ORIGINAL RESEARCH

Fluoropyrimidine-induced hand-foot syndrome and cardiotoxicity: recommendations for the use of the oral fluoropyrimidine S-1 in metastatic colorectal cancer

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Background: Fluoropyrimidines (FPs) are an essential part of the majority of systemic regimens in the treatment of metastatic colorectal cancer (CRC). The use of the oral FP S-1 has 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 CRC in whom it is not possible to continue treatment with another FP due to hand-foot syndrome (HFS) or cardiovascular toxicity (CVT). Subsequently, this indication has been included in the 2022 ESMO guidelines for metastatic CRC. Recommendations for use in daily practice are not available.
Patients and methods: Based on peer-reviewed published data on the use of S-1 in Western patients with metastatic CRC who switched from infusional 5-fluorouracil (5-FU) or capecitabine to S-1 for reasons of HFS or CVT, recommendations for its use were formulated by an international group of medical oncologists with expertise in the treatment of metastatic CRC and a cardio-oncologist.
Results: In patients who experience pain and/or functional impairment due to HFS during treatment with capecitabine or infusional 5-FU, a switch to S-1 is recommended without prior dose reduction of capecitabine/5-FU. S-1 should preferably be initiated at full dose when HFS has decreased to grade ≤ 1. In patients with cardiac complaints, in whom an association with capecitabine or infusional 5-FU treatment cannot be excluded, capecitabine/5-FU should be discontinued and a switch to S-1 is recommended.
Conclusions: These recommendations should guide clinicians in daily practice in the treatment of patients with metastatic CRC with FP-containing regimens.
Key words: fluoropyrimidines, colorectal cancer, cardiotoxicity, hand-foot syndrome, S-1, recommendations

INTRODUCTION

In colorectal cancer (CRC), the fluoropyrimidines (FPs) 5-fluorouracil (5-FU) and capecitabine are an essential part of all systemic treatment regimens in the (neo)adjuvant

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setting, all first-line regimens in the metastatic setting, except for patients with deficient mismatch repair tumors, and in many salvage regimens. Hand-foot syndrome (HFS) is a very commonly occurring toxicity of capecitabine and infusional 5-FU which, even after dose reductions, may compromise health-related quality of life (HRQoL) and daily functioning.[1] Cardiovascular toxicity (CVT) occurs in 4%-6% with these agents, and when this occurs, the administration of the FP is usually permanently discontinued to prevent potentially life-threatening recurrence of CVT.[2,3] The oral FP S-1 (Teysuno) is a combination of tegafur and two metabolic inhibitors designed to slow metabolism of 5-FU: gimeracil, a dihydropyrimidine dehydrogenase (DPD) inhibitor, and

potassium oxonate, an inhibitor of the orotate phosphoribosyltransferase that converts 5-FU to fluorouridine monophosphate.[4] S-1 has mainly been developed for use in Asian countries,[5] and its safety profile has been demonstrated to be associated with a decreased incidence of HFS compared with capecitabine or infusional 5-FU, and reports of cardiac toxicity associated with S-1 are extremely rare. The lower incidence of HFS during S-1 treatment has been confirmed in Western patients with metastatic CRC in a randomized study.[6] In Western patients with cancer developing CVT on 5-FU- or capecitabine-based therapy, a switch to S-1-based therapy has been shown to be safe and feasible, allowing them to continue their pivotal FP-based treatment.[7] A systematic review and noninferiority meta-analysis of randomized phase II/III trials of patients with metastatic CRC found S-1 to be noninferior to 5-FU-/capecitabine-based therapy in the treatment of metastatic CRC with regard to progression-free survival (PFS), and at least as efficacious as 5-FU-/capecitabine-based therapy in terms of overall response rate (ORR) and overall survival (OS).[8] These data support the use of S-1 in patients with metastatic CRC who are intolerant to 5-FU-/capecitabine-based treatment. Subsequently, S-1 was 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 CRC for whom it is not possible to continue treatment with another FP due to HFS or CVT that developed in the adjuvant or metastatic setting.[9] Following this indication, the updated 2022 ESMO guidelines for CRC recommend S-1 as an alternative FP when intravenous 5-FU- or capecitabine-based chemotherapy cannot be used due to CVT and/or HFS.[10] However, practical guidelines for the use of S-1 in these situations are not available. An international panel of experts in the management of patients with metastatic CRC (all authors) reviewed the available literature on the use of S-1 in patients with metastatic CRC, and consensus was reached on the formulation of guidance for the use of S-1 in daily practice for patients with metastatic CRC experiencing HFS or CVT during treatment with 5-FU- or capecitabine-based regimens.

