Original Article

The effectiveness of EVOSKIN®Palm and sole moisturizing cream in treating capecitabine-associated hand-foot syndrome: a randomized double-blind clinical trial

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Background: This study sought to test the effectiveness of EVOSKIN®Palm and sole moisturizing cream (PSMC) in preventing and treating hand-foot syndrome (HFS) during capecitabine chemotherapy.

Methods: Stage II/III colorectal cancer patients receiving capecitabine adjuvant chemotherapy were randomly allocated to receive either EVOSKINPSMC or physiological saline treatments for their hands and feet. Treatment was initiated along with adjuvant chemotherapy and continued till the end of chemotherapy. Participants' skin responses were evaluated every 3weeks.

Results: During the study, 51 participants in the EVOSKIN PSMC group and 54 participants in the physiological saline group completed at least three cycles of capecitabine chemotherapy. The total incidence of HFS in the EVOSKIN PSMC group was lower than that in the physiological saline group (56.8% *vs.* 75.9%, P=0.006), as was the incidence of Grade 3/4 HFS (6.0% *vs.* 18.5%, P=0.011). The incidence of HFS became significant after 6weeks of chemotherapy. Further, the incidence of severe HFS was significant from as early as 3weeks after the commencement of chemotherapy despite the use of EVOSKIN PSMC to manage the condition. Notably, the incidence of Grade 1/2 HFS was not statistically significant between the two groups (26/51 *vs.* 32/54, 52.0% *vs.* 59.2%, P=0.194).

Conclusions: The incidence of severe HFS among individuals using oral capecitabine can be reduced by the prophylactic treatment of EVOSKIN PSMC, this treatment is reasonable and acceptable for patients with capecitabine chemotherapy.

Keywords: Hand-foot syndrome (HFS); prevention; capecitabine; colorectal cancer

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Introduction

Adjuvant chemotherapy increases survival time and reduces tumor-related mortality after curative resection in colorectal cancer patients (about 5% in stage II and 15–20% in stage III) (1). Fluorouracil is a basic chemotherapy agent for colorectal cancer, and capecitabine is the most widely used oral fluoropyrimidine agent in adjuvant chemotherapy. As the capecitabine molecule has the priority to be activated in tumor tissue, rather than injected fluorouracil, its gastrointestinal side effects and bone marrow toxicity are reduced. However, some of the unique side effects of capecitabine still affect its application and patients' tolerance of chemotherapy.

Hand-foot syndrome (HFS) is the most frequent side effect of oral capecitabine. Symptoms of HFS include skin rashes, erythema, blistering, peeling and pain. The incidence of HFS has been reported to be 46–68% (2,3). According to the World Health Organization (WHO) (4) (see *Table 1*), the total incidence of HFS was approximately 68.3% among capecitabine-treated colorectal cancer patients, while the incidence of Grade 3/4 HFS was 11–24% among individuals taking oral capecitabine (5,6). Many therapies have been reported to reduce the incidence of HFS and relieve its clinical presentation, including capecitabine dose reductions, the use of COX-2 inhibitors, vitamin B6 and traditional Chinese medicines. Such therapies have been found to degrade 67.4% of Grade 3–4 HFS cases (5,7,8). Research has shown that 11–57% of patients are forced to terminate capecitabine treatment because of severe HFS (7). HFS is rarely life-threatening; however, the symptoms of HFS can significantly impair individuals' quality of life and interrupt the therapy process; thus, an effective treatment needs to be found to prevent and reverse capecitabine-related HFS.

Recently, the dermatologic adverse effects of oral capecitabine were examined in individuals presenting with cutaneous neural inflammation. Researchers found that lithium inhibits the initiation of the inflammatory reaction to chemotherapy or radiation therapy and relieves dermatologic toxicities (9,10). EVOSKIN®Palm and Sole Moisturizing Cream (PSMC) (Evaux Laboratories, Évaux-les-Bains, France) is made of Évaux thermal spring water, which is naturally rich in lithium. It has been used to manage dermatological toxicities caused by chemotherapy, radiation therapy and anti-epidermal growth factor receptor (EGFR) therapy. Based on the high incidence of HFS and the mechanism of HFS induced by oral capecitabine, this randomized double-blind clinical trial sought to evaluate the effectiveness and safety of EVOSKINPSMC in preventing capecitabine-associated HFS. We present the following article in accordance with the CONSORT reporting checklist (available at http://dx.doi.org/10.21037/apm-21-61).

