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Randomized controlled trial on the efficacy of topical urea-based cream in preventing capecitabine-associated hand-foot syndrome

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Abstract

Background Hand-foot syndrome (HFS) is a common adverse event of capecitabine causing treatment modifications. Topical urea cream can reduce sorafenib-induced hand-foot skin reaction. However, its benefit in preventing capecitabine-associated HFS was not seen early in the course and had been unknown with long-term use. The aim of this study was to evaluate the efficacy of urea cream for HFS prophylaxis throughout capecitabine treatment.

Methods Patients with cancer who received capecitabine were randomized (1:1) to receive usual care alone or in combination with urea-based cream. The incidence and degree of HFS were assessed at each capecitabine cycle. The primary endpoint was the proportion of patients with any grade HFS. The secondary endpoints included the proportion of patients with severe (≥ grade 3) HFS, modifications in capecitabine because of HFS, and HFS onset.

Results After a median of six capecitabine cycles, any grade HFS was reported by 68 of 109 patients (62.4%) who received usual care and by 60 of 107 patients (56%) who used urea cream ($p=0.36$). The patients who received usual care and urea cream had similar proportions of grade 3 HFS occurrence [52 (47.7%) vs. 44 (41.1%), respectively, $p=0.34$] and needed capecitabine modification because of HFS [20 patients (18.3%) vs. 17 patients (15.9%), respectively, $p=0.89$], as well as similar HFS onset.

Conclusions Urea-based cream did not prevent capecitabine-associated HFS, reduce capecitabine modification, and delay HFS onset. However, it had a tendency to lessen HFS severity, especially in the later cycles of capecitabine.

Clinical trial registration number ClinicalTrials.gov Identifier: NCT05348278, registered on April 21, 2022.

Keywords Hand-foot syndrome, Capecitabine, Urea cream, Prophylaxis

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Introduction

Hand-foot syndrome (HFS) is one of the common dermatologic adverse events (AE) of chemotherapy and targeted therapy. Nagore E et al. reported that the common chemotherapeutic agents that cause HFS include pegylated liposomal doxorubicin, docetaxel, and fluoropyrimidines, such as 5-FU, capecitabine, and TS-1 [1]. Although HFS usually does not lead to a life-threatening condition, it can cause discomfort, impair daily activities, and affect quality of life. In the early phase, patients frequently report hyperpigmentation, swelling, and redness of the palms and soles. Subsequently, these symptoms can progress to sores, fissures, blisters, or paronychia. As a result, in some patients, the inevitable chemotherapy interruption or dose modification might affect the outcomes of cancer therapy.

Capecitabine is a fluoropyrimidine-based chemotherapy that is widely used for gastrointestinal cancers and breast cancer. The reported incidence of capecitabine-associated HFS ranged from 22 to 77% [2]. In 28% of patients treated with capecitabine, severe HFS (≥ grade 3) affected the activities of daily living. The pathogenesis of capecitabine-associated HFS is unclear. One hypothesis is the epidermal accumulation of thymidine phosphorylase, which converts capecitabine to 5-FU and leads to skin damage. The pathological features of HFS include a well-defined band of acantholytic dyskeratotic keratinocytes, inflammation at the dermoepidermal junction with papillary dermal edema, blood vessel dilation, and lymphocytic infiltration. The standard measures to prevent HFS secondary to capecitabine include provision of initial information on the possible symptoms, advice to maintain skin moisture, and prevention of trauma to the hands and feet.

Many studies have been conducted on the use of several drugs to prevent anticancer treatment-associated HFS [3–7]. Urea cream, which is a topical moisturizer with moderate keratolytic effect, had been widely used to treat several cutaneous conditions, such as hyperkeratosis and eczema. In patients with disturbed activities of daily living because of HFS, urea cream is frequently prescribed as a symptom-based treatment, along with capecitabine modifications. Several reports on patients receiving sorafenib for liver cancer demonstrated that urea-based cream prophylaxis could reduce the incidence of HFS but provided few effects in terms of preventing sorafenib dose modifications [8, 9]. However, evidence-based data to support urea cream prophylaxis for capecitabine-associated HFS had been controversial. A meta-analysis reported that urea cream reduced the incidence of at least grade 2 HFS among patients receiving capecitabine [3]. In randomized study on patients who received capecitabine at dosage of 1,000 or 1,250 mg/m^2 twice daily for 14 days at 21-day interval for at least four cycles, the HFS incidence was low and the combination of urea cream/ lactic acid had no benefits in preventing HFS after the first cycle of capecitabine [5]. Another study on patients who received 6 weeks of capecitabine for gastrointestinal or breast cancer demonstrated that the proportion of patients who developed HFS was significantly lower in those who received urea cream (22.4%) than in those who applied the emerging drug Mapisal (Medac, Wedel, Germany) (39.5%) [4].

