RESEARCH ARTICLE

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A Randomized Single-Blinded Phase II Trial Comparing Efficacy and Quality of Life of Topical Aloe Vera Gel Plus Urea Cream Versus Urea Cream Alone for Prevention of Hand Foot Syndrome in Cancer Patients Receiving Capecitabine

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Abstract

Introduction: Capecitabine has been widely prescribed to treat various cancers. The hand foot syndrome (HFS) is the most troublesome adverse effect. Urea cream has been pre-emptively co-prescribed, even though its efficacy is doubtful. Aloe vera gel with urea cream might potentiate each other. This trial was intended to prove the efficacy of this combination. **Materials and Methods:** The investigators conducted a randomized single-blinded phase II study. The participants were randomized 1:1 to receive the combination of aloe vera gel and 10% urea cream (n = 30), the experimental A+U arm and 10% urea cream alone (n = 31), the U arm. The sample size was calculated to have 90% power to show the significant 20% reduction in the incidence of HFS grade 2–3 of the combination therapy with alpha level = 0.05. Both the CTCAE criteria version 5 and the dermatology life quality index (DLQI) were assessed to determine the severity of HFS and quality of life, respectively. **Results:** Most of the participants had rectal cancer (A+U: 43.3%; U: 41.9%). In the A+U group, 86.7% had grade 0–1 HFS and 13.3% had grade 2–3 HFS. In the U group, 64.5% had grade 0–1 HFS and 35.5% had grade 2–3 HFS (Mann-Whitney U test, p = 0.045). Grade 2–3 HFS was significantly lower in the combination group. **Conclusion:** Combination of aloe vera gel and 10% urea cream ameliorated the severity of HFS in participants taking capecitabine; however, no significant difference in DLQI between the groups was demonstrated.

Keywords: Aloe vera gel- hand foot syndrome- capecitabine

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Introduction

Capecitabine, a prodrug of fluoropyrimidine, is an oral anti-cancer drug commonly used to treat various types of cancer. In the COVID-19 era, capecitabine is widely used due to its oral route and efficacy, which is similar to that of fluoropyrimidine. Thus, patients can be treated with ambulatory care. Capecitabine can be used alone or in combination with other anti-cancer agents, such as oxaliplatin or irinotecan, depending on the type and stage of cancer. In Thailand, some cancers, such as breast, colorectal and gastric cancer, are commonly treated with capecitabine. Typically, a regimen of capecitabine takes approximately 6-8 cycles to complete. The average oral dose is 2000 mg/m^2 on days 1 to 14 when used in combination chemotherapy, and 2500 mg/m2 on days 1 to 14 when used as a single agent [1]. For some patients, toxicities require interruption or cessation of treatment, which can lead to decreased efficacy and worse cancer outcomes.

Common toxicities of capecitabine are HFS [2], stomatitis, and diarrhea. The incidence of all grades of HFS reportedly ranges from 50% to 60% [3] and the incidence of grade 3 HFS ranges from 10%-20%. The pathophysiology of HFS is thought to be due to its metabolite, "thymidine phosphorylase, which attacks blood vessels and sweat glands of the hands and feet, resulting in various grades and severities of skin dryness, skin sloughing, skin blistering, and possibly severe skin infection [4]. Another hypothesis believed to be the overexpression of cyclooxygenase (COX-2) in palm and feet by capecitabine and its metabolites [5]. According to the Common Terminology Criteria for Adverse Events version 5 (CTCAEv5.0), the capecitabine dosage should be reduced by one step when grade 2 occurs. The capecitabine dosage should be interrupted in the current cycle of treatment if grade ≥3 occurs or even if permanently stopped in more severe cases.

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In the past few years, various trials have compared the efficacy of urea cream with many comparator products. One study compared urea cream with Mapisal ointment, an antioxidant agent for reducing the incidence of HFS [6]. The incidences of HFS were 22.4% and 39.5% for urea cream and Mapisal ointment, respectively, which were significantly different. In a meta-analysis [7], urea cream was proven to reduce the incidence of grade ≥2 HFS in approximately 0.72 times [risk ratio 0.72, 95% confidence interval 0.58-0.90]. Urea cream is safe and effective.

In practice, besides skin-protective agents, other skin-protective strategies, such as avoiding washing hands and feet too frequently and avoiding the use of skin moisturizer products with alcohol-containing components, have been recommended [8]. However, in the COVID-19 pandemics era, behaviors have changed. Currently, people more frequently wash their hands and feet, especially with alcohol-containing agents. These factors may exacerbate HFS.