Methods

This randomized, double-blind, placebo-controlled trial was approved by the ethics committee of Guangzhou Medical University and all procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). Informed consent was obtained from each participant.

Participant eligibility

To be eligible to participate in this study, individuals from our clinic had to meet the following criteria: (I) be aged between 18–75; (II) have a histological confirmed diagnosis of colorectal adenocarcinoma with pathologic stage II/III (according to the National Comprehensive Cancer Network's (NCCN's) guidelines for colorectal cancer, 2013); (III) be prepared to initiate oral capecitabine or capecitabine plus oxaliplatin (CapOx) treatment within 8weeks of surgery; (IV) have no previous chemotherapy history; and (V) have laboratory-test confirmed normal hematologic, hepatic and renal functions. Individuals were excluded from this study if they: (I) had a Karnofsky Performance Status (KPS) performance score of ≤70; (II) were pregnant; (III) were known to have an allergy to fluorouracil; (IV) used an immune inhibitor, including anti-inflammatory or antibiotic drugs to treat other conditions; (V) had severe heart disease or abnormal cardiogram.

It was calculated that the sample size of this study should be 130 participants to detect hazard rates with 80% power (b=0.01) at a two-sided significance level of P=0.05. Based on our previous experience, it was that assumed that the follow-up rate of the study would be 15%, and thus, a randomization of 150 participants would be required.

Treatment

Eligible participants were assigned to apply either EVOSKIN PSMC or physiological saline cream via computerized randomization. The randomized results were only shown to the clinical research coordinator; the research

Table 1 HFS grading according to World Health Organization (WHO) criteria

Grade	Definition	Pain	Clinical lesion	Histological findings
1	Dysesthesia/paraesthesia, tingling in the hands and feet	–	Erythema	Dilated blood vessels of the superficial dermal plexus
2	Discomfort in holding objects (especially cool object) and walking, with painless swelling or erythema	–	1+ oedema	
3	Painful erythema and swelling of palms and soles, obvious periungual erythema and swelling	+	2+ fissuration	Isolated keratinocytes necrosis in higher layer of the epidermis
4	Desquamation, ulceration, blistering, with severe pain	++	3+ blister	Complete epidermal necrosis

+, degree of pain. HFS, hand-foot syndrome; WHO, World Health Organization.

crews and participants were blind to the randomization during the research period. Participants were allocated numbers. Randomization was not announced until the trial ended or a patient left the trial. The physiological saline cream produced was similar to the EVOSKIN PSMC in terms of color, texture and smell, and only distinguishable by the labeled number.

Cream application started on the same day as the initiation of the capecitabine chemotherapy. Participants in both the treatment and control groups were advised to daub the cream on their hands and feet twice a day. Participants continued to apply the cream until the termination of the capecitabine treatment. The NCCN's guidelines recommend that patients receive at least four cycles of capecitabine chemotherapy (11). Thus, oral capecitabine (1,250 mg/m^2) was administered twice a day for 14 consecutive days, every three weeks. The CapOx regimen comprised a three-hour intravenous infusion of oxaliplatin (130 mg/m^2) on the first day, followed by an oral capecitabine (1,000 mg/m^2, twice a day) for 14consecutive days, every three weeks. Chemotherapy was postponed in cases of severe toxicity, and the doses of capecitabine or/and oxaliplatin were then reduced to 75% in subsequent cycles. Chemotherapy was terminated in cases of unacceptable toxicity, such as leucopenia (total white blood cell <1.0×10^9/L), serious vomiting or severe HFS (Grade 3/4).

Evaluation

Clinical baseline physical examinations were undertaken and laboratory data were obtained for all participants. Within one week of trial registration, participants' KPS performance scores were also assessed. Blood was drawn to assess participants' hematological and biochemical parameters. Finally, participants underwent a complete skin appearance examination by participating oncologists to detect erythema, oedema, fissuration, blistering, paraesthesia or any other dermatological change. Standardized digital photographs were taken of participants' hands and feet. The dermatological changes to participants' hands and feet were evaluated and recorded every three weeks during the treatment period in accordance with the WHO's criteria for HFS (see *Table 1*).

Statistical analysis

The aim of this study was to investigate the difference in the incidence of HFS between the EVOSKIN PSMC group and the physiological saline group at the completion of the 6-month adjuvant chemotherapy period. The secondary endpoint was the difference in the incidence of Grade 3/4 HFS between the two groups post treatment, and the difference in the incidence of slight/severe HFS between the two groups during the capecitabine treatment.