Although previous studies have reported the potential benefits of urea cream for HFS prevention, guidance on application to real-world clinical practice had been limited. The efficacy of urea cream for HFS prevention in patients who received sorafenib, which is another anticancer therapy, has been previously demonstrated [8, 10]. To date, there had been no clinical trial that clearly demonstrated the efficacy of urea cream in preventing or reducing the severity of HFS after more than one cycle of capecitabine. Previous studies have demonstrated that the cumulative incidence of HFS increases with the number of capecitabine cycles administered [1, 12]. These findings align with real-world clinical observations at our institution. The results of previous trials might be inadequate to demonstrate a significant effect of urea cream on HFS prevention, because the duration of follow-up did not include the entire period of capecitabine treatment [4, 5]. Therefore, we conducted a randomized controlled study to evaluate the efficacy of urea cream in preventing capecitabine-associated HFS, in order to provide guidance for future practice and to improve the care for patients who usually receive capecitabine for up to 6 months.

Methods

Study design

In this randomized controlled open-label study, computer-generated mixed blocks of 2, 4, 6, and 8 allocation schedules were used to randomly assign at a 1:1 ratio all eligible patients to receive urea cream prophylaxis plus usual care or usual care only. Randomization was stratified by concomitant anticancer therapy (e.g., capecitabine monotherapy or capecitabine combined with another systemic anticancer drug). Urea cream application was assigned based on prior randomization using sequentially numbered, opaque sealed envelope generated by an investigator. All patients were followed up and assessed by a separate assessor until 4-week after the last cycle of capecitabine. The trial protocol was approved by the Siriraj Institutional Review Board and was supported by a grant from Siriraj Research Development Fund (Managed by the Routine to Research: R2R), Mahidol University, Protocol Number 679/2564(IRB2). The trial protocol was registered in ClinicalTrials.gov as clinical trial number

NCT05348278 on April 21, 2022. The trial adheres to CONSORT guideline.

Patients

The eligible patients were ≥18 years old; had confirmed solid malignancy; and were scheduled to start treatment with capecitabine, which was given at a dose of at least 2,000 mg/m^2/day on days 1–14 every 21 days for a minimum of three cycles, at the Division of Medical Oncology, Department of Medicine, Faculty of Medicine Siriraj Hospital between November 2021 and December 2022. Combination with another systemic anticancer therapy was allowed. Patients with previous dermatologic conditions, neuropathy, or known allergy to urea cream were ineligible. Patients who routinely used or were prescribed other topical agents for the hands and/ or feet were excluded. All patients provided written informed consent and were able to record all treatment-related symptoms by interview or in the self-completed electronic records as scheduled.

Procedures

All patients in both study arms were informed about the symptoms of HFS and other capecitabine-related toxicities and were advised to practice general HFS preventive measures, including keeping their hands and feet moisturized and avoiding traumatic abrasions. The urea cream group was instructed to apply 10% urea cream at 0.5 FTU or 0.25 g to each palm and at 1 FTU or 0.5 g to each sole twice daily from the initiation of capecitabine. On day 20 of each cycle, all patients were reminded by either phone or LINE Official application, as they preferred, to complete the electronic questionnaire and return any remaining urea cream (for the urea cream group) on the next visit. The left-over urea cream was weighed to determine estimate urea cream use. Once HFS occurred, marking the achievement of primary endpoint, the primary physician was given the discretion to treat patients who developed HFS, including the use of urea cream. The severity of HFS, along with the other adverse events and any modifications to capecitabine therapy, were continuously recorded until the completion of capecitabine therapy.

