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Predictive factors for the development of capecitabine-induced hand-foot syndrome: a retrospective observational cohort study

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Background: Capecitabine-induced hand-foot syndrome (HFS) is a common condition that significantly affects patients' quality of life. The exact underlying mechanisms are currently not clearly understood. Therefore, the study of predictive factors for HFS is of critical importance.

Materials and methods: This prognostic factor research used a retrospective observational cohort as the study design. Data collected from the medical records of 205 patients treated with capecitabine between January 2019 and June 2022 were subjected to univariable and multivariable regression analysis to determine the predictive factors for the development of grade 2 and grade 3 HFS.

Results: The incidence of grade 2 and grade 3 HFS was 26.8%. The independent predictive factors, such as age over 60 years (OR 4.80, 95% CI: 2.16–10.68, $P < 0.001$), capecitabine dose greater than 3000 mg/day (OR 2.47, 95% CI: 1.09–5.59, $P = 0.030$), and the number of cycles five or more in the total capecitabine regimen (OR 2.94, 95% CI: 1.29–6.71, $P = 0.01$), were significantly associated with the development of grade 2 and grade 3 HFS.

Conclusions: Independent predictive factors for the development of grade 2 and grade 3 HFS in patients treated with capecitabine include age over 60, capecitabine dose greater than 3000 mg/day, and patients who plan to undergo five or more cycles in the total capecitabine regimen. This knowledge can be valuable for guiding clinical monitoring and follow-up of patients.

Keywords: capecitabine, hand-foot syndrome, prognostic predictor

Introduction

Capecitabine is an oral chemotherapy drug belonging to the antimetabolite group, and it is a prodrug of fluorouracil (5-FU). After oral administration, capecitabine is metabolized in the liver to 5'-deoxy-5-fluorocytidine (5'-DFCR) and then to 5'-deoxy-5-fluorouridine (5'-DFUR) in both the liver and tumor tissues[1,2]. At the tumor site, 5'-DFUR is primarily converted into fluorouracil. Fluorouracil undergoes further metabolism in normal and tumor cells to form the active metabolites fluorodeoxyuridine monophosphate (FdUMP) and fluorouridine triphosphate (FUTP). Therefore, the active metabolites of capecitabine include FdUMP and FUTP[3,4]. FdUMP inhibits DNA synthesis and cell division by reducing normal thymidine

HIGHLIGHTS

- Capecitabine-induced hand-foot syndrome (HFS) is common, but there is limited data on predictive factors for its occurrence.
- The results of this study indicate that elderly patients treated with capecitabine dose exceeding 3000 mg/day as well as those who plan to undergo five or more cycles in the total capecitabine regimen, are at increased risk for developing grade 2 and grade 3 HFS.
- The benefits of this research can be applied to develop predictive models for predicting the occurrence of HFS grade 2 and grade 3.

production, while FUTP inhibits RNA and protein synthesis by competing with uridine triphosphate for incorporation into the RNA strand[5]. In clinical practice, capecitabine is mainly used to treat patients with gastrointestinal and breast cancers.

Capecitabine-induced hand-foot syndrome (HFS) is common in cancer patients treated with capecitabine[6,7]. The incidence ranged from 22 to 77%[8–10], and the severity of grade 3 HFS was ~10–15%[11]. Although the occurrence of HFS is common and frequently observed, the pathophysiology of HFS remains unclear[12–14]. Information from an in vitro study has revealed that capecitabine induces the death of keratinocyte cells through the activation of the apoptosis pathway and a reduction in mitochondrial membrane potential[13]. However, it is known that damage to the vascular endothelia in the hands and feet leads to an inflammatory reaction. Hence, there is data regarding the use of NSAIDs,

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such as topical diclofenac, for preventing HFS[15]. Previous studies found data about the predictors for the development of HFS that including concurrent administration of capecitabine with renin-angiotensin system inhibitors, high body surface area, and low albumin levels. Nonetheless, the data remains relatively limited[16].

The severity of HFS is assessed using various grading systems, with NCI/CTCAE 5.0 categorizing it into three grades, ranging from grade 1 to grade 3 (Table 1). Notably, grade 2 and grade 3 HFS represent severity levels that significantly affect patients' quality of life and can disrupt their treatment plans while taking capecitabine. It is important to note that the available data on predictors for the development of HFS did not specifically focus on the severity levels of grade 2 and grade 3, which are of particular interest and merit further emphasis.

