RESEARCH ARTICLE

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Usefulness of Hospital and Community Pharmacists Collaborating to Manage Capecitabine-induced Severe Hand-foot Syndrome in Patients with Breast Cancer

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Abstract

Background: The management of capecitabine-related hand-foot syndrome (HFS) is critical to avoid progression of the syndrome through early detection and early response; management of HFS involves joint medication management by physicians and pharmacists (hospital and community pharmacists). This study aimed to evaluate the effectiveness of collaborative medication management in cancer patients with HFS by comparing its effectiveness with the traditional response using monitoring reports from community pharmacists. **Patients and Methods:** Medical records of 120 breast cancer patients who received capecitabine therapy between September 2017 and August 2023 were retrospectively reviewed. Ninety-four patients who received 6 cycles of capecitabine therapy were included. Patients who received care with co-medication management were considered the co-medication group. **Results:** A total of 93 patients were included. The cumulative incidence of Grade 2 or higher HFS was 6% in the intervention group and 68% in the non-intervention group ($p<0.0001$). In addition, when examining factors associated with the development of Grade 2 or higher HFS, the investigators identified 68 years of age or older (OR: 3.07 ;1.06-8.88, $p=0.039$) and continuous pharmacist intervention (OR: 0.070 ;0.0048-0.97, $p=0.047$). **Conclusions:** The findings indicate that pharmacist co-management is an effective activity for capecitabine-related HFS to avoid increasing the severity of the disease.

Keywords: Breast cancer- severe hand-foot syndrome- capecitabine- hospital and community pharmacists

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Introduction

With 1.7 million new cases diagnosed annually, breast cancer is a worldwide concern [1] . Approximately 6–10% of patients with breast cancer present metastatic disease at the time of diagnosis, and more than 30% of patients with non-metastatic disease relapse [2] . Capecitabine is a widely used treatment modality for breast [3, 4], colon [5], and gastric cancers [6]. Capecitabine is often administered after second-line monotherapy or as adjuvant therapy in patients with metastatic breast cancer who are resistant to anthracyclines, taxanes, or both [7, 8].

Common capecitabine-induced adverse events include diarrhea, stomatitis, nausea, neutropenia, and hand-foot syndrome (HFS) [9, 10]. The HFS is characterized by tenderness, redness, and swelling of the palms of the hands and soles of the feet and, although not life-threatening, can debilitate patients and impair their quality of life. In breast and colorectal cancer clinical trials, the overall incidence of capecitabine-related HFS is approximately 50%, with 17% of patients reporting severe forms of the condition (i.e., grade 3) [11].

The clinical presentation of HFS has been well studied and includes numbness, dysesthesia/analgesia, tingling, erythema, swelling that is painless or accompanied by discomfort, and, in more severe cases, blistering, ulceration, desquamation, and severe pain in the palms and soles [12-14]. Many patients exhibit dysesthesia, usually presented as a prickling sensation in the palms and soles, which may progress to pain with swelling and erythema in 3–4 days. In severe HFS cases, discomfort is present and may interfere with the patient's daily activities, eventually even leading to treatment interruption.

Although HFS is treatable, it can rapidly worsen if not properly addressed, resulting in treatment interruption and consequently affecting its effectiveness [15]. The management of capecitabine-induced HFS involves applying moisturizers to the hands and feet and reducing excessive stress on the hands and feet in daily living. In addition, early detection and treatment initiation are

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considered important in the HFS. Although outpatient pharmacist visits knowingly improve treatment adherence for several drugs [16-19], to the best of our knowledge, no studies to date have examined the usefulness of an ongoing intervention conducted in collaboration with out-of-hospital pharmacists to reduce the severity of capecitabine-related HFS. Therefore, this study aimed to demonstrate the usefulness of ongoing pharmacist interventions for reducing the severity of capecitabine-induced HFS.

Materials and Methods

Participants

This single-center, retrospective, observational study was conducted at the Breast Surgery Department of the Hokkaido Cancer Center in Sapporo, Japan. The study protocols followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines, and data were extracted from patients' electronic medical records. Patients who fulfilled the following criteria were included in this study: (i) ≥20 years of age diagnosed with early breast cancer (adjuvant therapy) and metastatic breast cancer; (ii) received capecitabine administration between December 2017 and August 2023. The exclusion criteria were as follows: (i) incomplete data in the patient's medical record or missing baseline laboratory data; (ii) follow-up not possible due to hospital transfer; (iii) experiencing <2 courses of capecitabine administration.