With a sample size of 51 participants per group, there was a 90% probability of detecting differences in the incidences of HFS between the two study groups and thus of rejecting the null hypothesis of equal proportions with a P value of 0.05 using a two-sided test. Assuming a 15% dropout rate, it was determined that 61 participants would be required for each group.

Data and images were collected in hospital and saved in a computer which only be administrated by clinical research associate during study period. SPSS for Windows software (v19.0; IBM Corporation, Armonk, NY, USA) was used to undertake all the data analyses. Continuous variables were expressed as means ± standard deviations (SDs) and compared using a Student's t test. Categorical data were expressed as frequencies and compared using an analysis of variance. Pearson's chi-squared test and Fisher's exact test

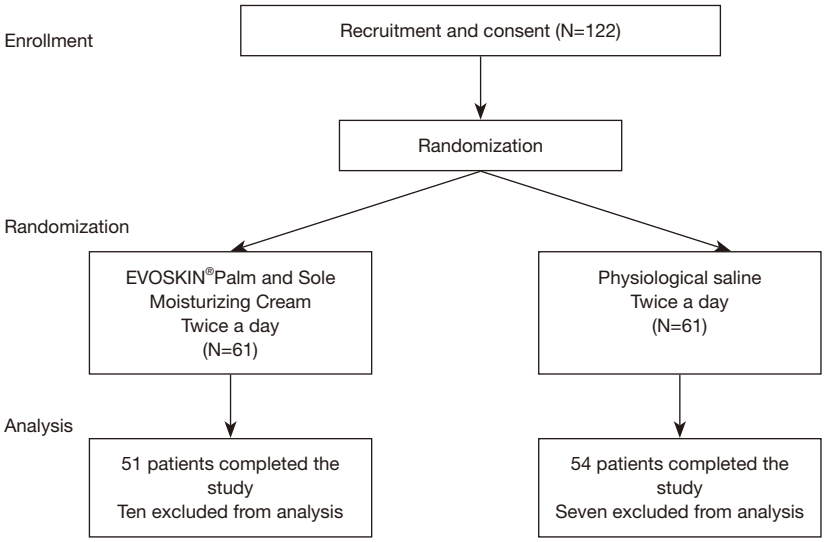

Figure 1 Study enrollment, randomization and attrition data.

were used to test any differences in the incidence of HFS. All of the significance levels reported refer to two-sided tests. A P value of 0.05 was considered significant.

Results

From September 2013 to August 2014, 122 individuals were identified who met the study criteria. Of these122 individuals, four refused to take part in the study. Thus,118 individuals agreed to participate in the study. The participants were randomly assigned either to the EVOSKIN PSMC group or the physiological saline group. For details of participant attrition during the study, see *Figure 1*. In total, 51 participants in the EVOSKIN PSMC group and 54 participants in the physiological saline group completed at least three cycles (over nine weeks) of capecitabine chemotherapy. The trial ended when all participants had finished all capecitabine and be followed up at least 4 weeks. There was no significant difference between the baseline characteristics of the two groups (see *Table 2*).

During the study, 29 participants (29/51, 56.8%) suffered from HFS in the EVOSKIN PSMC group, and 41 participants (41/54, 75.9%) suffered from HFS in the physiological saline group. Three participants in the EVOSKIN PSMC group suffered from severe (Grade 3/4) HFS (3/51, 6.0%), and nine participants suffered from severe (Grade 3/4) HFS (9/54, 16.7%) in the physiological saline group. Most participants with slight (Grade 1/2) HFS presented with paraesthesia, which usually included a tingling sensation in the hands and feet, or painless erythema, but showed no other obvious dermatological changes. Participants with severe HFS presented with symptoms that included painful erythema at the fingers or toes, and peeling of the palms and soles (see *Figure 2A,B,C*). These participants also complained that they experienced difficulty walking and enhanced pain when touching.

Five of nine participants suffered severe HFS in the physiological saline group during the end of the second/third chemotherapy cycle, and agreed to receive EVOSKIN PSMC treatment and persist with the rest of adjuvant chemotherapy. Four of these five participants experienced clinical symptom relief after at least two weeks of using EVOSKIN PSMC, such that their erythema dissipated, the blistering and peeling subsided, and they reported experiencing less pain (see *Figure 2D,E,F*).

