Long-Term Safety Data on S-1 Administered After Previous Intolerance to Capecitabine-Containing Systemic Treatment for Metastatic Colorectal Cancer

Cornelis J.A. Punt,[1] Johannes J.M. Kwakman,[2] Linda Mol[3], on behalf of the PLCRC working group[#]

Abstract

The oral fluoropyrimidine S-1 has mainly been tested in Asian patients and was shown to be a valid alternative to capecitabine in the treatment of metastatic colorectal cancer. We evaluated the outcome in 47 Western patients who switched from capecitabine to S-1 due to hand-foot syndrome or cardiac toxicity, derived from a prospective cohort study. S-1 was well tolerated in all patients, indicating that S-1 is of special interest for this patient population.

Introduction: The oral fluoropyrimidine S-1 has shown comparable efficacy to capecitabine in Asian and some Western studies on metastatic colorectal cancer. S-1 is associated with a lower incidence of hand-foot syndrome (HFS) and cardiac toxicity. We assessed the long-term tolerability of S-1 in patients who discontinued capecitabine for reasons of HFS or cardiac toxicity. **Patients and Methods:** Patients with metastatic colorectal cancer who switched from capecitabine to S-1, given as monotherapy or in combination with other agents, were identified in a Dutch prospective cohort study (2016-2021). The incidence and severity of HFS, cardiotoxicity and other toxicities were assessed. **Results:** Forty-seven patients were identified. The median duration of capecitabine treatment was 81 days (range 4-454). In 19 patients (40%) a dose reduction was applied prior to switch to S-1. Reasons for discontinuation of capecitabine were HFS in 36 (77%) patients, coronary artery vasospasms in 10 (21%) patients, and gastrointestinal toxicities in 1 patient (2%). The median number of S-1 cycles was 6 (range 1-36). The median time between last dose of capecitabine and first dose of S-1 was 11 days (range 1-49). After switch to S-1, all patients with prior HFS developed a lower grade or complete resolution of symptoms, and in all other patients symptoms did not recur. Other S-1-related adverse events were limited to grade 1-2. Six patients (13%) discontinued S-1 due to either known fluoropyrimidine-related or bevacizumab-related toxicities. Switch to S-1 did not appear to compromise treatment efficacy. **Conclusion:** S-1 is a valid alternative to capecitabine in case HFS or cardiotoxicity occurs.

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Keywords: Hand-foot syndrome, Cardiotoxicity, Capecitabine intolerance

Introduction

Capecitabine and S-1 are both oral fluoropyrimidines. Capecitabine is metabolized to 5-FU via a 3-step enzymatic cascade, and exploits the higher intratumoral concentrations of thymidine phosphorylase to achieve tumor-selective generation of 5-FU, resulting in increased concentrations of 5-FU in the tumor.[1] S-1 combines the 5-FU prodrug tegafur with gimeracil

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[1]Department of Epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht University, The Netherlands
[2]Department of Medical Oncology, Amsterdam University Medical Center, University of Amsterdam and Free University of Amsterdam, The Netherlands
[3]Netherlands Comprehensive Cancer Organization IKNL, Utrecht, The Netherlands

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Address for correspondence: Cornelis J.A. Punt, MD, PhD, Department of Epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht University, The Netherlands
E-mail contact: C.J.A.Punt@umcutrecht.nl

[#] PLCRC working group: Jeanine Roodhart, Department of Medical Oncology, University Medical Center, Utrecht University, Utrecht, The Netherlands; Mathijs Hendriks, Department of Internal Medicine, Noordwest Hospital Group, Alkmaar, The Netherlands; Frank Speetjens, Department of Medical Oncology, Leiden University Medical Center, Leiden, The Netherlands; Liselot van Iersel, Department of Medical Oncology, Maastricht University Medical Center, Maastricht, The Netherlands; Marija Trajkovic-Vidakovic, Department of Internal Medicine, Albert Schweitzer Hospital, Dordrecht, The Netherlands; Leontine Spierings, Department of Internal Medicine, Alrijne Hospital, Leiderdorp, The Netherlands; Geert-Jan Creemers, Department of Internal Medicine, Catharina Hospital, Eindhoven, The Netherlands; Helgi Helgason, Department of Internal Medicine, Haaglanden Medical Center, The Hague, The Netherlands; Jan Willem de Groot, Department of Internal Medicine, Isala Clinics, Zwolle, The Netherlands; Joyce van Dodewaard-de Jong, Department of Internal Medicine, Meander Medical Center, Amersfoort, The Netherlands; Maartje Los, Department of Internal Medicine, Antonius Hospital, Nieuwegein, The Netherlands; Rutger Koornstra, Department of Internal Medicine, Rijnstate Hospital, Arnhem, The Netherlands; Arnold Baars, Department of Internal Medicine, Hospital Gelderse Vallei, Ede, The Netherlands; Miriam Koopman, Department of Medical Oncology, University Medical Center, Utrecht University, Utrecht, The Netherlands; Geraldine Vink, Netherlands Comprehensive cancer Organization IKNL, Utrecht, The Netherlands.