HAND-FOOT SYNDROME

The incidence of HFS in clinical trials with capecitabine has been reported in ~60% of patients, with grade 3 occurring in 11%-24%.[1] The degree of HFS manifestation is dose dependent and, therefore, it is often necessary to suspend or modify therapeutic dosage.[11] A study that evaluated data from two large randomized trials involving 596 patients with metastatic CRC treated with capecitabine monotherapy reported an incidence of 54% of all-grade HFS, which was of grade 3 severity in 17% of patients.[12] In these studies, 31% of patients required capecitabine dose reductions or treatment interruptions for HFS. In the 23% of patients in whom the capecitabine dose was reduced for HFS, 33% had a recurrence of HFS (18% of grade 2 severity and 15% of grade 3 severity).[12] In a prospective study with

protracted infusional 5-FU monotherapy in patients with metastatic CRC, the incidence of all-grade HFS was 24%; data on the occurrence of grade 3 HFS were not reported.[13] The incidence of all-grade and grade 3 HFS in a study of adjuvant protracted infusional 5-FU was 72% and 7%, respectively.[14] In studies using biweekly 48-h infusional 5-FU, the incidence of grade 2-3 HFS is usually <10%.[15] No studies have been carried out on the outcome of HFS in patients who switched to this schedule after experiencing severe capecitabine-induced HFS. In a recent phase III study in patients with metastatic CRC comparing trifluridine–tipiracil with capecitabine, both plus bevacizumab, treatment with trifluridine–tipiracil was associated with less all-grade HFS (1% versus 53%) but with more hematological adverse events.[16] The reported incidence in patients with metastatic CRC of all-grade HFS in combination regimens with capecitabine plus oxaliplatin varies between 16% and 35% and between 5% and 25% with infusional 5-FU plus oxaliplatin, with reported incidences of grade 3 severity in 2%-6% and 1%-2%, respectively.[17-20] The lower incidence of HFS in combination schedules as compared with capecitabine monotherapy is likely due to the lower dose of capecitabine used in combination therapy.

In the Dutch phase III SALTO study, in which patients with metastatic CRC were randomized in first-line between capecitabine and S-1 monotherapy, with or without bevacizumab, the incidence of physician-assessed all-grade HFS was 73% for capecitabine and 45% for S-1 ($P = 0.0005$), and grade 3 HFS was 21% for capecitabine and 4% for S-1 ($P = 0.003$).[6] These results confirmed the lower incidence of HFS associated with S-1 treatment compared with capecitabine in a Western patient population. Of note, the incidence of HFS for both groups in this study was higher than reported in previous studies. This may be due to the fact that the incidence of HFS was the primary endpoint of the study, which may have prompted physicians to pay more attention to this event, and may also explain the wide variation in physician-assessed reported HFS in previous studies. Despite this, the incidence of HFS in the SALTO study as reported by patients was even slightly higher than that reported by physicians,[6] from which it may be concluded that HFS, even in this setting, may be underestimated by physicians.

Although HFS is usually self-limiting and rarely leads to hospitalization or life-threatening manifestations, the symptom burden can result in significant deficits in HRQoL and negatively affect the well-being of patients.[11,21] Accordingly, HFS may reduce treatment compliance. It should be noted that standard QoL questionnaires provide insufficient information on the extent of HFS on HRQoL impairment, and that most of the available clinical studies only report more severe HFS (i.e. grades 2 and 3). This has resulted in the development of questionnaires to measure HFS-related symptoms and their effect on daily activities.[21,22] With the more prolonged use of FPs in maintenance therapy in metastatic CRC,[23,24] low-grade HFS may already affect daily functioning, especially in elderly patients.