The aim of this study is to identify predictive factors associated with the occurrence of grade 2 and grade 3 HFS in patients treated with capecitabine.

Figure 1. Study flow diagram.

Materials and methods

The object design is prognostic factor research using a study base as a retrospective observational cohort design. Inclusion criteria include cancer patients receiving treatment with capecitabine, both as monotherapy and in combination therapy. Exclusion criteria comprise patients who initiated capecitabine treatment at other hospitals or have incomplete medical record documentation. Data of patients treated with capecitabine were collected from the e-medical records between January 2019 and June 2022 including gender; age; weight; height; body surface area (BSA); capecitabine dosage; creatinine levels; estimated glomerular filtration rate (eGFR); serum albumin; serum protein; the combination between chemotherapy and capecitabine; severity of HFS; and cycles of capecitabine.

Predictive factors for the development of grade 2 and grade 3 HFS were determined using univariable and multivariable regression analysis. A P-value of less than 0.05 was considered to be statistically significant and all analyses were performed using STATA version 18 (StataCorp). This study is conducted in accordance with the Strengthening the reporting of cohort, cross-sectional and case-control studies in surgery (STROCSS) criteria[17]. We conducted this retrospective chart review study in compliance with the principles of the Declaration of Helsinki. Ethical approval for this study was provided by the Institutional Review Board, on 28 April 2023.

Results

Clinical data of 205 patients treated with capecitabine were collected (Fig. 1). Of these, 88 were male and 117 were female, with 111 patients aged over 60 years. The majority exhibited
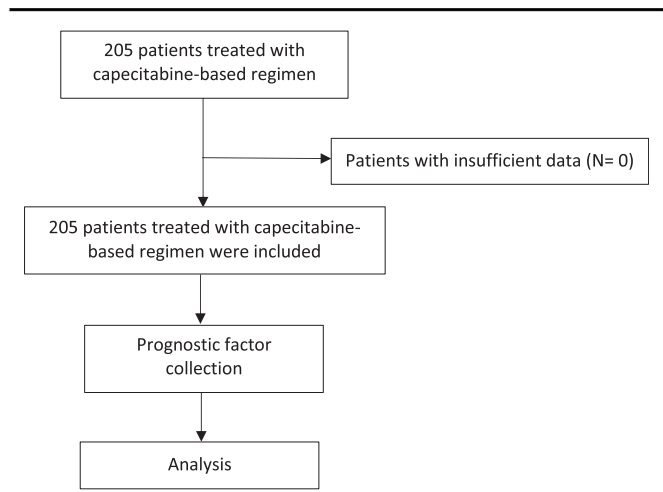
a body surface area (BSA) below 1.8 m², and 84.9% had Eastern Cooperative Oncology Group performance status (ECOG-PS) scores of 0–1. Additionally, 92.7% had adequate eGFR exceeding 60 ml/min. Colorectal cancer was the most prevalent diagnosis (72%). Oxaliplatin was mostly used for chemotherapy combination with capecitabine (55.6%), and 26.8% of patients had grade 2 and grade 3 HFS (Table 2).

The potential parameters were analyzed to determine the association between the development of grade 2 and grade 3 HFS, that is, sex, age, BSA greater than 1.8 m², capecitabine, the combination between capecitabine and chemotherapy, eGFR, serum albumin levels, and number of cycles in the total capecitabine regimen using univariable and multivariable logistic regression analysis.

The results of the univariable regression analysis revealed several significant associations. Age over 60 years (OR 2.74, 95% CI: 1.39–5.40, $P = 0.004$), BSA greater than 1.8 m² (OR 3.20, 95% CI: 1.14–9.01, $P = 0.028$), capecitabine dose greater than 3000 mg/day (OR 1.99, 95% CI: 1.05–3.78, $P = 0.034$), and the number of cycles five or more in the total capecitabine regimen (OR 2.42, 95% CI: 1.20–4.90, $P = 0.013$) were all identified as significant factors associated with the development of grade 2 and grade 3 HFS (Table 3).