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and oteracil. Gimeracil raises the levels of 5-FU in tumour tissue and blood serum by inhibiting dihydropyrimidine dehydrogenase (DPD), the enzyme largely responsible for the degradation of 5-FU. Oteracil prevents the phosphorylation of 5-FU in the digestive tract in order to reduce gastrointestinal toxicities.[2] S-1 has shown comparable efficacy results compared to 5-FU and capecitabine in both Asian and in Western patients with metastatic colorectal cancer (mCRC),[3,4] but is associated with a lower incidence of hand-foot syndrome (HFS) and cardiac toxicity compared with capecitabine.[4-6] In a retrospective analysis of 52 patients in whom capecitabine was discontinued and replaced with S-1 for reasons of severe symptoms of HFS, 94% of patients experienced a lower grade of HFS upon treatment with S-1 compared to the capecitabine-induced grade of HFS, with 56% of patients experiencing a complete resolution of HFS-related symptoms.[7] However, this study was limited to patients developing HFS, and patients were only followed until the maximum decrease of HFS symptoms without data on long-term follow-up. S-1 has recently been approved by the European Medicines Agency as monotherapy or in combination with oxaliplatin or irinotecan, with or without bevacizumab, for the treatment of patients with metastatic colorectal cancer for whom it is not possible to continue treatment with another fluoropyrimidine due to HFS or cardiovascular toxicity that developed in the adjuvant or metastatic setting.[8] We here present long-term safety data on S-1 administered after previous intolerance upon treatment with capecitabine, either due to HFS or cardiac toxicity, in a novel cohort of mCRC patients.

Methods

Data were collected from patients participating in the Dutch Prospective Colorectal Cancer Cohort (PLCRC) [9]. All CRC patients (stage I-IV) are eligible for inclusion in PLCRC. Participants give informed consent to register longitudinal clinical data and to use any further clinical data for scientific purposes upon approval by the scientific board of PLCRC. PLCRC patients in whom S-1 was administered at any stage of disease were identified, and patients with mCRC in whom treatment was switched from capecitabine to S-1 were eligible. The electronic records of eligible patients were examined for the following items: patient characteristics (age, gender, height, weight, WHO performance status) at time of switch to S-1, treatment setting before switch to S-1, schedule of capecitabine-containing regimen, starting dose of capecitabine, dose reduction of capecitabine, and if so, the underlying reason for capecitabine dose reduction, reason for switch to S-1, time interval between last dose of capecitabine and first dose of S-1, total number of cycles of S-1, dose reductions of S-1, and if so, the underlying reason for S-1 dose reduction, reason for permanent discontinuation of S-1, date of first disease progression after S-1 administration, and any adverse events occurring during treatment with capecitabine and S-1 of which the maximal grade was recorded using CTC criteria (CTCAE version 5.0). Data were recorded from the start of treatment with capecitabine until the end of treatment with S-1. Patients were excluded if they had been included in 2 previous retrospective studies on a treatment switch from capecitabine to S-1.[4,6] Data were collected from June 1, 2016, and the cut-off date was June 15, 2021. The study was approved by the scientific board of the PLCRC.

Table 1 Patient Characteristics.

	n (%)	median (range)
n	47 (100)	
Age (years)		62 (40-84)
Women	22 (47)	
Men	25 (53)	
Height (cm)		175 (162-195)
Weight (kg)		74 (55-100)
WHO PS 0	18 (38)	
WHO PS 1	27 (57)	
WHO PS 2	2 (4)	

Results

A total of 47 eligible patients were identified, who had been treated in 13 different Dutch hospitals. Patient characteristics are shown in Table 1. Median age was 62 years (range 40-84), 22 (47%) patients were women, and median WHO PS was 1 (0-2).