In our practice, we suggest that throughout every cycle, all patients who receive capecitabine apply 10% urea cream to prevent HFS. However, the incidence of HFS is still approximately 20% [7]. Interrupting any chemotherapy cycle or reducing the dosage of capecitabine may worsen outcomes. Therefore, there is a need to find a better treatment for patients to decrease the incidence of HFS. Hopefully, all of our patients can be treated with capecitabine alone or in combination while maintaining good quality of life (QOL).

Aloe vera gel contains 99%-99.5% water and 1%-1.5% antioxidants that are believed to be good anti-inflammatory agents [9]. Various medical trials have used aloe vera gel for prevention and treatment of many skin conditions.

Aloe vera's healing properties depend on interactions with growth factor receptors on fibroblasts leading to increased synthesis of collagen, especially type III collagen [9]. Aloe vera gel also contains C-glucosyl chromone that has a role in anti-inflammatory effects by inhibiting cyclooxygenase and contains mucopolysaccharide that contributes a moisturizing effect. All of these properties improve skin integrity [10]. Mucopolysaccharide stimulates fibroblasts, which produce collagen and elastin, an important component in the cohesive effect of epithelial tissue, therefore the effect is mostly within a superficial skin layer. This helps soften and heal stretched and flaking skin [9]. In one study, aloe vera gel improved skin dryness, integrity, and erythema from occupational exposure [11]. A study showed that in patients with grade 3 HFS, application of aloe vera gel helped improve skin integrity and QOL, which enabled patients to quickly return to their chemotherapy schedules [12].

In Thailand, aloe vera gel with 87.4% aloe vera was approved by the Thai FDA for burned skin, but it has not yet been approved for HFS. An earlier meta-analysis showed that urea cream was safe and efficacious, therefore urea cream has become the standard of care for preventing and treating HFS. However, to date, there have been no reports from studies of aloe vera gel combined with urea cream for preventing HFS in patients with cancer treated with capecitabine. In Vajira Hospital, the only product containing aloe vera (87.4%) is Radiara Gel.

This study aimed to compare the efficacies of aloe vera gel combined with 10% urea cream with that of 10% urea cream alone for decreasing the incidence of grade 2–3 HFS in patients receiving capecitabine according to CTCAEv5.0. We also assessed QOL according to the dermatology life quality index (DLQI) [13]. This study has been registered at www.thaiclinicaltrials.org (TCTR20230411005).

Materials and Methods

This was a randomized single-blinded phase II trial conducted at Vajira Hospital in Bangkok, Thailand. Screening and randomization were conducted from December 2021 through January 2023. The inclusion criteria were patients ≥18 years of age who had been diagnosed with cancer and were being treated with capecitabine, either alone or in combination with another drug. The patients had never received capecitabine before randomization and they were asked to not use other skin products other than those in their assigned group. The exclusion criteria were patients with a history of allergic response to aloe vera gel or urea cream and those with widespread skin conditions, such as diffuse systemic sclerosis or erythrodermic psoriasis.

Block of four randomization was performed to assign the patients 1:1 to either a group that received aloe vera gel combined with 10% urea cream (the A+U group) or to a group that received 10% urea cream alone (the U group). Informed consent was obtained from all participants before the study start in the oncology out-patient clinic. The patients in the A+U group received one box of aloe vera gel (35 g) and one box of 10% urea cream (35 g). The products were required to be applied in order starting with aloe vera gel 1 FTU (fingertip unit) followed by 10% urea cream in the same amount administered twice daily. The patients in the U group received only one box of 10% urea cream applied 1 FTU of the product twice daily. The primary endpoint was the incidence of grade 2–3 HFS and the secondary endpoint was the DLQI score.

Each patient was evaluated, starting at the first visit and then every 3 weeks or at day1 of each cycle of chemotherapy until the last cycle of capecitabine, for HFS and patients' DLQI as well as the accuracy of applying the products.

Grading of HFS according to CTCAEv5.0 was performed by a dermatologist blinded to the treatment used for each patient. That is classified as grade 0-3, i.e. grade 0: no symptoms, grade 1: minimal skin changes without pain, grade 2: skin changes (e.g, peeling, blisters, bleeding, edema, or hyperkeratosis) with pain, limiting instrumental activities of daily living (ADL), grade 3: severe skin changes with pain, limiting self-care ADL.