Diagnosis of HFS

The severity of HFS depends on visual inspection of the palms of the hand and soles of the feet, and the presence or absence of pain and functional impairment. Several grading systems have been developed for HFS.[25] The most commonly used scale is the National Cancer Institute's Common Toxicity Criteria (NCI CTC), which defines grade 1 as minimal skin changes (erythema, edema, or hyperkeratosis) without pain; grade 2 as skin changes (peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain, limiting instrumental activities of daily life; and grade 3 as severe skin changes (peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain, limiting self-care activities of daily life.[26] Options for symptomatic and topical treatment have been reviewed.[25]

Continuation of FP treatment after HFS-associated pain and/or functional impairment

With dose reductions of capecitabine being administered in many patients experiencing HFS, the question arises regarding whether this reduces the efficacy of treatment. In studies with capecitabine monotherapy, there have been no reports of increased risk of disease progression (or death in patients with no evidence of disease progression) after the first dose reduction. For other efficacy parameters, such as ORR and OS, the data were insufficient for an objective assessment of the impact of dose reduction.[12] In a study that investigated different schedules of capecitabine in patients with metastatic CRC, a dose-intensified schedule proved to be more effective in terms of ORR and PFS.[27] In a systematic review involving various types of cancer, patients with capecitabine-induced HFS showed improved PFS and OS.[28] This review included a study in patients with metastatic CRC in which HFS was an independent predictor of survival.[29] Together, these data suggest that for its greatest efficacy, capecitabine may need to be used at a dose level that is associated with the development of HFS.

Retrospective studies have shown that capecitabine can safely be replaced by S-1 at full dose in Western patients with cancer who cannot continue capecitabine-based treatment due to HFS.[30,31] In a study of 52 patients with different types of cancer, 49 (94%) experienced a lower grade of HFS upon treatment with S-1 compared with the capecitabine-induced grade of HFS, with 29 patients (56%) experiencing a complete resolution of HFS-related symptoms.[30] S-1 was initiated in 33 patients (63%) without waiting for a decrease in HFS-related symptoms. Among these patients, a reduction of symptoms was achieved in 28 (85%) within two cycles of S-1, whereas ongoing grade 2 or 3 HFS was observed in 3 (12%). Upon switch to S-1, the overall incidence of any grade HFS was 44% (23 patients) and of grade 3 HFS was 2% (1 patient).[30] In another study with long-term follow-up, all 36 patients with metastatic CRC who switched from capecitabine- to S-1-based first-line treatment for reasons of HFS experienced a lower grade of HFS or complete resolution of symptoms after switch to S-1.[31] Adverse events during S-1 treatment were known

FP-related toxicities and were limited to grade 1-2. S-1 was started at full dose in all patients, except in four patients with known partial DPD deficiency who started both capecitabine and S-1 at reduced doses. Patients received S-1 for a median number of six cycles (range 1-36), and the switch to S-1 did not appear to compromise treatment efficacy.[31]

Recommendation

The expert panel concluded that HFS is a very common problem during FP treatment, significantly affecting HRQoL, especially with the use of capecitabine, which warrants dose reductions or treatment interruptions in many patients. As its incidence may be underestimated, the panel recommended that providers carry out visual inspections of the palms of the hands and soles of the feet in addition to taking history on HFS-related symptoms prior to each cycle. The panel agreed that any pain and/or functional impairment due to HFS should be reason to intervene. Given (i) the fact that the efficacy of reduced doses of capecitabine is uncertain, (ii) the observation that grade $\geq$2 HFS recurs in about one-third of patients in whom the capecitabine dose is reduced, and (iii) the observed safety of switching to S-1 at full dose in patients experiencing serious complaints from HFS in whom symptoms of HFS subsequently decreased or completely disappeared, the panel made the following recommendation: In patients who experience pain and/or any functional impairment due to HFS during treatment with capecitabine or infusional 5-FU, a switch to S-1 at full dose (30 mg/m^2 two times per day as monotherapy and 25 mg/m^2 in combination therapy) is recommended without prior dose reduction of capecitabine/5-FU. S-1 should preferably be initiated when HFS has decreased to grade $\leq$1, because earlier administration, albeit safe, may be less effective in decreasing HFS-related symptoms in a minority of patients.