Prior Treatment With Capecitabine

The initial starting dose of capecitabine was either 1250 mg/m^2 bid or 1000 mg/m^2 bid when given as monochemotherapy, and 1000 mg/m^2 bid when given in combination with oxaliplatin (Table 2). In 4 patients, a lower starting dose was applied due to partial DPD deficiency.

The median duration of capecitabine treatment was 81 days (range 4-454). In 19 patients (40%) a dose reduction was applied prior to switch to S-1. Reasons for dose reduction were HFS (n = 13), diarrhea (n = 2), HFS + diarrhea (n = 1), HFS + mucositis (n = 1), HFS + neutropenia (1), and HFS + nausea + diarrhea (n = 1). The reason for switch to S-1 was HFS in 36 patients (77%), cardiac toxicity in 10 patients (21%). One patient (2%) did not wish to continue capecitabine for reasons of dyspepsia, nausea, anorexia and dyspnea which toxicities had also been experienced by this patient during previous adjuvant treatment with capecitabine.

Treatment With S-1

The starting dose of S-1 was either 30 mg/m^2 bid or 25 mg/m^2 bid when given as monochemotherapy, or 25 mg/m^2 bid when given in combination with oxaliplatin (Table 3). In 4 patients, a lower starting dose of S-1 was applied due to partial DPD deficiency. In 6 patients with capecitabine-induced grade 2 HFS, S-1 monochemotherapy was started without delay and therefore initiated at 25 mg/m^2. The median number of S-1 cycles was 6 (range 1-36). Treatment cycles were administered without breaks in all patients. The median time between last dose of capecitabine and first dose of S-1 was 11 days (range 1-49). Reasons for discontinuation of S-1 were progressive disease (24 patients, 51%), a wait-and-see strategy (9 patients, 19%), toxicity (6 patients, 13%), patient request (1 patient, 2%), and comorbidity (1 patient, 2%). In 6 patients (13%) S-1 treatment was still ongoing at the time of data cut-off.

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Table 2 Treatment Preceding Switch to S-1.

	n (%)
Total	47 (100)
Treatment line	
1st line	45 (96)
2nd line	1 (2)
3rd line	1 (2)
capecitabine treatment initiated as	
capecitabine monotherapy	2 (4)
capecitabine + bevacizumab	20 (43)
capecitabine + oxaliplatin	2 (4)
capecitabine + oxaliplatin + bevacizumab	23 (49)
Starting dose of capecitabine	
≤850 mg/m^2 bid	4 (8)
1000 mg/m^2 bid	36 (77)
1250 mg/m^2 bid	7 (15)
Dose reduction of capecitabine	
No	28 (60)
Yes	19 (40)
Reason to switch to S-1	
Cardiac toxicity	10 (21)
Handfoot syndrome	36 (77)
Other	1 (2)

Abbreviation: bid = twice per day.

Table 3 Treatment With S-1.

Number of Cycles (n)	n (%)	Median (Range) 6 (1-36)
Starting Dose of S-1		
15 mg/m^2 bid	1 (2)	
20 mg/m^2 bid	3 (6)	
25 mg/m^2 bid	19 (41)	
30 mg/m^2 bid	24 (51)	
Dose Reductions of S-1		
No	40 (85)	
Yes	7 (15)	
Reason Discontinuation of S-1		
Disease Progression	24 (51)	
Toxicity	6 (13)	
Other	11 (23)	
Treatment Ongoing	6 (13)	

Abbreviation: bid = twice per day.

Adverse events are presented in Table 4. In 6 patients treatment with S-1 was discontinued for reasons of toxicity, which were mucositis grade 2, fever grade 2, and ongoing fatigue grade 1 (1 patient), terminal ileitis grade 2, proteinuria grade 3, hypertension grade 2, and deterioration of preexisting renal insufficiency from grade 2 to grade 3 (1), nausea grade 2 and abdominal cramps grade 1 (1), nausea grade 2 and fatigue grade 2 (1), diarrhea grade 2 and fatigue grade 2 (1), and interstitial pneumonitis grade 2 (1). All toxicities were reversible. No treatment related deaths were observed.