The DLQI assessment was performed by the patients at every visit which total scores are divided in 5 levels, i.e. score of 0-1: no impact on QOL, score of 2-5: little impact on QOL, score of 6-10: moderate impact on QOL, scores of 11-20: significant impact on QOL, scores of 21-30: significant impact on QOL so much.

The accuracy of application of aloe vera gel and 10% urea cream was evaluated by the investigator. The

patients had to bring back all the tubes of medicine. The investigator evaluated the amount remaining in each visit. The good compliance means most of the cream or gel were not left in the tube and patients did not forget the apply by schedule.

Statistical analysis

The sample size for this study was calculated to provide 90% power to show a 20% reduction in the incidence of HFS grade 2-3 with aloe vera gel plus 10% urea cream at a significance level of 5% (2-sided test). The expected incidence of HFS grade 2-3 in the U group was 22.4% based on historical data [6], therefore 59 patients needed to be included in this study. For a dropout rate of 10%, the total enrollment needed to be 66 patients (33 patients per group). We used descriptive statistics to describe the baseline characteristics of the patients. The Mann–Whitney U test was performed to compare HFS according to the CTCAEv5.0 and QOL assessed by the DLQI at each patient's visit between the two groups. Differences with values of $p < 0.05$ were accepted as statistically significant. IBM SPSS Statistics, version 27 (IBM Corp. Armonk, NY) was used for all statistical analyses.

Results

The randomization of the patients for placement in the two groups was performed from December 2021 until January 2023. A total of 66 patients were enrolled, but five patients were lost to follow-up after 1 cycle of chemotherapy, leaving a total sample size of 61. There were 30 patients in the A+U group and 31 patients in the U group. The demographic data are presented in Table 1. Sixty percent of the patients were female in the A+U group, and 77.4% were female in the U group. Most of the patients were ≥50 years of age. Rectal cancer was the most common type and affected 43.3% of the patients in the A+U group and 41.9% in the U group. Colon cancer was the second most common type and was 30% and 19.3% in the A+U group and the U group, respectively. Most of the patients had stage IV disease (70% in the A+U group and 77.4% in the U group). The most common chemotherapy was oxaliplatin (63.3% in the A+U group and 54.8% in the U group). The percentage of patients with occupations that might have been associated with HFS was 73.3% in the A+U group and 29% in the U group. Application compliance was 76.7% in the A+U group and 80.6 % in the U group.

Dose reduction of capecitabine due to HFS was 13.3% in the A+U group and 16.1% in the U group. After 1 dose-level reduction, the patients were continued on their chemotherapy courses. The median number of hand washings per day was 5.5 and 5 times in the A+U group and the U group, respectively. The median number of foot washings and liquid alcohol use was two times per day in both groups. The median total number of capecitabine cycles were 6.5 and 8 in the A+U group and the U group, respectively.

In the A+U group, HFS grade 2 started to occur in the second cycle (3.3%) and reached a maximum in the sixth cycle (10%), whereas HFS grade 3 started to occur in the third cycle (3.3%) and reached a maximum in the fourth to sixth cycle (3.3%).

In the U group, HFS grade 2 started to occur in the second cycle (3.2%) and reached a maximum in the fourth cycle (19.4%), whereas HFS grade 3 first occurred in the third cycle (3.2%) and reached a maximum in the sixth cycle (9.7%). The maximum CTCAE grades at each visit for the patients with HFS are presented in Table 2. Grade 3 HFS occurred approximately in the third cycle, but the difference between the two groups was not statistically significant.

The incidence of all HFS grades was 46.7% in the A+U group and 71% in the U group. Given that HFS grades 2–3 have some clinically significant effects on a patient's QOL, we compared the HFS rate between the patients who had grades 0–1 HFS with the patients who had grades 2–3 in Table 3 and Figure 1.