In this study, we created a collaborative work follow-up between pharmacists and physicians regarding HFS control for capecitabine. A particularly important point is early HFS countermeasures using follow-up reports prepared by community pharmacists.

The following is a detailed description of the procedure.

STEP 1

Doctor prescribes capecitabine, moisturiser and, if necessary, steroid ointment.

STEP 2

The hospital pharmacist confirms the doctor's prescription (dosage and type of ointment).

STEP 3

The insurance pharmacy pharmacist conducts a telephone follow-up to assess side-effects and confirm adherence to prescribed drugs. Survey reports on the evaluation of steroid rank-up and use of moisturisers are prepared and emailed to the hospital pharmacist.

STEP 4

After reviewing the report from the insurance pharmacy, the hospital pharmacist assesses the need for early response to side effects, reports to the prescribing physician and responds with additional prescriptions or dose reductions.

The group in which this flow was introduced was defined as the with pharmacist intervention group, and the group before the introduction of the flow was defined as the without pharmacist intervention group (Figure 1). The protocol for the present study was approved by the Ethics Committee of the Hokkaido Cancer Center (approval number: R6-21), and the present study was conducted according to the Declaration of Helsinki and the Ethical Guidelines for Research on Medicine and Medical Technology Involving Human Subjects, issued by the Ministry of Education, Culture, Sports, Science and Technology, and the Ministry of Health, Labor, and Welfare. Owing to the retrospective nature of the study, the need for obtaining informed consent was waived by the Ethics Review Committee, and patients were given the option to be excluded from the study using the opt-out approach through a form on the official website of the hospital.

Surveyed Items and Data Collection

Patient data were de-identified and analyzed anonymously. Data related to the following parameters were recorded for each patient: age; body mass index (BMI); reason for capecitabine treatment discontinuation; and laboratory examination results recorded immediately before treatment initiation, including white blood cell, neutrophil, and platelet counts, and serum albumin, total bilirubin, aspartate aminotransferase, alanine aminotransferase, and serum creatine levels. The follow-up period for the patients ended on July 31, 2023.

Endpoints

The primary endpoint was the comparison of time to develop grade ≥2 HFS between groups with and non-continuous pharmacist intervention in six months. When used as adjuvant therapy after surgery, the observation period was set at 6 months, since the duration of its use is approximately 6 months.

The secondary endpoint was the identification of patient-related risk factors for developing grade ≥2 HFS using multivariate logistic regression analyses. These endpoints were evaluated according to the Common Terminology Criteria for Adverse Events (v5.0).

Statistical Analysis

Patient data were summarized using descriptive statistics such as frequencies and percentages. Continuous variables were reported as medians (ranges), whereas categorical variables were presented as absolute numbers (percentages). Multivariate logistic regression analyses were performed to evaluate the association between patient-related risk factors and grade ≥2 HFS. From the potential explanatory variables reported in several previous studies, we included age, BMI, presence of continuous pharmacist intervention, and steroid ointment prescription at the start of capecitabine treatment as covariates in the multivariate models.

The results were presented as odds ratios (ORs) and 95% confidence intervals (CI). Statistical significance was set at a P-value <0.05 for all analyses. All statistical analyses were performed using the EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for

Statistical Computing, Vienna, Austria)

Results

Background of the Patient Population

Among the 106 patients initially identified, 13 were excluded from the study based on the exclusion criteria. The characteristics of the 93 included participants are shown in Table 1. The median baseline age and BMI of the patients were 60 years (range, 34–87) and 22.4 kg/m^2 (range, 14.1–56.8), respectively.

The incidence of grade ≥2 HFS within 6 months of follow-up was 46.3% (n=43), and the optimal cutoff values for baseline age and BMI for predicting grade ≥2 HFS were determined to be 68 years and 24.5 kg/m^2, respectively (Table 2).

Multivariate Analysis of Risk Factors for Grade ≥2 HFS

The multivariate model included four factors, and the multivariate analysis revealed that a higher age (OR, 3.07; 95% CI, 1.06–8.88; P=0.039) and continuous pharmacist intervention (OR, 0.068; 95% CI, 0.048–0.97; P=0.047) were significantly associated with an increased risk of developing a grade ≥2 HFS (Table 2).