Cardiovascular toxicity

CVT is a potentially lethal complication of FP administration with a reported incidence of >10% in some studies. However, cardiologist-verified population- or trial-based reports demonstrate symptomatic CVT incidence rates of 4%-6% in patients receiving capecitabine or infusional 5-FU.[2,3,7,31-34] Subclinical or asymptomatic CVT [typically a sign of ischemia on the electrocardiogram (ECG)] has been reported by continuous Holter monitoring much more frequently, up to 19%, and typically occurs already during the first cycle.[35] The overall reported mortality rate for 5-FU- or capecitabine-associated CVT in prospective studies varies between 0% and 2.2%.[36]

Angina-like chest pain is the predominant clinical presentation, frequently occurring during or immediately following the initial courses of FP administration. Less frequently, cardiac arrhythmias, myocardial infarction, and even sudden death have been reported.[3,33,36] The risk of myocardial infarction during FP treatment is two times as high compared with what is expected (0.7% in FP compared with 0.3% in a matched cohort).[37]

Previous heart disease is not predictive for FP-related CVT because most cases occur in patients without previous coronary disease.[32] A recent study showed that well-known cardiovascular risk factors, such as hypertension, diabetes, hyperlipidemia, and smoking, were not predictive for developing coronary vasospasm.[38] Patients with FP-induced CVT were typically younger, had no underlying cardiovascular disease, and were less likely to have these traditional cardiovascular risk factors. This highlights the difficulty in predicting those at risk and explains the overall disappointing results of conventional 'upfront' treatment with cardiovascular drugs in preventing FP-induced CVT. However, in a recent meta-analysis on risk factors of FP-induced CVT, the authors concluded that patients receiving FP-based combination therapy were at a higher risk than those receiving FP monotherapy (relative risk 1.6) and that patients with preexisting cardiac disease had a higher risk of symptomatic CVT (relative risk 3.3).[39]

The pathophysiology of FP-induced CVT is still a matter of debate, but the most prevalent hypothesis assigns FP-induced CVT to coronary vasospasm induced by 5-FU and its metabolites.[40] These vasospasms are the result of endothelial dysfunction and/or primary smooth muscle dysfunction leading to vasoconstriction in the absence of underlying coronary artery disease.[34] In addition, ECG analyses have shown silent myocardial ischemia and asymptomatic arrhythmias in asymptomatic patients, indicating a higher frequency of subclinical cardiac influence.[33] Reports on the role of biomarkers in predicting CVT are scarce and, so far, have not resulted in clinically useful recommendations. As myocardial ischemia may lead to myocardial cell injury, (high-sensitive) cardiac troponin could, in theory, be a valuable screening tool. However, in asymptomatic FP-associated ischemia, there does not seem to be any role for troponin, most likely because moderate ischemia does not necessarily result in cardiomyocyte damage and its consequent plasma release of intracellular troponin.[35] Whether troponin would be valuable in clinically overt ischemia remains to be established. Another potential biomarker is N-terminal pro-B-type natriuretic peptide (NT-pro-BNP), an inactive peptide released along with the active peptide hormone BNP when the walls of the heart are stretched or there is pressure overload on the heart. A prospective study including 106 patients with CRC receiving adjuvant FOLFOX reported myocardial neuroendocrine changes with increasing plasma NT-pro-BNP. Patients developing CVT (mainly angina) had significantly higher levels than asymptomatic patients.[41]