In the A+U group, 86.7% had grades 0–1 HFS and

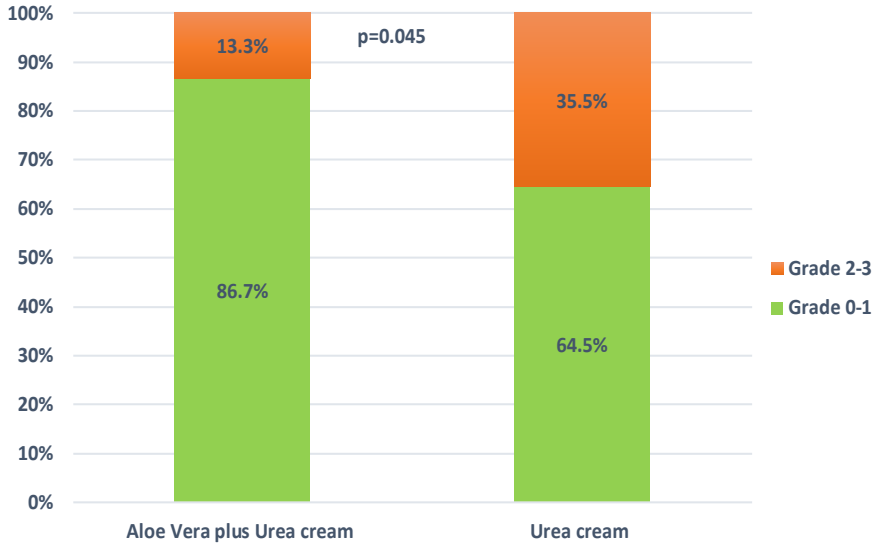

Figure 1. Severity of Hand Foot Syndrome Grouped as Grade 0-1 and 2-3

Table 1. Demographic Data

Baseline Characteristics	Aloe Vera plus Urea cream (n=30)	Urea cream (n=31)	p-value
Gender			
Male	12 (40%)	7 (22.6%)	0.142
Female	18 (60%)	24 (77.4%)	
Age (years), mean ± SD.	58.67 ± 9.83	63.77 ± 11.92	
<50	3 (10%)	3 (9.7%)	0.101
50- 65	21 (70%)	14 (45.2%)	
>65	6 (20%)	14 (45.2%)	
Type of malignancy			
Anus	1 (3.3%)	0 (0%)	0.734
Appendix	1 (3.3%)	1 (3.2%)	
Breast	5 (16.7%)	6 (19.4%)	
Cholangiocarcinoma	0 (0%)	1 (3.2%)	
Colon	9(30%)	6 (19.3%)	
Duodenum	0 (0%)	1 (3.2%)	
Esophagus	0 (0%)	1 (3.2%)	
Hepatocellular carcinoma	0 (0%)	1 (3.2%)	
Periampullary	1 (3.3%)	0 (0%)	
Rectum	13 (43.3%)	13 (41.9%)	
Sebaceous skin	0 (0%)	1 (3.2%)	
Stage of malignancy (AJCC 8th)			
Stage I	0(0%)	0 (0%)	0.624
Stage II	2 (6.7%)	1 (3.2%)	
Stage III	7 (23.3%)	6 (19.4%)	
Stage IV	21 (70%)	24 (77.4%)	
BMI (kg/m2)			
<18.5	4 (13.3%)	7 (22.6%)	0.453
18.5-22.9	15 (50%)	11 (35.5%)	
>23	11 (36.7%)	13 (41.9%)	
BSA			
< 1.4	5 (16.7%)	9 (29%)	0.468
1.4-1.6	12 (40%)	12 (38.7%)	
>1.6	13 (43.3%)	10 (32.3%)	
Creatinine Clearance, median (IQR)			
30-40	1 (3.3%)	3 (9.7%)	0.096
41-60	6 (20%)	13(41.9%)	
>60	23 (76.7%)	15 (48.4%)	
Albumin, median (IQR)	4.04 (3.7, 4.3)	3.9 (3.6, 4.3)	
3-3.5	5 (16.7%)	7 (22.6%)	0.682
>3.5-4	9 (30%)	12 (38.7%)	
>4	14 (46.7%)	12 (38.7%)	
Unknown	2 (6.7%)	0 (0%)	
Dose of Capecitabine (mg)			
1500-2000	2 (6.7%)	2 (6.5%)	0.347
2001-3000	21 (70%)	26 (83.9%)	
3001-4000	7 (23.3%)	3 (9.7%)	

*Occupation = occupation that may be confounded the skin between palm and sole or hand and foot i.e., carpenter, driver, gardener, janitor, laborer, mechanic, painter, sculptor, cleaner; **, stomatitis, diarrhea; ***, Compliance: 100% = Good, <100% =Less; Abbreviation: SD, standard deviation; AJCC, American Joint Committee on Cancer; BMI, body mass index; BSA, body surface area; IQR, interquartile range