Occurrence of Capecitabine-Induced HFS

The incidence of grade ≥2 HFS in the 93 patients analyzed was 46.3%, and the overall grade was 67.7%. While the incidence of grade ≥2 HFS in the pharmacist intervention group was 5.8%, that in the non-pharmacist intervention group was 55.3%. Furthermore, the pharmacist intervention group had a median time to develop of grade ≥2 HFS not reached median time, while the non-intervention group had a median time to develop of grade ≥2 or HFS of 3.7 months (95% CI 2.1–4.9; P=0.006) (Figure2-a). Therefore, the pharmacist intervention group presented a significantly prolonged time for the onset of grade ≥2 HFS. Additionally, when the same validation was performed for all grades, the pharmacist intervention group reached a time until

Table 1. Patient Characteristics.

Characteristics	
Age (years): Median (range)	60 (34–87)
BMI: median (range)	22.4 (14.1–56.8)
Timing of treatment, n (%)	
Early breast cancer (Adjuvant)	49*
Advanced breast cancer	44
Baseline laboratory data, median (range)	
Albumin (mg/dL)	4.0 (2.1–5.1)
Aspartate aminotransferase	22 (10-147)
Alanine aminotransferase	18 (7-168)
Serum creatinine	0.58 (0.36-1.11)
Estimated Glomerular Filtration Rate	84.9 (40.0-137)
Creatinine clearance	87.0 (30.0-197)
White blood cells	4520 (1880-19500)
Hemoglobin	12.1 (8.0-15.5)
Platelet count	21.8 (5.3-51.5)
Neutrophil count	2620 (780-16500)

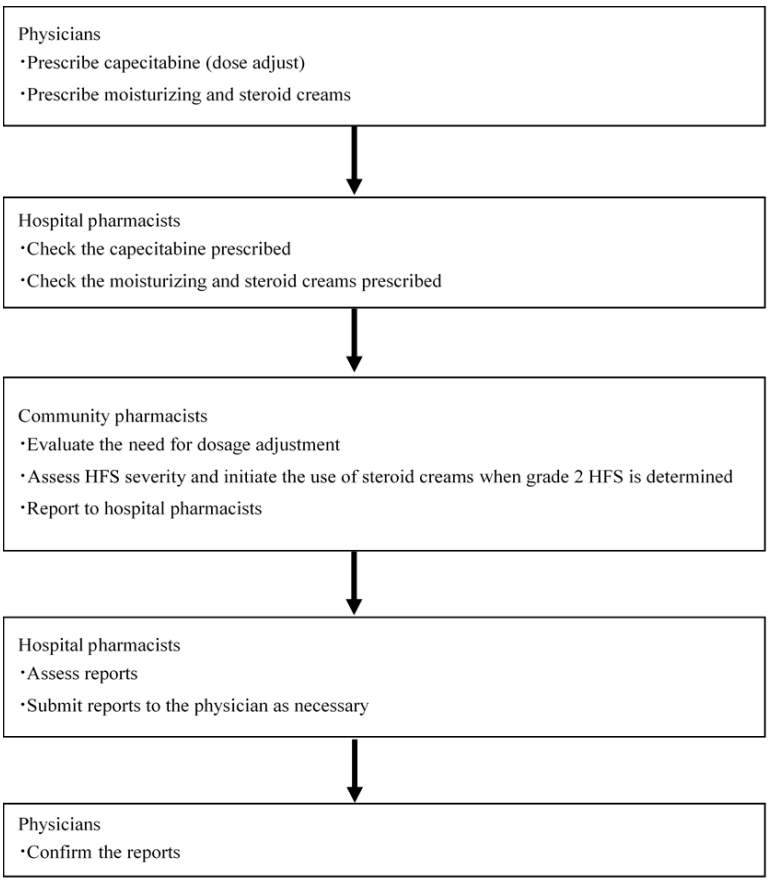
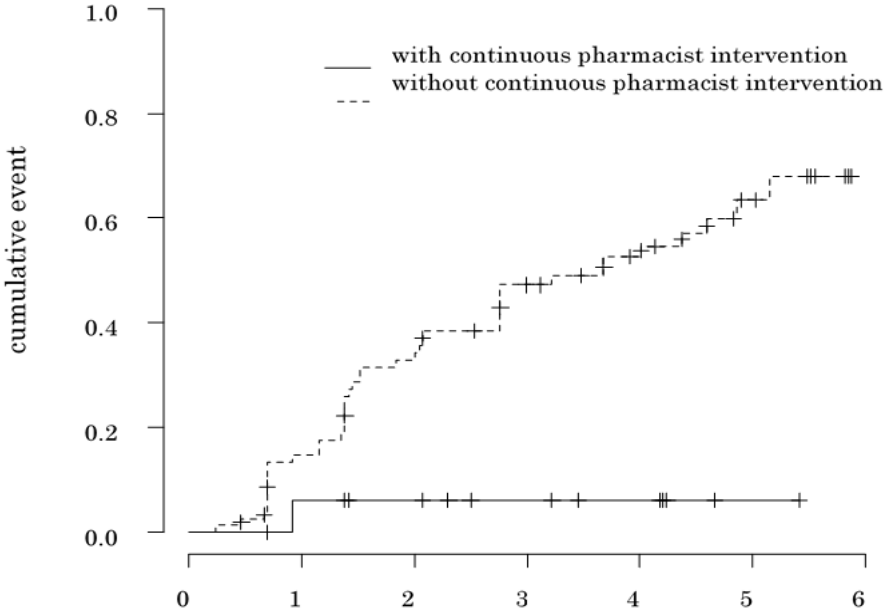