In addition to coronary spasms, other mechanisms may contribute to CVT including endothelial injury followed by thrombosis, increased metabolism leading to energy depletion and ischemia, oxidative stress causing cellular damage, and direct effects on the myocardium.[33,42]

Diagnosis of CVT

Baseline assessment by a cardiologist prior to FP treatment in all patients is not recommended (Figure 1). Evaluation of baseline cardiovascular risk by the treating oncologist should be considered (history taking on risk factors, blood pressure, lipids, HbA1c, ECG) to identify potential relevant cardiovascular comorbidities, in particular in the curative setting aimed at long-term reduction of cardiovascular morbidity and mortality. Treatment of modifiable cardiovascular risk factors

Diagnostic tests	Baseline	Anginal complaints	Acute myocardial infarction
Cardiology consultation	−	+	+
Cardiovascular lab	+	+	+
Troponin	−	+	+
ECG	+	+	+
Echocardiogram	−	−	+
CT scan	−	+/−	+/−
Angiography	−	−	+

Figure 1. Recommendations for cardiology workup prior to fluoropyrimidine treatment.
CT, computed tomography; ECG, electrocardiogram.

(by either lifestyle interventions or pharmacological therapy) according to the current guideline recommendations is advised before, during, and/or after treatment.[43] Whether this reduces the incidence and severity of FP-induced CVT remains unknown. Screening for preexisting significant coronary artery disease may be considered in selected high- and very high-risk patients before FP treatment and should be carried out in those experiencing cardiac complaints before the initiation of therapy.[44] The presence of significant coronary calcium on noncontrast, non-ECG-triggered computed tomography (CT) scans should alert the treating physician to underlying cardiovascular disease and this should be acted on accordingly.[45]

Patients presenting with complaints that are suspicious for myocardial ischemia (including chest pain, chest discomfort, dyspnea on exertion, palpitations, or transient loss of consciousness) during treatment should be assessed immediately to further characterize the likelihood of FP-associated chest pain and evaluated in multidisciplinary discussion prior to next FP administration.

Patients presenting with ongoing chest pain and/or signs of myocardial infarction should be sent to the emergency department without delay for diagnostic workup and treatment. Additional tests according to current (inter)national guidelines are recommended including an ECG, laboratory testing including high-sensitive troponin, and additional cardiovascular imaging as needed. In patients with ongoing chest pain unresponsive to nitroglycerin administration, those with clear ST elevation myocardial infarction on the ECG, and/or patients with marked elevated cardiac markers, an invasive angiogram is recommended. In young patients with a low or intermediate cardiovascular risk profile, those who become symptom free after vasodilator treatment, and where the clinical picture is aligned with the expected time course after FP treatment, a cardiac CT scan is recommended to rule out coronary artery disease.

The management strategy for patients with evidence of asymptomatic ischemia (i.e. ST segment changes on ECG or Holter monitoring without complaints) is unknown. As the subsequent risk for myocardial infarction in these patients does not seem to be elevated, it seems to be inappropriate to withhold FP treatment or subject these patients to additional investigations such as a CT scan.

Treatment options after FP-induced CVT

As discontinuation of FP treatment due to CVT is associated with increased cancer mortality,[38] this highlights the need for therapeutic strategies that protect the heart while providing optimal anticancer treatment (Figure 2).