Assessment

On day 20 of each cycle, all patients were required to complete the electronic record of AEs, degree of HFS, satisfaction, estimate use of urea cream (the urea cream group), and other topical agents used. The patients were followed up until the fourth week from day 1 of the last capecitabine cycle and were asked to complete the final record. The severity of HFS was based on the Common Terminology of Adverse Event CTCAE v.5.0 [13]. The presence and degree of HFS were categorized as patient- and physician-reported outcomes. The patient-reported outcomes were reported using electronic questionnaires at every cycle. Physician-reported HFS and the other AEs of chemotherapy were recorded based on the primary oncologists' assessment. The patient- and physician-reported degree and occurrence of HFS were separately reported. All AEs were measured by the CTCAE criteria at baseline and every 3 weeks. The onset of HFS was based on the patient- and physician-reported first occurrence HFS during the capecitabine cycle. Occurrence of HFS and compliance to topical drugs, including other extra-protocol topical agent (if any) taken after enrollment, were collected from enrollment to HFS onset. Alternatively, worst HFS degree and capecitabine modification because of AEs were recorded throughout the duration of capecitabine therapy, regardless of any HFS treatment or capecitabine dose modification.

Statistical analysis

The primary hypothesis was that urea cream prophylaxis was superior to usual care in terms of the rate of HFS prevention. Based on the hypothesis of HFS rate reduction from 60% [14] to 40% among patients who received urea cream prophylaxis, 97 evaluable patients per group were required to achieve 80% power and two-sided alpha error of 0.05. To account for a 10% dropout rate, the accrual targets were adjusted to a total of 107 patients in each arm.

The primary endpoint was any grade patient-reported HFS rate during capecitabine therapy. The secondary endpoints included incidence of severe (≥grade 3) HFS, onset of HFS, and percentage of patients who needed capecitabine dose modification and/ or discontinuation because of HFS or other AEs.

All demographic data were reported using descriptive statistics, i.e. median and range for continuous data and frequency with percentage for categorical data. Occurrence of HFS, degree of HFS, capecitabine modification, and other AEs were analyzed by the Pearson's Chi-square test. HFS occurrence was reported as a frequency in each cycle and was compared using Chi-square test. All analyses were based on an intention-to-treat design. Two-sided p values were used throughout the study. All statistical analyses were performed using SPSS version 20 (SPSS Statistics, IBM Corp. Armonk, NY, USA).

Results

Patient characteristics

A total of 216 patients were enrolled during the study period; 109 and 107 patients were randomly assigned to receive usual care only and urea cream with usual care, respectively. The demographic and clinical characteristics were similar between the two groups (Table 1). Majority of the patients were treated for colorectal cancer (86.6%) with either oxaliplatin combined with capecitabine or

Table 1 Baseline demographic and clinical characteristics

Characteristics	Usual care (*N* = 109)	Urea cream + Usual care (*N* = 107)
Age, years		
Mean (SD)	60.8 (11.2)	59.8 (11.4)
Sex, n (%)		
Male	63 (57.8)	47 (43.9)
Female	46 (42.2)	60 (56.1)
ECOG performance score, n (%)		
0	11 (10.1)	12 (11.2)
1	97 (89)	89 (83.2)
2	1 (0.9)	6 (5.6)
Cancer types, n (%)		
Colorectal	94 (86.2)	93 (86.9)
Hepatobiliary	7 (6.4)	3 (2.8)
Breast	5 (4.6)	9 (8.4)
Others	3 (2.8)	2 (1.9)
Combined agent, n (%)		
None	23 (21.1)	21 (19.6)
Oxaliplatin	83 (76.1)	84 (78.5)
Others	3 (2.8)	2 (1.9)
Preexisting comorbidity, n (%)		
Diabetes	16 (14.7)	14 (13.1)
Hypertension	27 (24.8)	30 (28)
Chronic kidney disease	2 (1.8)	1 (0.9)

ECOG, Eastern Cooperative Oncology Group

Table 2 Worst grade of HFS throughout capecitabine therapy

Degree of worst HFS	Usual care (*N* = 109)	Urea cream + Usual care (*N* = 107)	*p* value
HFS grade based on patients' report, n (%)			
Any grade	70 (62.8)	60 (56.1)	0.36
≥grade 2	64 (58.7)	59 (55.1)	0.35
≥grade 3	51 (46.8)	43 (40.2)	0.2
HFS grade by physician assessment, n (%)			
Any grade	49 (45)	38 (35.5)	0.17
≥grade 2	37 (33.9)	31 (29)	0.46
≥grade 3	16 (14.7)	10 (9.3)	0.3