The multivariable regression analysis results suggested that the independent predictive factors significantly associated with the development of grade 2 and grade 3 HFS included age over 60 years (aOR 4.80, 95% CI: 2.16–10.68, $P = <0.001$), capecitabine dose greater than 3000 mg/day (aOR 2.47, 95% CI: 1.09–5.59, $P = 0.030$), and the number of cycles five or more in the total capecitabine regimen (aOR 2.94, 95% CI: 1.29–6.71, $P = 0.01$) (Table 3).

Table 1		
Severity of hand-and-foot syndrome (HFS) with NCI/CTCAE 5.0		
Severity		**NCI/CTCAE 5.0**
Mild	Grade 1: Minimal skin changes or dermatitis (e.g. erythema, edema, or hyperkeratosis) without pain	
Moderate	Grade 2: Skin changes (e.g. peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain; limiting instrumental activities of daily living (ADL)	
Severe	Grade 3: Severe skin changes (e.g. peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain; limiting self care ADL	

Baseline characteristics of patients treated with capecitabine (N = 205)

Patient characteristics	Number (%)
Sex	
Male	88 (42.9)
Female	117 (57.1)
Age	
≤ 60 year	94 (45.8)
> 60 year	111 (54.2)
BMI	
≤ 18 kg/m^2	29 (14.1)
18.01–25 kg/m^2	134 (65.4)
> 25 kg/m^2	42 (20.5)
Body Surface Area (BSA)	
≤ 1.8 m^2	189 (92.2)
> 1.8 m^2	16 (7.8)
ECOG-Performance status	
ECOG-PS 0	85 (41.5)
ECOG-PS 1	89 (43.4)
ECOG-PS 2	23 (11.2)
ECOG-PS 3	6 (2.9)
ECOG-PS 4	2 (1.0)
Estimated glomerular filtration rate (eGFR)	
≤ 60 ml/min	15 (7.3)
> 60 ml/min	190 (92.7)
Type of cancer	
colorectal cancer	148 (72.2)
breast cancer	48 (23.4)
pancreatobiliary tract cancer	8 (3.9)
gastric cancer	1(0.5)
Capecitabine dosage	
2000 mg/day	9 (4.4)
2500 mg/day	38 (18.5)
3000 mg/day	86 (41.9)
3500 mg/day	61 (29.8)
4000 mg/day	11 (5.4)
Combination drugs	
none	82 (40.0)
oxaliplatin	114 (55.6)
gemcitabine	8 (3.9)
carboplatin	1 (0.5)
Total cycles of capecitabine	
≤ 4 cycles	80 (39.0)
5–8 cycles	122 (59.5)
≥ 9 cycles	3 (1.5)
Hand-and-foot syndrome (HFS)	
none	138 (67.3)
grade 1 (mild)	12 (5.9)
grade 2 (moderate)	41 (20.0)
grade 3 (severe)	14 (6.8)

Potential variables for predicting HFS in univariable and multivariable regression analysis

Potential variables	Univariable analyses			Multivariable analyses		
	uOR	95% CI	P	aOR	95% CI	P
Age						
≤ 60 year	1.00	Reference	0.004[a]	1.00	Reference	< 0.001[a]
> 60 year	2.74	1.39–5.40		4.80	2.16–10.68	
Body Surface Area (BSA)						
≤ 1.8 m^2	1.00	Reference	0.028[a]	1.00	Reference	0.069
> 1.8 m^2	3.20	1.14–9.01		3.05	0.92–10.18	
Dosage						
≤ 3000 mg/day	1.00	Reference	0.034[a]	1.00	Reference	0.030[a]
> 3000 mg/day	1.99	1.05–3.78		2.47	1.09–5.59	
Combination drugs						
Oxaliplatin	0.94	0.49–1.82	0.867	0.62	0.30–1.30	0.207
Gemcitabine	2.32	0.57–9.47	0.240	4.02	0.82–19.60	0.086
Other drugs	1.00	Reference		1.00	Reference	
–None	1.00	Reference		1.00	Reference	
Estimated glomerular filtration rate (eGFR)						
≤ 60 ml/min	0.42	0.09–1.92	0.263	0.34	0.06–1.84	0.209
> 60 ml/min	1.00	Reference		1.00	Reference	
Serum albumin						
Albumin <3 g/dl	0.48	0.13–1.70	0.252	0.98	0.23–4.14	0.980
Albumin ≥ 3 g/dl	1.00	Reference		1.00	Reference	
Number of cycles in the total capecitabine regimen						
< 5 cycles	1.00	Reference	0.013[a]	1.00	Reference	0.010[a]
≥ 5 cycles	2.42	1.20–4.90		2.94	1.29–6.71	

[a]Statistically significant P values; uOR, unadjusted odds ratios; aOR, adjusted odds ratios

Discussion

The cut-off point of dosage of capecitabine at greater than 3000 mg/day was used in this study because this value represented the peak of the normal data distribution. A BSA cut-off point at 1.8 m^2 was also used because the average BSA in patients with cancer was 1.79 m$^{2[18]}$.

