndrome associated with chemotherapeutic agents and targeted drugs. J Oncol Pharm Pract. 2021;27:919-29.
2. Miller KK, Gorcey L, McLellan BN. Chemotherapy-induced hand-foot syndrome and nail changes: a review of clinical presentation, etiology, pathogenesis, and management. J Am Acad Dermatol. 2014;71:787-94.
3. Degen A, Alter M, Schenck F, Satzger I, Volker B, Kapp A, et al. The hand-foot-syndrome associated with medical tumor therapy: classification and management. J Dtsch Dermatol Ges. 2010;8:652-61.
4. Lou Y, Wang Q, Zheng J, Hu H, Liu L, Hong D, et al. Possible pathways of capecitabine-induced hand-foot syndrome. Chem Res Toxicol. 2016;29:1591-601.
5. SupadElixir. Product: Binterin Solution 400-W [Internet]. Chuncheon: SupadElixir; 2023 [cited 2023 Jan 9]. Available from: http://www.supadelixir.com/product/item.php?it_id=1522724645&ca_id=10.
6. SupadElixir. Product: Winhibin Solution 200 [Internet]. Chuncheon: SupadElixir; [cited 2023 Jan 9]. Available from: http://www.supadelixir.com/product/item.php?it_id=1522723742&ca_id=10.
7. Lee KJ, Kim Y, Yoo YH, Kim MS, Lee SH, Kim CG, et al. CD99-derived agonist ligands inhibit fibronectin-induced activation of beta1 integrin through the protein kinase A/SHP2/extracellular signal-regulated kinase/PTPN12/focal adhesion kinase signaling pathway. Mol Cell Biol. 2017;37:e00675-16.
8. Zou DP, Chen YM, Zhang LZ, Yuan XH, Zhang YJ, Inggawati A, et al. SFRP5 inhibits melanin synthesis of melanocytes in vitiligo by suppressing the Wnt/beta-catenin signaling. Genes Dis. 2021;8:677-88.
9. Liu J, Xiao Q, Xiao J, Niu C, Li Y, Zhang X, et al. Wnt/beta-catenin signalling: function, biological mechanisms, and therapeutic opportunities. Signal Transduct Target Ther. 2022;7:3.
10. Bos JD, Meinardi MM. The 500 Dalton rule for the skin penetration of chemical compounds and drugs. Exp Dermatol. 2000;9:165-9.
11. Common Terminology Criteria for Adverse Events (CTCAE) version 5 [Internet]. Bethesda, MD: National Cancer Institute; 2017 [cited 2017 Dec 27]. Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm.
12. Anderson RT, Keating KN, Doll HA, Camacho F. The hand-foot skin reaction and quality of life questionnaire: an assessment tool for oncology. Oncologist. 2015;20:831-8.
13. Nam SH, Choi HJ, Kang WD, Kim SM, Lim MC, Park SY, et al. Development and validation of the Korean version of Hand-Foot Skin Reaction and Quality of Life Questionnaire (HF-QoL-K). J Korean Med Sci. 2016;31:1969-75.
14. Kang YK, Lee SS, Yoon DH, Lee SY, Chun YJ, Kim MS, et al. Pyridoxine is not effective to prevent hand-foot syndrome associated with capecitabine therapy: results of a randomized, double-blind, placebo-controlled study. J Clin Oncol. 2010;28:3824-9.
15. Zhou Y, Peng L, Li Y, Chen L. Prophylactic pyridoxine was not able to reduce the incidence of capecitabine-induced hand-foot syndrome: a meta-analysis. Biomed Rep. 2013;1:873-8.
16. Chen M, Zhang L, Wang Q, Shen J. Pyridoxine for prevention of hand-foot syndrome caused by chemotherapy: a systematic review. PLoS One. 2013;8:e72245.
17. Yap YS, Kwok LL, Syn N, Chay WY, Chia JWK, Tham CK, et al. Predictors of hand-foot syndrome and pyridoxine for prevention of capecitabine-induced hand-foot syndrome: a randomized clinical trial. JAMA Oncol. 2017;3:1538-45.