HFS, hand-foot syndrome

capecitabine as a single agent. There were 23 patients (21.1%) in the usual care group and 21 patients (19.6%) in the urea cream group who received single-agent capecitabine. Almost all patients received capecitabine at a dose of 2,000 mg/m^2 twice daily for 14 days every 21 days. The most common comorbidity in both groups was hypertension, followed by diabetes and mild chronic kidney disease in a few patients.

HFS occurrence and severity

Table 2 shows the occurrence and degree of HFS. Of 216 patients, 66 (62.8%) who received usual care and 58 (56.1%) who received urea-based cream reported at least grade 1 HFS ($p = 0.34$). Severe HFS at any point during capecitabine therapy was reported by 51 patients (46.8%) and 43 patients (40.2%) who received usual care and urea-based cream, respectively ($p = 0.2$). In the usual care and urea-based cream groups, the physician-reported HFS onset was any grade HFS in 49 patients (45.0%) and 38 patients (35.5%), respectively ($p = 0.17$) and severe HFS in 14.7% and 9.4% patients, respectively ($p = 0.3$).

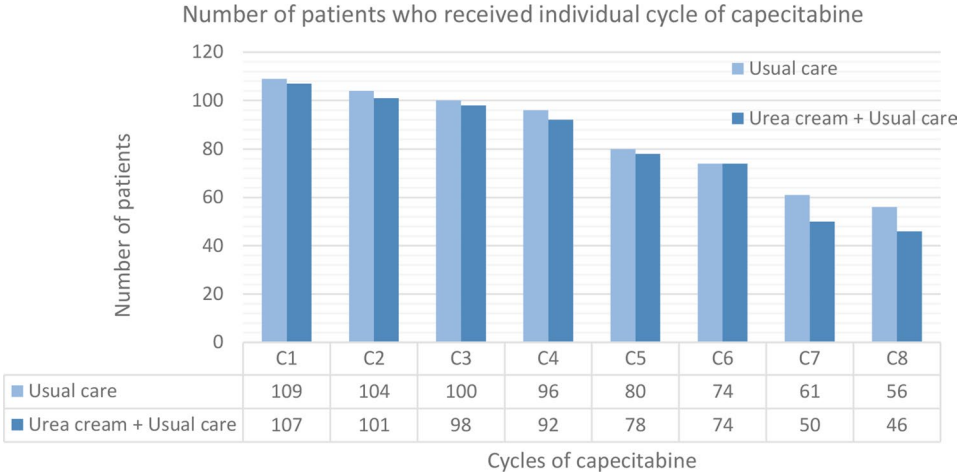
The number of patients who received each cycle of capecitabine is demonstrated in Fig. 1. Overall and in each group, the median number of capecitabine cycles was six. Majority of patients (37%) reported HFS onset during the first or second cycle (Fig. 2a). Conversely, physician-reported HFS onset was most frequent during the second cycle, followed by the third cycle (Fig. 2b). The percentage of patients with HFS in each cycle is demonstrated in Fig. 3. There was a trend of increasing percentage of patients with HFS over time, with more patients having HFS after the fourth cycle of treatment (Fig. 3a). Similarly, the severity of HFS increased with the duration of capecitabine therapy (Fig. 3b). The percentage of patient-reported any grade HFS and severe HFS during the fifth and sixth cycles of capecitabine tended to be higher in the usual care group. Noticeably, the incidence of HFS during the first to the fourth cycles of capecitabine therapy was similar between the two groups.

Capecitabine modifications

Table 3 shows the capecitabine modifications (i.e., dose reduction, delay, or discontinuation) because of AEs. Capecitabine modifications because of significant HFS were required in 20 patients (18.3%) who received usual care and in 17 patients (15.9%) who received urea cream ($p = 0.69$). Capecitabine discontinuation because of severe HFS was needed in two patients (2.5%) in each group. The number of patients who required capecitabine discontinuation because of AEs other than HFS was higher in the usual care group than in the urea cream group.