Dose reductions of S-1 were applied in 7 patients (15%). Reasons for dose reduction included ongoing HFS grade 2 (1 patient), ongoing oxaliplatin-induced peripheral neurotoxicity (1), thrombocytopenia grade 1 (1), mucositis grade 2 (2), mucositis grade 2, fever grade 2, and ongoing fatigue grade 1 (1), and diarrhea grade 1 and abdominal cramps grade 1 (1).

Toxicities that occurred during treatment with S-1 which were not observed during prior treatment with capecitabine were documented in 26 patients (55%), and included fever grade 3 and ileus grade 2, considered related to progression of primary tumor (1 patient), thromboembolism (pulmonary embolism) grade 3 with accompanying chest pain grade 2 (1), pulmonary embolism grade 3 (1), mucositis grade 2 (2), mucositis grade 2 and fever grade 2 (1), terminal ileitis grade 2, vomiting grade 1, and fatigue grade 1 in combination with bevacizumab-related proteinuria, hypertension, and impaired renal function (1), nausea grade 2 and fatigue grade 2 (1), diarrhea grade 2 (1), diarrhea grade 1, mucositis grade 2, and fatigue grade 1 (1), diarrhea grade 2 and fatigue grade 2 (1), thrombopenia grade 2 and mucositis grade 1 (1), diarrhea grade 1, mucositis grade 1, fever grade 2, and terminal ileitis grade 1 (1), mucositis grade 1 (1), mucositis grade 1, anorexia grade 1, and HFS grade 1 (1), thrombocytopenia grade 1 (1), neutropenia grade 1 (1), abdominal cramps grade 1 (1), diarrhea grade 1 and abdominal cramps grade 1 (2), diarrhea grade 1 (2), pain grade 2 considered related to osteoporotic fracture in vertebra (1), abdominal cramps grade 1 (1), anorexia grade 1 (1), and fever grade 1 (1).

Hand-Foot Syndrome (HFS)

In 13/36 patients (36%) who switched for reasons of HFS, the dose of capecitabine was first reduced prior to switch to S-1. According to standard practice at initiation of capecitabine treatment, all patients were instructed to use emollients and creams as prophylactic treatment for HFS which treatment was intensified at the appearance of first symptoms of HFS. In all patients experiencing HFS during treatment with capecitabine, its severity decreased or completely resolved during treatment with S-1. Since S-1 was usually initiated without delay, some patients continued to experience the same grade of HFS during the first treatment cycle of S-1. One patient who discontinued capecitabine early in the 1st cycle due to cardiac toxicity developed HFS grade 1 during treatment with S-1.

Cardiac Toxicity

A diagnosis of cardiac toxicity was based on the occurrence of chest pain suggestive for coronary spasms. In most cases this diagnosis was confirmed by a cardiologist. Symptoms occurred already during the 1st cycle in 6/10 patients. Management concerned

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withdrawal of capecitabine, without administration of cardiac medication. Myocardial infarction did not develop in any patient. In none of the 10 patients who switched to S-1 for reason of cardiac toxicity did cardiac toxicity recur during treatment with S-1.

Gastrointestinal Toxicity

Two patients (4%) developed terminal ileitis during S-1 treatment. The first patient, a 73-year-old man with a history of hypertension and diabetic nephropathy, discontinued capecitabine plus bevacizumab after 4 days due to coronary spasms. He developed bloody diarrhea during his 3rd cycle of S-1. He developed hypertension grade 2 which was controlled by medication, proteinuria grade 3, and deterioration of renal function from grade 2 to grade 3. All these toxicities were reversible after discontinuation of treatment, with recovery of renal function to pretreatment level, and were considered related to bevacizumab. A diagnosis of terminal ileitis (grade 2) was made by colonoscopy, and patient fully recovered.

The second patient, a 57-year-old woman, developed grade 1 diarrhea with, on CT scan, a thickening of the wall of the ileum during her 25th cycle of S-1. A diagnosis of terminal ileitis was made by colonoscopy. Her diarrhea resolved spontaneously and she resumed treatment with S-1 at the same dose, without recurrence of diarrhea. In this patient, the relationship between ileitis and S-1 treatment was considered unlikely for 2 reasons. Firstly, diarrhea had not occurred during previous administration of 10 cycles of capecitabine (of which 8 in the adjuvant setting) and 24 cycles of S-1, while all documented cases of fluoropyrimidine-related ileitis have occurred within the first 4 cycles. Secondly, symptoms of ileitis did not recur after 2 subsequent cycles of S-1 which were given at the same dose.