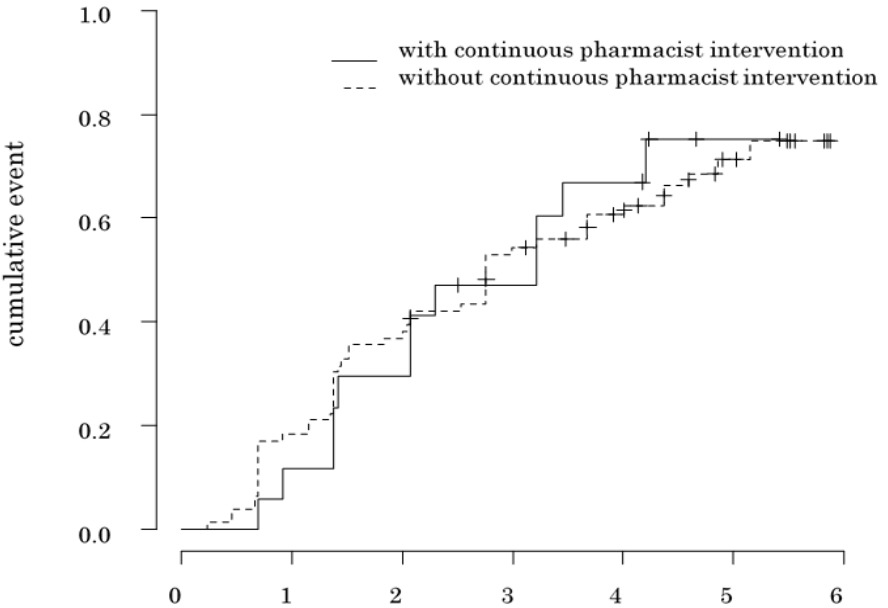
Figure 1. Workflow of the Collaborative Pharmacist Intervention.



Number at risk

with pharmacist intervention	17	15	12	8	5	1	0
without pharmacist intervention	76	62	48	31	23	9	0

Figure 2 (a). Comparison of Cumulative Event Rate of Hand-Foot Syndrome in Grade 2 or more with and without Continuous Pharmacist Intervention with Kaplan–Meier Curves. The continuous pharmacist intervention group significantly prolonged the days to onset of hand-foot syndrome compared to without continuous pharmacist intervention group (not reached vs. 3.7 months [95% CI 2.1–4.9]; P=0.0060). The continuous pharmacist intervention group had a significantly lower cumulative event rate of hand-foot syndrome events compared to the group without continuous pharmacist intervention (6% vs. 68%, P=0.00062).



Number at risk

with pharmacist intervention	17	15	12	8	5	1	0
without pharmacist intervention	76	62	48	31	23	9	0

Figure 2 (b). Comparison of Cumulative Event rate of Hand-foot Syndrome in Grade 1 or more with and without Continuous Pharmacist Intervention with Kaplan–Meier Curves. The continuous pharmacist intervention group significantly prolonged the days to onset of hand-foot syndrome compared to without continuous pharmacist intervention group (3.2 months [95% CI 1.4–4.2] vs. 2.8 months [95% CI 2.0–4.0]; P=0.60). The continuous pharmacist intervention group did not have a significantly different cumulative event rate of hand-foot syndrome events compared to the group without continuous pharmacist intervention (75% vs. 74%, P=0.85).