Compliance and adverse events of topical urea cream

In the urea cream group, compliance on the use of this topical agent was good. The weight of the remaining urea cream after each cycle was recorded. Based on the weight of the remaining urea cream after each cycle, 86 patients (80.4%) adhered to the assigned topical treatment, with reported consumption of >50% of the prescribed urea cream. There was no significant difference in HFS occurrence between patients who adhered to the prescribed urea cream (59.3%) and those who did not (47.9%). Use of an outside-protocol topical agent for the hands or feet was reported by nine patients (8.3%) in the usual care group and by 11 patients (10.3%) in the urea cream group ($p = 0.64$). There was no other skin reaction, except HFS, were observed in either group.



	C1	C2	C3	C4	C5	C6	C7	C8
Usual care	109	104	100	96	80	74	61	56
Urea cream + Usual care	107	101	98	92	78	74	50	46

Fig. 1 Number of patients who received individual cycle of capecitabine

Discussion

Several HFS prevention strategies have been tested in randomized controlled trials, but none has been distinctly proven to be successful. During the past decade, pyridoxine had been one of the most frequently studied candidates, but it failed to show efficacy in HFS prevention [6, 7, 15]. Recently, one study reported the potential of celecoxib to prevent HFS by reducing the overexpression of cyclooxygenase-2 in tissue injury and necrosis induced by systemic anticancer agents [16]. Some meta-analyses showed that celecoxib could effectively reduce chemotherapy-induced grade 2 or higher HFS [17–19]. Despite its potential efficacy in preventing HFS, long-term celecoxib should be used with caution because of the associated cardiovascular side effects.

Urea-based cream is an inexpensive, readily available, and well-tolerated moisturizer and keratolytic agent. The hypothesized mechanisms of urea cream in preventing HFS include hyperkeratosis prevention, induction of keratocyte necrosis, and inhibition of chemotherapy-induced cutaneous inflammation [3]. The preventive property of urea cream for hand-foot skin reaction was demonstrated in patients receiving sorafenib for hepatocellular carcinoma [9]. However, several randomized controlled trials and meta-analyses on capecitabine- or chemotherapy-induced HFS reported that when compared with placebo, urea cream had insignificant efficacy in HFS prevention [5, 17–19]. A recent meta-analysis by Pandy et al. implied that both urea cream and celecoxib were effective in preventing HFS in patients receiving systemic cancer therapy [10]. Although urea cream for HFS prophylaxis was determined as ineffective in a randomized clinical trial [5], it was reported to be beneficial in the meta-analyses of patients receiving capecitabine and sorafenib [3, 10]. In addition, urea cream application from the initiation of capecitabine is a common practice of some experts in Thailand. Considering the aforementioned, this study was conducted to evaluate the potential of urea cream as an HFS preventive strategy in patients receiving capecitabine. Compared with previous randomized controlled trials, this study had a longer follow-up that covered the entire period of capecitabine treatment. Moreover, we determined the degree of HFS during each visit and prospectively recorded drug compliance and outside-protocol topical agent use.

To our best knowledge, our report was the first randomized controlled study on the potential benefit of urea cream for capecitabine-associated HFS, with extensive follow-up throughout the entire period of capecitabine therapy. We demonstrated trends of lower HFS incidence and lower proportion of severe HFS in patients who received urea cream than in those who received usual care alone. Although this report failed to show a significant benefit of urea cream in decreasing the HFS rate as a primary endpoint, there was a trend toward a 6% improvement in the rate of any grade HFS.

Our study observed an HFS incidence that was in the low end of the previously reported range [20–23]. One possible reason was that most of our patients received capecitabine at a daily dose of 2,000 mg/m^2 rather than a larger dose of 2,500 mg/m^2. This substantial reduction in the capecitabine dose was needed to prevent other AEs, such as myelosuppression, because majority of our patients received capecitabine in combination with other chemotherapy agents, mainly oxaliplatin. This situation might explain the absence of a demonstrable significant benefit of urea cream for capecitabine-associated HFS prevention in our real-world practice. Moreover, the insufficient benefit of urea cream in reducing severe HFS can explain the reduced need for capecitabine modifications.