The patient who did not wish to continue capecitabine for reasons of dyspepsia, nausea, anorexia and dyspnea did not experience any of these toxicities after switch to S-1.

Other Toxicities

Any peripheral neurotoxicity occurring during S-1 was restricted to patients who were previously treated with oxaliplatin. In patients experiencing oxaliplatin-induced neurotoxicity, the severity of neurotoxicity did not increase in any patient upon initiation of S-1, and was either unchanged or decreased during S-1 treatment.

Two patients developed pulmonary embolism during treatment with S-1, 1 patient was diagnosed after evaluation of symptoms of chest pain and the other patients was asymptomatic and an accidental diagnosis was made by routine CT scan. Both patients responded well to anticoagulant treatment.

One patient (2%), a 56-year-old women, developed bilateral ground glass lesions on CT scan of thorax which was made after 3 cycles of capecitabine, oxaliplatin, and bevacizumab. She complained of dyspnea, eventually increasing to grade 3, which was initially considered to be related to her COPD. During the 4th cycle, she developed chest pain which, upon consultation of a cardiologist, was suggestive for coronary spasms. Therefore, capecitabine was replaced by S-1 in the 5th cycle. Her chest pain did not recur, and ground glass lesions disappeared on CT scan together with dyspnea. Her metastases were successfully treated with surgery. Seven months later disease progression was observed for which treatment with S-1 plus bevacizumab was resumed. A CT scan after 3 cycles showed stable disease but with reappearance of bilateral ground glass lesions. Patient had experienced dyspnea during the last 2 cycles which gradually had increased to grade 3. A pulmonologist conducted extensive pulmonary analysis, including pulmonary function tests, bronchoscopy with lavage, and COVID-19 testing, but no specific diagnosis was made. Antibiotics did not improve symptoms. Treatment with S-1 was discontinued with continuation of bevacizumab, and patient fully recovered within 2 weeks and a subsequent CT scan showed complete disappearance of ground glass lesions. A diagnosis of drug-induced interstitial pneumonitis was made, with a definite relationship to capecitabine and S-1 treatment.

Progression-Free Survival

The median time from initiation of treatment with capecitabine to first documented progression of disease after initiation of treatment with S-1 was 414 days (95% confidence interval 332-568 days).

Subgroup Analysis of Patients Who Switched to S-1 for Reason of HFS

Separate analysis of patients who switched for reason of HFS showed no significant differences in any outcome parameter as discussed above (data not shown).

Discussion

This study demonstrates that capecitabine can be safely replaced by S-1 upon the occurrence of HFS or cardiac toxicity in patients with mCRC. Toxicities that were the reason for discontinuation of capecitabine either decreased in severity or completely resolved during treatment with S-1. Most toxicities that occurred during treatment with S-1 concerned gastro-intestinal side effects and were limited to grade 1-2. These data were derived from PLCRC, a Dutch prospective cohort study. Since more than 90% of patients give informed consent to participate, patients in the PLCRC cohort are considered to represent daily practice.

The major reason for a switch to S-1 was the development of HFS. A switch from capecitabine to S-1 was often performed already at the occurrence of grade 2 HFS, which reflects the potential impact of prolonged grade 2 HFS on quality of life and daily activities, especially in elderly patients.

We describe 2 patients who developed terminal ileitis during treatment with S-1, which was confirmed by colonoscopy in both patients. In one of these patients the relationship with treatment was uncertain. In the literature, only 9 cases of terminal ileitis during treatment with capecitabine have been presented [summarized in [10]]. Diagnosis was made within the first 4 cycles in all patients, and all patients fully recovered. However, its pathophysiology and management remain unclear. It was concluded that a diagnosis of terminal ileitis should be considered more often when the pattern of diarrhea and other complaints are not typical for capecitabine-induced mucositis.[10] Since colonoscopy with biopsies are not always performed in such patients, terminal ileitis may be an underreported side effect of capecitabine. To date, no data