Table 2. Multivariable Analysis for Occurrence Hand-Foot-Syndrome of Grade > 2 during the Six Cycles.

Clinical variables		Multivariate Analysis	
		OR (95% CI)	P Value
Age	**≥68** v.s. < 68	**3.07 (1.06–8.88)**	**0.039**
Body Mass Index	≥24.5 v.s. < 24.5	0.76 (0.28–2.04)	0.59
Early breast cancer (Adjuvant)	adjuvant v.s. other	0.89 (0.34–2.31)	0.82
Continuous Pharmacist intervention	**yes** v.s. no	**0.070 (0.0048–0.97)**	**0.047**

OR (95% CI) results for significant predictors are in bold.

onset of 3.2 months (95% CI 1.4–4.2), while that in the non-pharmacist intervention group was 2.8 months (95% CI 2.0–4.0), however, without a significant difference between the groups (P=0.60) (Figure2-b). The incidence of Grade 1 hand-foot syndrome with or without pharmacist intervention was 11% and 9%, respectively. However, the incidence of Grade 2 hand-foot syndrome was 1% in with continuous pharmacist intervention group, compared to 28% in the without continuous pharmacist intervention group. Furthermore, Grade 3 did not occur in the intervention group, and the rate was 14% in the non-intervention group (Figure 3).

Discussion

This study provides valuable evidence that pharmacists provide ongoing interventions in the postoperative management of side effects in patients with advanced and early-stage breast cancer treated with capecitabine during outpatient consultations, alongside physicians, reducing the severity of capecitabine-induced HFS. The effectiveness of joint management by an out-of-hospital pharmacist and a hospital pharmacist (pharmacist co-management) for capecitabine-related HFS in patients with cancer was compared to the conventional pharmacotherapy (non-pharmacist intervention) group.

Telephone follow-up by an out-of-hospital pharmacist has been reported to help achieve high adherence and maintain the adequate curative effects of capecitabine [19, 20]. However, most of the previous reports on pharmacist interventions focused on monitoring adverse events of capecitabine therapy through interventions such as telephone follow-up. In the current study, the pharmacist co-management group had adverse events monitored and moisturizing and steroid creams prescribed as necessary, without delays by the out-of-hospital or hospital pharmacists.

Specific interventions performed by the pharmacists in this study included: (i) evaluating the presence of preventive measures for the onset or exacerbation of HFS in daily life; (ii) assessing continuous moisturizer use through telephone follow-up; (iii) early initiation of steroid ointments; and (iv) performing capecitabine dose reduction and withdrawal if necessary. Our results showed that continuous pharmacist intervention significantly prolonged the number of days until the onset of grade ≥2 HFS in the pharmacist intervention group, with multivariate analysis revealing that pharmacist intervention was a risk-reducing factor for the onset of grade ≥2 HFS (Table 2, Figure 2). We found an incidence