Although urea-based cream had no clear benefit in reducing the rate of any grade HFS in this study, it had a tendency to lessen the degree of HFS at a specific time

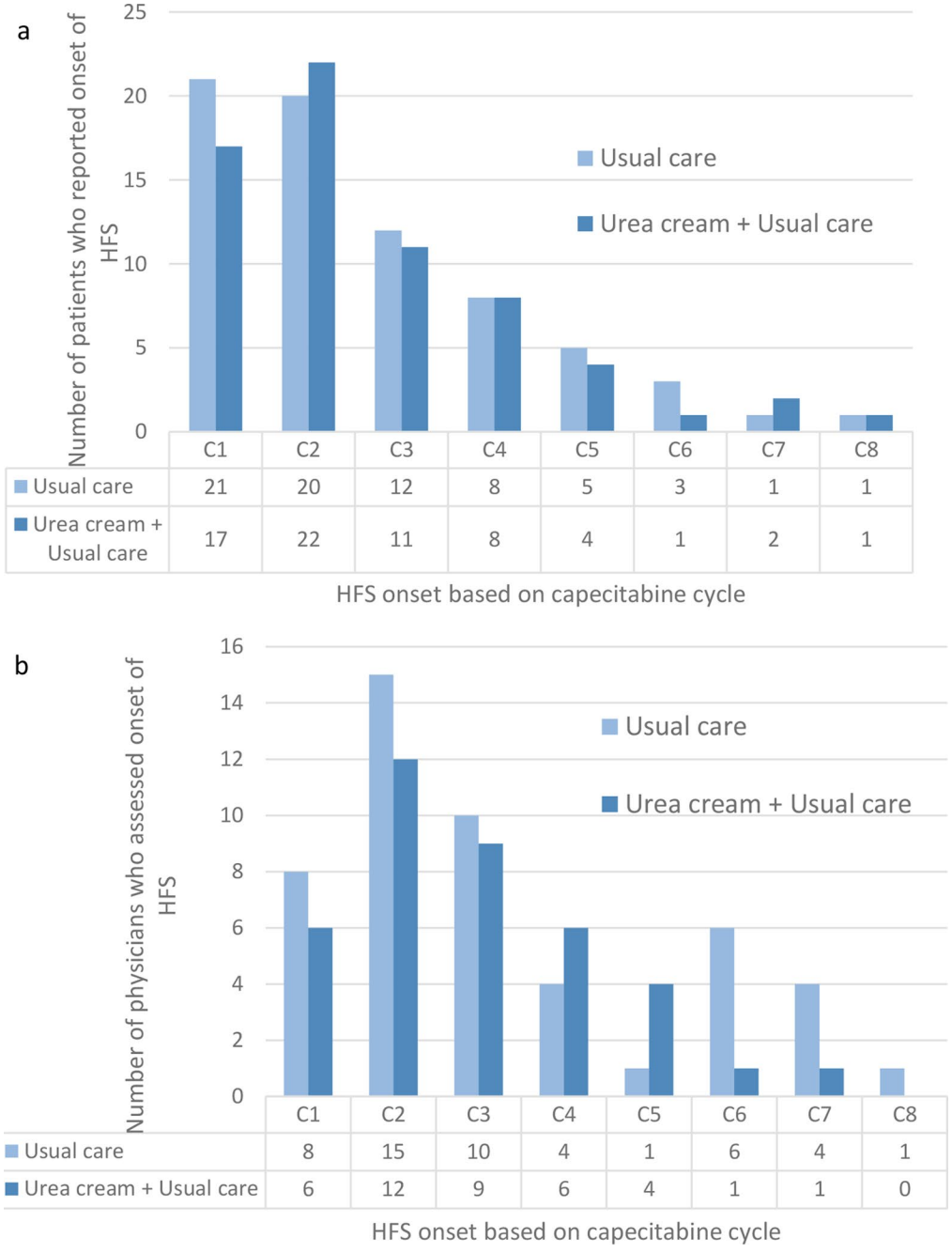


Fig. 2 Prevalence of hand foot syndrome onset during each cycle of capecitabine (**a**) patient-reported and (**b**) physician-assessed.