The total incidence rate of HFS in the EVOSKIN PSMC group was lower than that in the physiological saline group (56.8% *vs.* 75.9%, P=0.006), as was the incidence rate of Grade 3/4 HFS in these groups (6.0% *vs.* 16.7%, P=0.011). As *Figure 3* shows, the difference in the incidence of HFS became significant after two cycles (6 weeks) of chemotherapy, and the severe incidence of HFS was significant from as early as one cycle after (i.e., 3 weeks) chemotherapy. Notably, the difference in the incidence of Grade 1/2 HFS between the two groups was not statistically significant (26/51 *vs.* 32/54, 52.0% *vs.* 59.2%, P=0.194). Further, no connection was found between the incidence of

Table 2 Baseline characteristics of enrolled patients

	EVOSKIN®Palm and Sole Moisturizing Cream group (N=51)	Physiological saline group (N=54)	P value
Gender			0.571
Male	26 (51.0)	30 (55.6)	
Female	25 (49.0)	24 (44.4)	
Stage			0.368
II	23 (45.1)	20 (37.0)	
III	28 (54.9)	34 (63.0)	
Tumor location			0.495
Colon	27 (52.9)	29 (53.7)	
Rectum	25 (47.1)	25 (46.3)	
KPS			0.600
≥90	48 (94.1)	52 (96.3)	
<90	3 (5.9)	2 (3.7)	
Age, years	56.00±11.88	57.79±11.43	0.479
White blood cells (10^9/L)	6.25±2.20	6.56±1.79	0.441
Hemoglobin (g/L)	117.53±15.71	110.98±22.27	0.097
Platelets (10^9/L)	287.06±80.43	276.96±83.64	0.544
Albumin (g/L)S	40.55±4.38	41.11±6.45	0.617
Total bilirubin (μmol/L)	10.59±4.06	10.82±10.41	0.888
Serum creatinine (μmol/L)	67.72±25.54	71.80±28.96	0.466

KPS, Karnofsky Performance Status.

HFS and participants' clinical-laboratory data during the study period. Indeed, the laboratory data of the EVOSKIN PSMC group and the physiological saline group were comparable.

Discussion

HFS is the most frequent side effect of oral capecitabine and one of the main reasons for chemotherapy termination. This study was designed to evaluate the effectiveness of EVOSKIN PSMC in the management of capecitabine-associated HFS. The results showed that EVOSKIN PSMC reduces the incidence of severe HFS more than physiological saline cream after at least three cycles of capecitabine chemotherapy.

HFS was first reported in 1974 (12), and was recently characterized as causing painful erythematous lesions that mainly affect palmoplantar surfaces (such lesions are referred to as palmoplantar erythrodysesthesia and chemotherapy-induced acral erythema) (13). Most HFS is associated with fluorouracil chemotherapy. Indeed, increasing numbers of HFS cases have been reported to be a side effect of targeted cancer therapy, such as those that use the multikinase-inhibitors (MKIs) sorafenib and sunitinib. As the mechanisms and clinical presentations of HFS during targeted therapy differ to the mechanism and clinical presentation of HFS in chemotherapy, some researchers have distinguished between classic HFS and MKI-associated HFS (14).

The mechanism of capecitabine-associated HFS is still unclear. Some believe it is dose-dependent and probably related to capecitabine metabolite accumulation in skin, which is caused by high levels of enzyme thymidine phosphorylase from cutaneous keratinocytes (15). Pathological examinations have shown that tissue affected by HFS displays general inflammatory changes, dilated