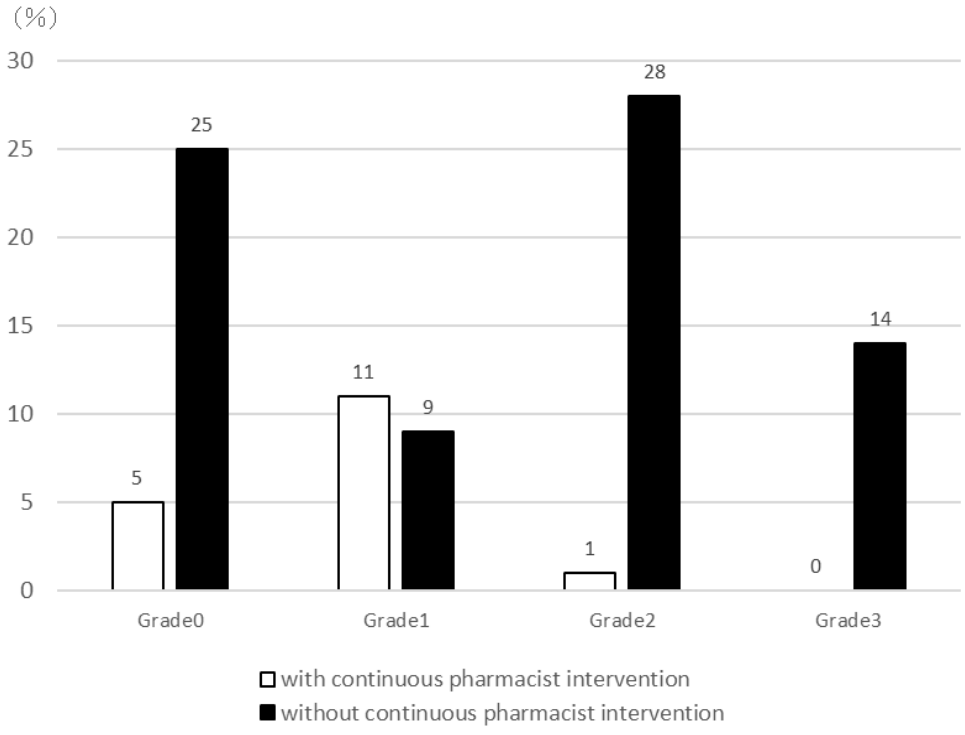


Figure 3. Comparison of Hand-foot Syndrome Occurrence by Grade.

of all grades of HFS of 69%, similar to that of 73% described in previous reports. However, the incidence of grade ≥2 disease in such reports was 36%, which was higher than the 13% identified in our pharmacist intervention group [7].

In our pharmacist intervention group, patients with grade 2 HFS continued to receive capecitabine, with HFS severity improving to grade 1 during the study period, preventing the discontinuation of the capecitabine therapy. In contrast, 14 patients presented HFS that worsened to grade 3 in the non-pharmacist intervention group, with six patients having their capecitabine treatment discontinued due to such adverse effects. Nakamura et al. reported that the introduction of protocol-based pharmacotherapy management for the prescription of moisturizers and steroid creams for managing capecitabine-induced HFS could significantly reduce the occurrence of grade 2 HFS [21]. Thus, we believe that pharmacist intervention can significantly reduce the severity of capecitabine-related HFS.

An age >68 years was identified as a risk factor for the occurrence of capecitabine-related HFS. Although few reports have identified age as a risk factor for capecitabine-associated HFS, careful intervention is required in the elderly, especially to maintain treatment adherence and HFS care. Moreover, the safety and efficacy of capecitabine and oxaliplatin combination therapy in patients with metastatic colorectal cancer aged ≥75 years have been reported [22]. In an analysis of age and capecitabine adherence, a trend toward worse adherence was reported in a group of patients aged >80 years [23]. However, the severity of capecitabine-induced HFS in the elderly has not been adequately studied. Moreover, an increased incidence of grade 3 or 4 adverse events has been reported to be associated with moderate renal dysfunction [24]. In this study, we evaluated the impact of renal function and found no association with the occurrence of HFS.

This study had several limitations. Because the validation was limited to patients who underwent breast surgery at a single institution, we were not able to evaluate patients with gastroenterological diseases treated with capecitabine. Second, this study did not evaluate progression-free or overall survivals, which are employed as indices of treatment efficacy, as it involved patients undergoing treatment for recurrent metastases and postoperative adjuvant therapy. Third, genetic differences in capecitabine-metabolizing enzymes were not evaluated. The mechanism of capecitabine-induced HFS is believed to be related to the accumulation of 5-fluorouracil metabolites in the skin and other factors [25, 26]; Loganayagam [26] reported that single nucleotide polymorphisms in methylenetetrahydrofolate reductase(MTHFR) and thymidylate synthase(TYMS), which are involved in capecitabine metabolism, are associated with capecitabine-induced HFS. Additionally, most 5-fluorouracil is inactivated by the metabolic enzyme dihydropyridine dehydrogenase (DPD), and the genetically reduced activity of this enzyme often results in adverse effects [26]. Although we could not confirm such mutations in our patients, they may be important to better assess the risk of HFS.

In conclusion, to our knowledge, this is a rare study to analyze the effectiveness of a joint physician-pharmacist (hospital and community pharmacist) intervention in preventing capecitabine-related HFS severity. country (Japan) and enhances the current knowledge on capecitabine for the treatment of breast cancer. This study demonstrates that active intervention by pharmacists is an important matter.

Author Contribution Statement

ST, KU, TK, YK, YF, KS, MY, HM NT, KW and HH confirmed the medical assessment and designed this study. KU, TK, YK, and YF provided advice regarding statistical analyses. ST and KU performed the statistical analyses. ST, KU and HH edited the manuscript. All authors have discussed the results and commented on the manuscript.

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Conflicts of Interest

The Authors declare no conflicts of interest in association with the present study.

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