Table 1. Continued

Baseline Characteristics	Aloe Vera plus Urea cream (n=30)	Urea cream (n=31)	p-value
Dose of capecitabine per BSA			
1500-2000	30 (100%)	31 (100%)	N/A
Chemotherapy partner			
None	8 (26.7%)	9 (29%)	0.421
Irinotecan	1 (3.3%)	4 (12.9%)	
Irinotecan/bevacizumab	1 (3.3%)	0 (0%)	
Mitomycin	1 (3.3%)	0 (0%)	
Oxaliplatin	19 (63.3%)	17 (54.8%)	
Trastuzumab	0 (0%)	1 (3.2%)	
Occupation*			
Yes	22 (73.3%)	9 (29%)	0.001
No	8 (26.7%)	22 (71%)	
Frequency of hand washing (times per day), median (IQR)	5.5 (3, 10)	5 (4, 8)	0.747
Frequency of hand washing (times per day), mean (min, max)	5.7 (2,20)	6(2,15)	
Frequency of foot washing (times per day), median (IQR)	2 (2, 3)	2 (2, 3)	0.585
Frequency of foot washing (times per day), mean (min, max)	2.6(2,6)	2.9(2,10)	
Frequency of Liquid Alcohol use (times per day), median (IQR)	2 (0, 6)	2 (0, 4)	0.964
Frequency of Liquid Alcohol use (times per day), mean (min, max)	2.9(0,10)	2.9(0,10)	
Frequency of Gel alcohol use (times per day), median (IQR)	0 (0, 2)	0 (0, 2)	0.86
Frequency of Gel alcohol use (times per day), mean (min,max)	1.4(0,10)	1.1(0,15)	
Total cycles of capecitabine regimen, median (IQR)	6.5 (3, 8)	8 (6, 8)	0.193
Dose reduction			
No	24 (80%)	23 (74.2%)	0.854
Dose reduction due to hand foot syndrome	4 (13.3%)	5 (16.1%)	
Dose reduction due to other causes**	2 (6.7%)	3 (9.7%)	
Compliance ***			
Less	7 (23.3%)	6 (19.4%)	0.704
Good	23 (76.7%)	25 (80.6%)	

*Occupation = occupation that may be confounded the skin between palm and sole or hand and foot i.e., carpenter, driver, gardener, janitor, laborer, mechanic, painter, sculptor, cleaner; **, stomatitis, diarrhea; ***, Compliance: 100% = Good, <100% =Less; Abbreviation: SD, standard deviation; AJCC, American Joint Committee on Cancer; BMI, body mass index; BSA, body surface area; IQR, interquartile range

13.3% had grades 2–3. In the U group, 64.5% had grades 0–1 HFS and 35.5% had grades 2–3. The differences between the two groups were statistically significant (p = 0.045).

The DLQI results for QOL are presented in Table 4 below. At second cycle, the mean DLQI score was slightly lower in the A+U group (p = 0.048), but the DLQI scores in both groups (DLQI scores of 2–5) indicated only small effects on QOL. There were no significant differences in the DLQI scores at each visit between the two groups in the other cycles.

Due to DLQI scores ≥2 have significant effects on a patient's QOL. So, we compare DLQI between scores of 0-1 (no impact on a patient's QOL) and scores of 2–30 (at least small impact) and also compare between scores of 0-1 and scores of 6-30 (at least a moderate impact) in both groups that showed no significant differences in Table 5. However, there were trends toward lower percentages in the DLQI scores of 2-5 and 6-30 in the A+U group than in the U group.

Discussion

Capecitabine is a commonly used chemotherapeutic agent in clinical practice. One of the most common side effects of capecitabine is HFS, which varies in severity. For more severe HFS, capecitabine must be interrupted or permanently stopped. In clinical practice, 10% urea cream is frequently used as a preemptive strategy to prevent HFS.

In this study, the severity of HFS was significantly lower the A+U group than in the U group (p = 0.045), but there was no significant difference in the DLQI scores. This significant benefit was found despite our demographic analysis findings showing that there were more patients with occupations that might be associated with an increased risk of HFS in the A+U group than in the U group. However, there was no clinically significant when adjusted with univariate analysis.