The reintroduction of capecitabine/5-FU without cardioprotective prophylaxis in patients in whom FP-related CVT has occurred is not recommended because CVT has been reported to recur in 82%-100% of these patients with 18% mortality.[42] Mortality appears to be low in those who receive intensive cardiac pretreatment after cardiotoxicity (including high doses of calcium antagonist, long-acting nitrates, and chemotherapy administration on the cardiac care unit). In a retrospective single-center study of >6000 patients, 115 patients (1.7%) developed FP-associated coronary vasospasm.[46] A total of 34 patients discontinued FP, and 81 patients were rechallenged with FP. Among 78 patients who were referred to a cardio-oncologist for cardioprotective pretreatment with long-acting nitrates and/or calcium channel blockers, 15 (19%) developed recurrent chest pain. Two-third of patients without prophylaxis had recurrent symptoms. The authors concluded that rechallenge after prophylactic treatment may be safe and allow the continued administration of FP.[46] Patients who continued FP with prophylaxis had a decreased risk of death (hazard ratio 0.42) and a trend toward decreased cancer progression (hazard ratio 0.60) compared with patients who discontinued FP. Recurrence of chest pain in these patients was also significantly reduced from 67% to 19%.[46] However, prophylaxis is laborious, time-consuming, and expensive. One could question whether such an intensive treatment strategy with a recurrence rate of almost one in five patients is optimal, raising the question of whether alternative treatment strategies may be preferred. Although a switch to
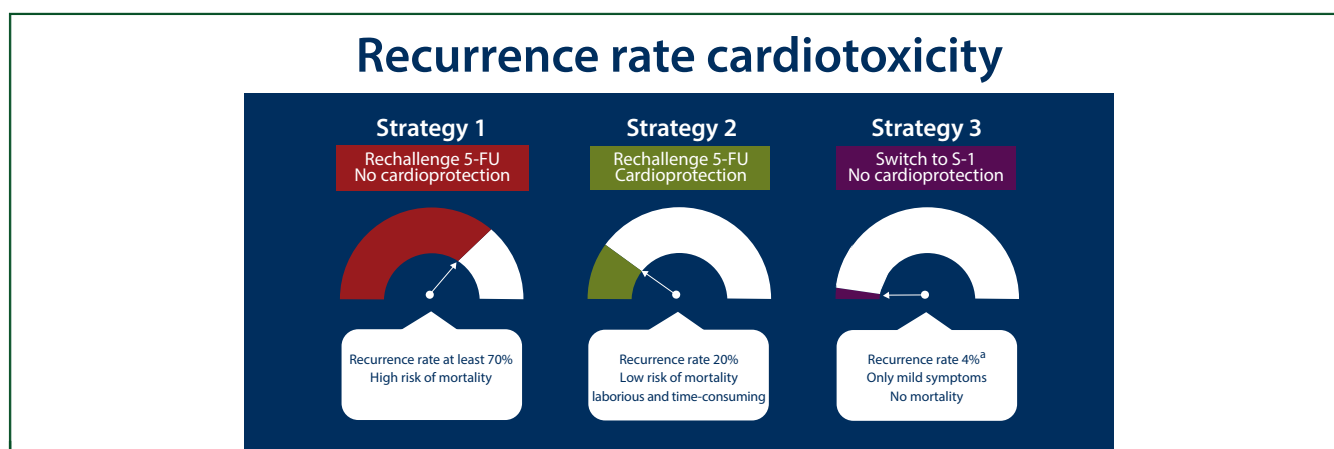

Figure 2. Recurrence rates for different management strategies for fluoropyrimidine-induced cardiotoxicity.
5-FU, 5-fluorouracil.
[a]8% in the subgroup with metastatic colorectal cancer.

bolus 5-FU is a safer option in terms of CVT, the efficacy and overall toxicity profile differs from capecitabine and infusional 5-FU.[47] Previous options in a patient diagnosed with FP-induced CVT were limited to a switch of cancer treatment to a non-FP regimen, or continuation of the FP regimen with cardio-prophylactic medications.

Therefore, in patients experiencing FP-induced CVT, alternative strategies should be considered. During the administration of raltitrexed, little or no cardiotoxicity has been observed.[48-50] However, raltitrexed is associated with a higher incidence of other toxicities, with mortality rates up to 6%.[48] As a result, raltitrexed is no longer available in several countries.