Multivariable logistic regression analysis showed that the independent predictive factors associated with the development of grade 2 and grade 3 HFS included age over 60 years, capecitabine dose greater than 3000 mg/day, and the number of cycles five or more in the total capecitabine regimen.

Thus, older patients treated with a capecitabine dose exceeding 3000 mg/day, as well as those who plan to undergo five or more cycles in the total capecitabine regimen, are at a high risk of developing HFS. Therefore, these patients should receive close monitoring and follow-up, such as possibly using telemedicine for patient tracking during medication administration or providing detailed guidance on self-observation of symptoms and how to respond to the side effects.

Previous studies by Kanbayashi et al.[16] indicated that a high BSA and low serum albumin were prognostic predictors for the development of HFS. High BSA in this study was not an independent predictive factor, but the odds ratio was still high, along with the marginally significant P-value (OR 3.05, 95% CI: 0.92–10.18, P = 0.069). The presence of a larger BSA has been shown to increase the risk of developing HFS. This phenomenon can be explained by the fact that as patients' body surface area increases, they receive higher doses of capecitabine. Importantly, a high dose of capecitabine serves as a statistically significant predictive factor for the occurrence of grade 2 and grade 3 HFS. However, low serum albumin was not found to be associated with the development of HFS in this study.

Although there is currently data regarding genes associated with the occurrence of HFS during capecitabine treatment, it has been found that CES1 1165–33 C > A, CDA 266 + 242 A > G, DPYD variant, MACF1 and SPRY2 have statistically significant correlations with HFS grade 2 and grade 3 in patients treated with capecitabine[9,19]. However, the practical application of these findings in general clinical practice remains limited.

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This study had some limitations. 1) This was a retrospective study and some recorded data possibly contained errors. For example, mild HFS which only caused skin discoloration might not have been recorded or diagnosed by the physicians, resulting in a low incidence of mild HFS. By contrast, patients with grade 2 and grade 3 HFS could feel the pain, and these patients were more likely to be diagnosed with HFS in the medical records. This was one of the reasons why this study used grade 2 and grade 3 HFS as the clinical endpoint of interest. 2) This study was implemented at a single institute with small sample size. Multicenter studies or meta-analyses would better confirm our study results. 3) In this study, the analysis did not incorporate factors related to the use of other medications due to unclear pathogenesis data. However, these factors might potentially act as confounders affecting HFS outcomes.

The benefits of this study extend beyond providing into the predictive factors for the occurrence of grade 2 and grade 3 HFS in patients receiving capecitabine. It also enables the potential development of a predictive model utilizing these factors to predict the risk of grade 2 and grade 3 HFS. Further research in this area should be considered for future study.

Conclusions

Independent predictive factors for the development of grade 2 and grade 3 HFS in patients treated with capecitabine included age over 60, capecitabine dose greater than 3000 mg/day, and the number of cycles five or more in the total capecitabine regimen. These results can be applied to enhance clinical monitoring and patient follow-up.

Ethical approval

The study protocol was approved by the Institutional Review Board of Buddhasothorn Hospital, number BSH-IRB 020/2566. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Consent

Written informed consent was not required due to the retrospective design of the study. The Institutional Review Board (IRB) has determined that formal consent is unnecessary, as the data are anonymized and the requirement for informed consent has been waived.

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Author contribution

C.C.: designed the study, reviewed the paper, collected data, analyzed data, drafted the manuscript, and edited the final version; N.S.: collected data and reviewed the paper. Both authors have approved the final version of the manuscript.

Conflicts of interest disclosure

The authors confirm that there are no relevant financial or non-financial competing interests to
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Research registration unique identifying number (UIN)

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Data availability statement

All data generated and analyzed during the study will be made available upon publication. Interested parties can request access from the corresponding author.

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