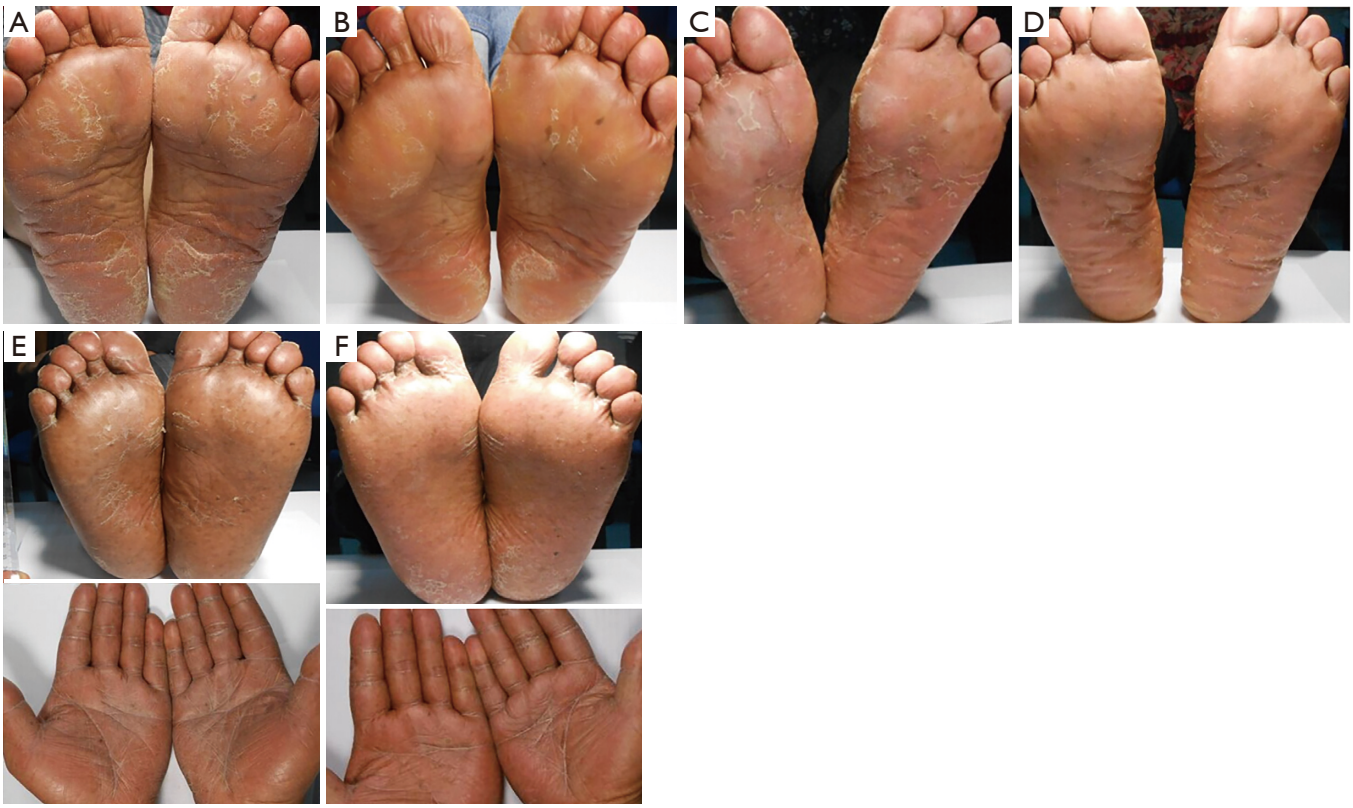

Figure 2 Case 1: A male patient, who received 3 cycles of capecitabine plus oxaliplatin (CapOx) adjuvant treatment, had severe peeling, fissuration and pain appearance on soles (A). Clinical symptoms had been soothed after EVOSKIN®Palm and Sole Moisturizing Cream management (B). Case 2: A male patient had severe peeling on soles after 3 cycles of oral capecitabine (C), symptom had been relieved after using of EVOSKIN®Palm and Sole Moisturizing Cream (D). Case 3: A male patient had peeling and pain on soles and painful erythema on hands after four months of CapOx therapy (E). Symptoms were relieved after using of EVOSKIN®Palm and Sole Moisturizing Cream for 4 weeks (F).

blood vessels, oedema, and white blood cell infiltration (4,7). Recently, the presentation of peripheral neural inflammation was considered to indicate chemotherapy-induced HFS. Notably, substance P (SP) is the essential medium of this reaction. SP is a neurotransmitter that is released from the peripheral terminals of primary sense afferents. It plays an important role in the process of mediating neuropathic pain transmission (16). It is believed that SP levels are up-regulated during the cutaneous inflammation in HFS to maintain reactions to and the transmission of pain. Thus, the inhibition of SP may be a key to treating chemotherapy-induced HFS.

In 2008, researchers found that lithium acts as an anti-inflammatory element on keratinocytes, as it increases the expression of anti-inflammatory cytokine interleukin-10 and decreases the expression of Toll-like receptors 2 and 4 (17). Lithium has also been found to have an inhibitory effect on SP expression. Thus, lithium is known to inhibit cutaneous inflammatory reactions induced by chemical or radioactive stimulations. Agents containing lithium have been widely used to treat inflammatory dermatitis, such as seborrheic dermatitis (18). Clinical trials have also reported that agents rich in lithium (2.20 mg/L) could help to prevent severe rashes associated with targeted treatments (19). The results of the present study showed that the incidence of HFS and severe HFS in individuals using oral capecitabine could be reduced via the use of EVOSKIN PSMC; however, it should be noted that the use of EVOSKIN PSMC did not significantly reduce the incidence of Grade 1/2 HFS. In relation to its effectiveness, EVOSKIN PSMC was shown to dissipate erythema, sooth pain, and reduce blistering and peeling in most participants. Further, EVOSKIN PSMC