point during capecitabine therapy. The lack of significant difference in capecitabine modifications may be due to the minimal difference in severe HFS. Physicians may have been hesitant to adjust the dosage due to concerns about compromising anti-cancer efficacy, particularly in patients with prior dose reductions due to other adverse events (approximately one-third of participants in our study). The peak onset of HFS was in early period of capecitabine therapy, but any grade HFS and severe HFS after the fourth cycle of capecitabine were less frequent in the urea cream group than in the usual care group. In the other words, the frequency of any grade HFS and severe HFS did not differ between the two groups during the first to the fourth capecitabine cycles. The potential benefit of administering preventive topical urea cream in patients undergoing long-term capecitabine therapy may be associated with the increased incidence of capecitabine-associated HFS, which occurs as a result of its cumulative effects. These findings might be useful for the adjustment of HFS preventive measures in clinical

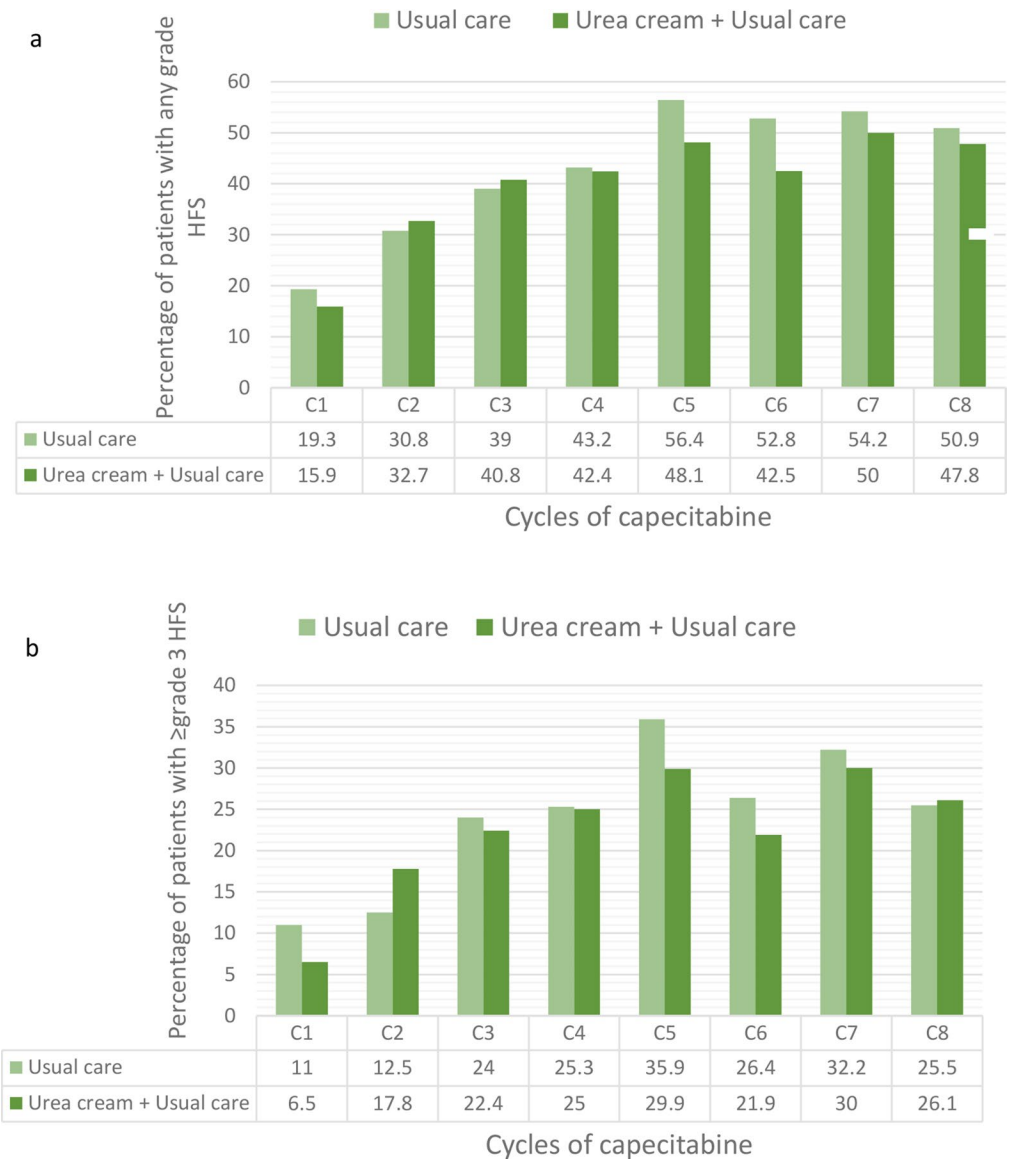


Fig. 3 Percentage of patients with hand foot syndrome (HFS) during each cycle of capecitabine-containing regimen. (**a**) any grade HFS and (**b**) ≥ grade 3 HFS

Table 3 Capecitabine modifications

Capecitabine modifications	Usual care (*N* = 109)	Urea cream + Usual care (*N* = 107)	*p* value
Capecitabine dose reduction and/or delay, n (%)			0.89
No	55 (50.5)	56 (52.3)	
Yes, because of HFS	20 (18.3)	17 (15.9)	
Yes, because of other AEs	34 (31.2)	34 (31.8)	
Cause of capecitabine discontinuation, n (%)			0.18
HFS	3 (2.8)	3 (2.9)	
Other AEs	21 (19.8)	9 (8.7)	
Disease progression	11 (10.4)	17 (16.5)	
Patient preference	5 (4.7)	6 (5.8)	

HFS, hand-foot syndrome; AE, adverse event

practice. The use of urea cream for HFS prevention might not be suitable for patients in whom only 3 months of capecitabine therapy (i.e., CAPEOX in low-risk stage III colon cancer) is planned. Alternatively, urea cream prophylaxis may have some benefits for HFS prevention or lessen the degree of HFS among patients who will undergo 6 months of capecitabine therapy. In addition, the timing of urea cream initiation remains questionable. Based on our results, initiation of urea cream prophylaxis may be delayed to the second or third cycle. Future well-planned randomized controlled trial is needed to confirm these inferences.

The main limitation of the study was the opened-label design, which might have potentiated some biases. At the time of any grade HFS occurrence, any treatment,