Clinical and preclinical data suggested that S-1 may be a safer choice compared with other FPs in terms of CVT; however, only limited prospective studies have been conducted. The S-1 component gimeracil is a DPD inhibitor that is 200-fold more potent than uracil and, therefore, the levels of α-fluoro-β-alanine (FBAL) and other downstream metabolites in the catabolic pathway are very low during S-1 treatment.[48] Theoretically, low levels of FBAL during treatment with S-1 should protect against CVT. Indeed, cardiac complications have been reported less frequently for tegafur with uracil than for 5-FU or capecitabine, and murine studies adding uracil to tegafur clearly reduced CVT as compared with tegafur alone.[33,36,51] In a recent review, no serious cardiovascular events were reported in published phase II or III studies with S-1.[52]

As data on the incidence of CVT of S-1 in Western patients were limited, the retrospective CardioSwitch study was conducted in 13 centers in Finland, Sweden, Norway, Denmark, The Netherlands, and Ireland.[7] This study included 200 patients with cancer who had developed CVT (grade 3-4 in 56%) and who subsequently switched to S-1. This is by far the largest study presented on this topic. The primary endpoint was recurrence of CVT after switch to S-1-based treatment from any other FP due to CVT. Patients were treated between 2011 and 2020, and 159 patients (80%) had CRC, of whom 72 had metastatic disease. Survival data for 53 of these 72 patients were also available.[53] Of these 53 patients with metastatic CRC, the median time to onset of symptoms was 6 days (interquartile range 2-32 days) and symptoms occurred during the first or second cycle in the majority of patients. The most frequent cardiac events were chest pain (45%) and acute coronary syndrome (36%). S-1 was continued in combination with other drugs in all 53 patients, and 49 patients (92%) had no recurrent CVT upon switch to S-1 and continued with S-1 (Table 1). Four patients had recurrent but mild cardiac symptoms (all grade 1) which occurred at a median of 59 days from treatment start (interquartile range 15-145 days). Including these four, all completed S-1 treatment, and thus their planned duration of therapy. The median OS of this group with metastatic CRC was 26 months.[7]

In conclusion, the CardioSwitch study showed that a switch to S-1-based therapy is safe, feasible, and easy to manage in patients who develop CVT on 5-FU- or

Table 1. Results from the CardioSwitch study for all patients and patients with colorectal cancer

Before switch to S-1	Solid tumors (n = 200)	Metastatic CRC (n = 53)
Median time to onset of symptoms before switch to S-1 in days (IQR)	5 (2-16)	6 (2-32)
Most frequent cardiotoxicity: chest pain; ACS/infarction (%)	63; 35	45; 36
After switch to S-1		
Recurrence of cardiotoxicity upon switch to S-1, n (%)	8 (4)[a]	4 (8)[b]
Median time to recurrence after switch in days (IQR)	16 (7-67)	59 (15-145)
Completed planned therapy, n (%)	198 (98)	53 (100)
Overall survival metastatic disease, months (95% CI)	22 (16-28) n = 72	26 (22-31) n = 53

ACS, acute coronary syndrome; CI, confidence interval; CRC, colorectal cancer; IQR, interquartile range.
[a]Six grade 1, two grade 2.
[b]Four grade 1.

capecitabine-based therapy. This switch to S-1 allows patients to continue their recommended FP-based therapy.[7]

Recommendation

The expert panel concluded that CVT is a potentially life-threatening event that occurs in 2%-4% of patients during FP treatment. A rechallenge of the FP under prophylaxis may reduce, but not prevent, recurrence and risk of death, but is laborious. Given the much lower recurrence rate and observed safety of switching to S-1 at full dose in patients experiencing cardiac complaints, the panel made the following recommendation: In patients who experience CVT during therapy with capecitabine or 5-FU, a switch to S-1 at full dose [30 mg/m^2 b.i.d. (two days) as monotherapy and 25 mg/m^2 in combination therapy] is recommended without any attempt to rechallenge patients with capecitabine/5-FU.

Conclusions

S-1 can safely replace 5-FU or capecitabine when these agents are causing HFS or CVT that prevents or complicates their continued administration. These recommendations may guide clinicians in their daily care for patients with metastatic CRC who are being treated with capecitabine or 5-FU.

FUNDING

DISCLOSURE

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