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Table 4 Adverse Events

	CTC Grade	During Capecitabinen (%)	During S-1n (%)
Any Adverse Event	None	0	8 (17)
	1	1 (2)	15 (32)
	2	26 (55)	20 (43)
	3	20 (43)	4 (9)
Coronary Spasms	None	37 (79)	47 (100)
	1	1 (2)	0
	2	4 (9)	0
	3	5 (11)	0
Constipation	None	41 (87)	47 (100)
	1	5 (11)	0
	2	1 (2)	0
Diarrhea	None	35 (74)	34 (70)
	1	6 (13)	9 (19)
	2	3 (6)	5 (11)
	3	3 (6)	0
Mucositis	None	38 (81)	37 (79)
	1	7 (15)	6 (13)
	2	2 (4)	4 (9)
Terminal Ileitis	None	47 (100)	45 (96)
	1	0	1 (2)
	2	0	1 (2)
Anorexia	None	39 (83)	42 (89)
	1	6 (32)	5 (11)
	2	2 (4)	0
Fatigue	None	21 (45)	28 (60)
	1	20 (43)	14 (30)
	2	5 (11)	5 (11)
	3	1 (2)	0
Fever	None	46 (98)	44 (94)
	1	0	1 (2)
	2	1 (2)	2 (4)
Infection	None	45 (96)	46 (98)
	1	0	0
	2	2 (4)	1 (2)
Periperal Neuropathy	None	21 (45)	34 (72)
	1	12 (26)	8 (17)
	2	13 (28)	5 (11)
	3	1 (2)	0
Dyspnoea	None	45 (96)	46 (98)
	1	0	0
Pneumonitis	2	1 (2)	0
	3	1 (2)	1 (2)
	None	46 (98)	46 (98)
	1	0	0
	2	1 (2)	1 (2)

(*continued on next page*)

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Table 4 (*continued*)

	CTC Grade	During Capecitabinen (%)	During S-1n (%)
Renal	None	46 (98)	46 (98)
	1	0	0
	2	1 (2)	0
	3	0	1 (2)
Handfoot Syndrome	None	9 (19)	31 (66)
	1	2 (4)	15 (32)
	2	26 (55)	1 (2)
	3	10 (21)	0
Thromboembolic Events	None	46 (98)	45 (96)
	1	0	0
	2	0	0
	3	1 (2)	2 (5)
Hypertension	None	43 (91)	46 (98)
	1	2 (4)	0
	2	2 (4)	1 (2)

have been published on an association of terminal ileitis with S-1.

One patient developed reversible interstitial pneumonitis during both capecitabine and S-1 treatment. Chemotherapy-induced interstitial pneumonitis is rare but well documented,[11] and has been associated with fluoropyrimidine-containing treatments. In a large survey of 4283 patients treated with capecitabine and lapatinib, 7 patients (0.2%) with interstitial pneumonitis were observed.[12] Interstitial pneumonitis has also been documented during treatment with regimens of 5-fluorouracil, capecitabine, oxaliplatin, and bevacizumab.[13,14] A total of 9 case reports have been published on its occurrence during treatment with S-1.[15,16]

Fluoropyrimidines are an essential part of standard first-line treatment for patients with mCRC. We have shown non-inferiority for S-1 in a systematic review and meta-analysis on currently published results of randomized studies comparing S-1-based schedules with capecitabine or 5-fluorouracil-based schedules in mCRC patients.[17]

Due to the relatively small number of patients, the heterogeneity of treatment schedules and the varying timepoints of initiation of treatment with S-1, our study does not allow a valid assessment of clinical outcome in terms of progression-free survival. However, with progression-free survival being in the upper range of outcomes as observed in clinical studies on first-line treatment with capecitabine-based regimens in patients with metastatic colorectal cancer,[3,18,19] our data do not suggest any detrimental effect on progression-free survival. A switch to S-1 allowed patients to continue systemic treatment that is known to significantly prolong survival, and to postpone the initiation of salvage regimens.

In conclusion, our data strongly support the replacement of capecitabine with S-1 in patients with metastatic colorectal cancer in case of intolerance to capecitabine due to HFS or cardiac toxicity, which indication has recently been approved by the European Medicines Agency.

Clinical Practice Points

- All patients with capecitabine-induced hand-foot syndrome experienced a lower grade or complete resolution of symptoms after switch to S-1.
- All patients with capecitabine-induced coronary artery vasospasm did not experience recurrent chest pain after switch to S-1.
- S-1 is well tolerated in patients with capecitabine-induced toxicities.
- A switch from capecitabine to S-1 does not appear to compromise efficacy of treatment.

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Disclosure

CJAP reports an advisory role for Nordic Pharma.

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