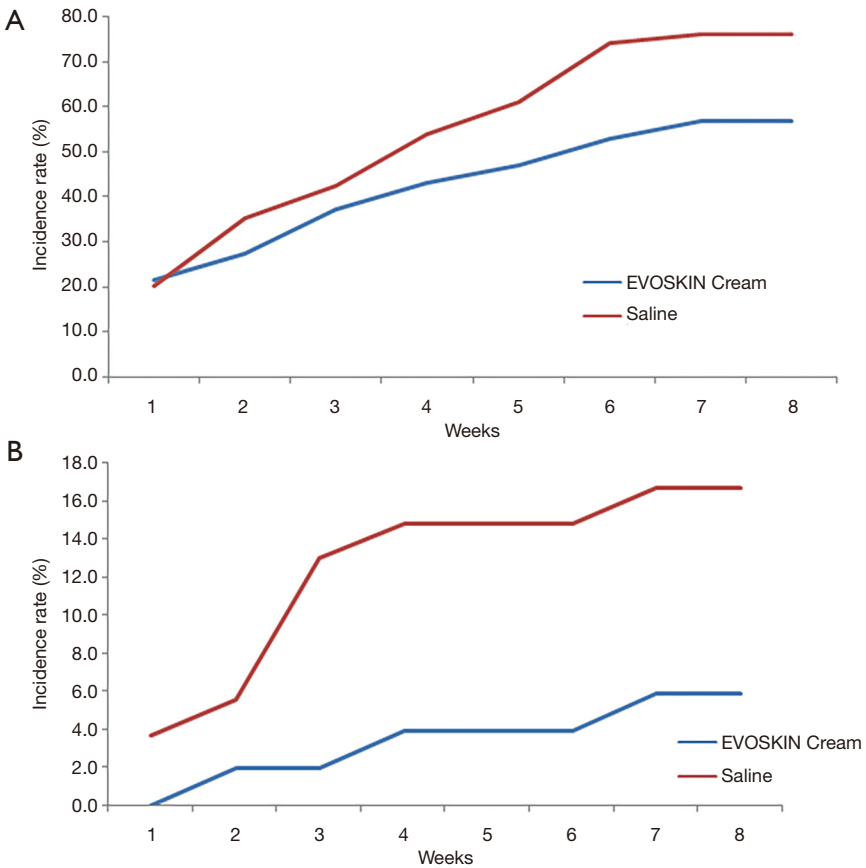

Figure 3 The total incidence rate of HFS (A) and severe HFS (B) in EVOSKIN®Palm and Sole Moisturizing Creamgroup was lower than that in physiological saline group (A: 56.8% *vs.* 75.9%, P=0.006; B: 6.0% *vs.* 16.7%, P=0.011) during the whole study period. HFS, hand-foot syndrome.

was also found to relieve the symptoms of some participants with severe HFS in the physiological saline control group.

Manganese has been found to promote wound coalescence and skin tissue proliferation (20). As EVOSKIN PSMC is rich in lithium and contains manganese, these mechanisms and results may explain why EVOSKIN PSMC relieves the dermatological toxicities caused by oral capecitabine.

The results of this study showed that EVOSKIN PSMC reduces the incidence of severe HFS resulting from the intake of oral capecitabine; however, it should be noted that6% of participants in the present study continued to suffer from severe HFS even when they continued to use the cream.

One limitation of this study relates to the number of participants who participated in the study. Further clinical trials should be conducted to validate the effectiveness of using EVOSKIN PSMC to treat patients with HFS after chemotherapy. Future research should also compare the effectiveness of EVOSKIN PSMC and other anti-HFS agents, and test the effects of EVOSKIN PSMC on individuals suffering from MKI-associated HFS.

Conclusions

The incidence of severe HFS among individuals using oral capecitabine can be reduced by the prophylactic treatment of EVOSKIN PSMC. The use of EVOSKIN PSMC represents a reasonable and acceptable treatment for patients undergoing capecitabine chemotherapy.

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Footnote

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Data Sharing Statement: Available at http://dx.doi.org/10.21037/apm-21-61

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-21-61), Dr. Lu reports grants from Department of science and technology of Guangdong Province, during the conduct of the study. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This randomized, double-blind, placebo-controlled trial was approved by the ethics committee of Guangzhou Medical University. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013) Informed consent was obtained from each participant.

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