18. Zhang RX, Wu XJ, Wan DS, Lu ZH, Kong LH, Pan ZZ, et al. Celecoxib can prevent capecitabine-related hand-foot syndrome in stage II and III colorectal cancer patients: result of a single-center, prospective randomized phase III trial. Ann Oncol. 2012;23:1348-53.
19. Chen JC, Wang JC, Pan YX, Yi MJ, Chen JB, Wang XH, et al. Preventive effect of celecoxib in sorafenib-related hand-foot syndrome in hepatocellular carcinoma patients, a single-center, open-label, randomized, controlled clinical phase III trial. Am J Cancer Res. 2020;10:1467-76.
20. Macedo LT, Lima JP, dos Santos LV, Sasse AD. Prevention strategies for chemotherapy-induced hand-foot syndrome: a systematic review and meta-analysis of prospective randomised trials. Support Care Cancer. 2014;22:1585-93.
21. Huang XZ, Chen Y, Chen WJ, Zhang X, Wu CC, Wang ZN, et al. Clinical evidence of prevention strategies for capecitabine-induced hand-foot syndrome. Int J Cancer. 2018;142:2567-77.
22. Wolf SL, Qin R, Menon SP, Rowland KM Jr, Thomas S, Delaune R, et al. Placebo-controlled trial to determine the effectiveness of a urea/lactic acid-based topical keratolytic agent for prevention of capecitabine-induced hand-foot syndrome: North Central Cancer Treatment Group Study N05C5. J Clin Oncol. 2010;28:5182-7.
23. Hofheinz RD, Gencer D, Schulz H, Stahl M, Hegewisch-Becker S, Loeffler LM, et al. Mapisal versus urea cream as prophylaxis for capecitabine-associated hand-foot syndrome: a randomized phase III trial of the AIO Quality of Life Working

Group. J Clin Oncol. 2015;33:2444-9.
24. Lan TC, Tsou PH, Tam KW, Huang TW. Effect of urea cream on hand-foot syndrome in patients receiving chemotherapy: a meta-analysis. Cancer Nurs. 2022;45:378-86.
25. Gialaim Purcino Dos Reis FC, Meneses AG, Mazoni SR, Pereira Silveira RC, Diniz Dos Reis PE, Vasques CI. Topical interventions for preventing hand-foot syndrome resulting from antineoplastic therapy: a scoping review. Rev Esc Enferm USP. 2023;57:e20220107.
26. Pandy JG, Franco PI, Li RK. Prophylactic strategies for hand-foot syndrome/skin reaction associated with systemic cancer treatment: a meta-analysis of randomized controlled trials. Support Care Cancer. 2022;30:8655-66.
27. Barcella CA, Lamberts M, McGettigan P, Fosbol EL, Lindhardsen J, Torp-Pedersen C, et al. Differences in cardiovascular safety with non-steroidal anti-inflammatory drug therapy: a nationwide study in patients with osteoarthritis. Basic Clin Pharmacol Toxicol. 2019;124:629-41.
28. Garcia-Rayado G, Navarro M, Lanas A. NSAID induced gastrointestinal damage and designing GI-sparing NSAIDs. Expert Rev Clin Pharmacol. 2018;11:1031-43.
29. Harvey J, Lax SJ, Lowe A, Santer M, Lawton S, Langan SM, et al. The long-term safety of topical corticosteroids in atopic dermatitis: a systematic review. Skin Health Dis. 2023;3:e268.
30. Shinohara N, Nonomura N, Eto M, Kimura G, Minami H, Tokunaga S, et al. A randomized multicenter phase II trial on the efficacy of a hydrocolloid dressing containing ceramide with a low-friction external surface for hand-foot skin reaction caused by sorafenib in patients with renal cell carcinoma. Ann Oncol. 2014;25:472-6.