including urea cream, was allowed based on the physician's discretion. In real-world practice, some oncologists prescribe topical drugs for grade 1 HFS, even if it is temporary and may spontaneously resolve, whereas some oncologists initiate topical agents for ≥ grade 2 or significantly longer HFS. This difference might have affected the severity of the reported HFS but not the primary outcome. Despite appropriate instructions and reminders on compliance every visit, some patients reported incomplete urea cream use. Moreover, approximately 10% of patients in the usual care group preferred to seek for and use other topical agents. Nevertheless, most patients in the urea group adhered to the protocol with good compliance, and only a minority in control group reported the use of outside-protocol topical agents. We believed that these did not affect the main outcome of the study. Other limitations include the study's single-institution design, the heterogeneity of the patient population with various cancer diagnoses, and the administration of different doses of capecitabine, either as monotherapy or in combination with other chemotherapeutic agents.

Conclusions

Urea-based cream did not prevent capecitabine-associated HFS, reduce the need to modify capecitabine, and delay HFS onset. While this study does not support routine use of urea cream to prevent capecitabine associated HFS, it may offer some benefit for patients undergoing longer treatment regimens, particularly after the fourth cycle of capecitabine.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-13684-1.

Supplementary Material 1

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Author contributions

Conceptualization: C.W, K.C, S.I; Methodology: C.W, K.C, A.L, A.N, S.I; Formal analysis and investigation: C.W, K.C, S.I, A.L; Writing - original draft preparation: C.W, K.C, S.I; Writing - review and editing: All authors; Funding acquisition: S.I, A.N; Resources: K.C, A.L; Supervision: A.N, L.C, S.I.

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Data availability

The data that support the findings of this study are available from the Faculty of Medicine Siriraj Hospital, but restrictions apply to the availability of these data, which were used under licence for the current study and so are not publicly available. The data are, however, available from the authors upon reasonable request.

Declarations

Ethical approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Siriraj Hospital, Mahidol University (Date October 15, 2021/COA No.SI 790/2021).

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent to publish

Not applicable.

Competing interests

The authors declare no competing interests.

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