Table 2. Severity of Hand Foot Syndrome Per Each Visit

Time Point	Treatment	N	Grade 0	Grade 1	Grade 2	Grade 3	Mean CTCAE Grade ± SD	P-value
1st cycle	Aloe Vera	30	30 (100%)	0 (0%)	0 (0%)	0 (0%)	0.03 ± 0.18	0.999
	Urea cream	31	30 (96.8%)	1 (3.2%)	0 (0%)	0 (0%)	0.16 ± 0.37	
2nd cycle	Aloe Vera	30	22 (73.3%)	7 (23.3%)	1 (3.3%)	0 (0%)	0.1 ± 0.4	0.227
	Urea cream	31	16 (51.6%)	14 (45.2%)	1 (3.2%)	0 (0%)	0.35 ± 0.61	
3rd cycle	Aloe Vera	28	17 (56.7%)	9 (30%)	1 (3.3%)	1 (3.3%)	0.21 ± 0.5	0.797
	Urea cream	29	12 (38.7%)	14 (45.2%)	2 (6.5%)	1 (3.2%)	0.62 ± 1.21	
4th cycle	Aloe Vera	20	11 (36.7%)	6 (20%)	2 (6.7%)	1 (3.3%)	0.65 ± 0.88	0.248
	Urea cream	26	10 (32.3%)	9 (29%)	6 (19.4%)	1 (3.2%)	0.92 ± 0.89	
5th cycle	Aloe Vera	17	7 (23.3%)	8 (26.7%)	2 (6.7%)	0 (0%)	0.71 ± 0.69	0.504
	Urea cream	24	9 (29%)	9 (29%)	5 (16.1%)	1 (3.2%)	0.92 ± 0.88	
6th cycle	Aloe Vera	17	7 (23.3%)	6 (20%)	3 (10%)	1 (3.3%)	0.88 ± 0.93	0.675
	Urea cream	24	9 (29%)	8 (25.8%)	4 (12.9%)	3 (9.7%)	1.04 ± 1.04	
7th cycle	Aloe Vera	15	7 (23.3%)	5 (16.7%)	3 (10%)	0 (0%)	0.73 ± 0.8	0.9
	Urea cream	20	9 (29%)	7 (22.6%)	3 (9.7%)	1 (3.2%)	0.8 ± 0.89	
8th cycle	Aloe Vera	13	6 (20%)	6 (20%)	0 (0%)	1 (3.3%)	0.69 ± 0.85	0.256
	Urea cream	17	6 (19.4%)	5 (16.1%)	4 (12.9%)	2 (6.5%)	1.12 ± 1.05	

Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events; SD, standard deviation

Table 3. Severity of Hand Foot Syndrome

CTCAE Version 5 (Maximum Grade)	Aloe Vera plus Urea cream (n=30)	Urea cream (n=31)	P-value
Grade 0	16 (53.3%)	9 (29%)	
Grade 1	10 (33.3%)	11 (35.5%)	
Grade 2	2 (6.7%)	5 (16.1%)	
Grade 3	2 (6.7%)	6 (19.4%)	
Grade 0-1	26 (86.7%)	20 (64.5%)	
Grade 2-3	4 (13.3%)	11 (35.5%)	0.045*

Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events

A strength of our study is that HFS was graded by one dermatologist who was blinded to the skin treatments used by the patients throughout the study. Second, we provided the patients with a protocol on how to apply the aloe vera cream and urea cream, which included sequences and doses of the products, and at every visit, we re-checked and asked the patients if they had correctly applied the aloe vera and urea cream. Finally, this trial was conducted in the COVID-19 era in which the patients' behaviors probably changed; e.g., the patients tended to wash their hands more frequently or even use alcohol gel or liquid more often than without the presence of COVID-19 in the community, but our results still showed that aloe vera gel

Table 4. Dermatology Life Quality Index Score Per Each Visit

Time Point	Treatment	N	Mean ± SD	Median (IQR)	P-value
1st cycle	Aloe Vera	30	0.03 ± 0.18	0 (0, 0)	0.174
	Urea cream	31	0.16 ± 0.37	0 (0, 0)	
2nd cycle	Aloe Vera	30	0.1 ± 0.4	0 (0, 0)	0.048
	Urea cream	31	0.35 ± 0.61	0 (0, 1)	
3rd cycle	Aloe Vera	28	0.21 ± 0.5	0 (0, 0)	0.36
	Urea cream	29	0.62 ± 1.21	0 (0, 1)	
4th cycle	Aloe Vera	20	1 ± 2	0 (0, 1)	0.954
	Urea cream	26	1 ± 3	0 (0, 1)	
5th cycle	Aloe Vera	17	1.11 ± 2.42	0 (0, 1)	0.566
	Urea cream	24	1.71 ± 3.13	0 (0, 2)	
6th cycle	Aloe Vera	17	1.24 ± 2.93	0 (0, 1)	0.629
	Urea cream	24	1.88 ± 3.55	0 (0, 2)	
7th cycle	Aloe Vera	15	1 ± 2.36	0 (0, 1)	0.396
	Urea cream	20	1.75 ± 2.94	0 (0, 2)	
8th cycle	Aloe Vera	13	0.38 ± 0.77	0 (0, 0)	0.088
	Urea cream	17	1.94 ± 3.31	1 (0, 2)	

Abbreviation: SD, standard deviation; IQR, interquartile range

Table 5. Classified Dermatology Life Quality Index According to Affect to Quality of Life

DLQI Score (Maximum Score)	Aloe Vera plus Urea cream (n=30)	Urea cream (n=31)	P-value
Score 0-1	23 (76.7%)	20 (64.5%)	0.655
Score 2-5	5 (16.7%)	6 (19.4%)	
Score 6-10	1 (3.3%)	3 (9.7%)	
Score 11-20	1 (3.3%)	2 (6.5%)	
Score 21-30	0 (0%)	0 (0%)	
Score 0-1	23 (76.7%)	20 (64.5%)	0.298
Score 2-30	7 (23.3%)	11 (35.5%)	
Score 0-1	23 (76.7%)	20 (64.5%)	0.221
Score 6-30	2 (6.6%)	5 (16.1%)	

Abbreviation: DLQI, dermatology life quality index

plus 10% urea cream was more effective in significantly decreasing the incidence of HFS than 10% urea cream alone. The baseline demographic characteristics showed that there was no significant difference in the frequency of alcohol usage in gel or liquid form between the two groups.

Given that this trial was conducted during the COVID-19 pandemic, there was no suitable time period between which the incidences of HFS could be compared, but a previous study reported that grade 3 toxicity occurred in 10%-20% of the study group subjects treated with urea cream [7]. In our trial, the incidence of grade 3 HFS was 6.7% in the A+U group but only 19.4% in the U group, which is a result similar to that of the historical report above. However, this is a cross-comparison, therefore more studies are needed to better evaluate this aspect.

Additionally, a previous study about topical diclofenac in the prevention of HFS in patients receiving capecitabine also showed the significantly associated with lower grade 2 or 3 HFS compare with placebo [14]. So, the further study that compare between the topical diclofenac and the aloe vera gel plus urea cream may be interested.

A limitation is first, our study was that it was conducted at a single institution (Vajira Hospital), which may mean that the findings might not be representative for a larger population. Second, due to the limitation of time to follow-up of the subjects in this study, all patients visited to follow up at the third cycle. At that time, some of patients were confirmed progressive disease that need to change chemotherapy regimen as well as after the third cycle, some of patients still not visit for next cycle and few patients were loss to follow up with unknown reason. Those things make a difference in the median total number of capecitabine cycles that were 6.5 and 8 in the A+U group and the U group, respectively. However, the onset of HFS was reported at 2-3 months or 3-4 cycles after received capecitabine. Thus, longer follow up may clearly define the efficacy of treatments. Third, application compliance was poor, 76.7% in the aloe vera plus 10% urea cream group and 80.6 % in the 10% urea cream alone group. Finally, this study was phase II trial, further phase III study may need to conduct to confirm the efficacy of aloe vera gel plus 10% urea cream for HFS prevention. Interestingly, the future research about aloe vera gel in aspect of other skin problems may be conducted.

In conclusion, the incidence of high-grade HFS was significantly lower when treated with a combination of aloe vera gel with 10% urea cream than when treated with 10% urea cream alone in patients with cancer treated with capecitabine. There was no significant difference in DLQI QOL between the two groups.

Author Contribution Statement

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Ethical approval

This study was approved by Vajira institutional Review Board (COA 236/2564).

Conflict of interest

The authors declare that there is no conflict of interest in this study. The principal investigator can provide the data of this study if requested.

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