Randomized phase III trial of S-1 versus capecitabine in the first-line treatment of metastatic colorectal cancer: SALTO study by the Dutch Colorectal Cancer Group


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Background: Hand–foot syndrome (HFS) is a common side-effect of capecitabine. S-1 is an oral fluoropyrimidine with comparable efficacy to capecitabine in gastrointestinal cancers but associated with a lower incidence of HFS in Asian patients. This study compares the incidence of HFS between S-1 and capecitabine as first-line treatment in Western metastatic colorectal cancer (mCRC) patients.

Patients and methods: Patients with previously untreated mCRC and planned treatment with fluoropyrimidine monochemotherapy were randomized 1:1 to receive either capecitabine (1250 mg/m² orally for patients <70 years; 1000 mg/m² for patients ≥70 years, twice daily on days 1–14) or S-1 (30 mg/m² orally twice daily on days 1–14) in 3-weekly cycles, with bevacizumab optional in both groups. The primary endpoint was the incidence of any grade HFS, as assessed by both physicians and patients (diaries). Secondary endpoints included grade 3 HFS, other toxicities, relative dose intensity, progression-free survival, response rate and overall survival.

Results: A total of 161 patients were randomized in 27 centres. The incidence of any grade HFS as assessed by physicians was 73% in the capecitabine group (n = 80) and 45% in the S-1 group (n = 80) [odds ratio (95% confidence interval) 0.31 (0.16–0.60), P = 0.0005]. The incidence of grade 3 HFS was 21% and 4% (P = 0.003), respectively. Patient-assessed any grade HFS was 84% and 58%, respectively (P = 0.004). Grade 3 anorexia was more common in the S-1 group (3% versus 13%, P = 0.03). Median relative dose intensity was 88% in the capecitabine group and 95% in the S-1 group (P = 0.026). There were no statistically significant differences in median progression-free survival, response rate and overall survival rates.

Conclusion: Treatment with S-1 in Western mCRC patients is associated with a significantly lower incidence of HFS compared with capecitabine, with comparable efficacy.

ClinicalTrials.gov registration number: NCT01918852.

Key words: S-1, capecitabine, hand–foot syndrome, metastatic colorectal cancer

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Chemotherapy remains the backbone of first-line systemic treatment of metastatic colorectal cancer (mCRC), with a fluoropyrimidine as monotherapy or in combination with oxaliplatin and/or irinotecan.

The oral fluoropyrimidine capecitabine is often preferred over intravenous 5-fluorouracil due to its patient convenience and superior tolerability profile [1, 2]. Its major toxicity is hand–foot syndrome (HFS), which is observed in up to 77% of patients in clinical trials [3]. HFS is characterized by erythema, dysaesthesia and oedema of the palms, fingers and soles of feet. In advanced stage, desquamation, ulceration and blistering may occur. Although not life threatening, it can cause serious discomfort and impairment of function. This is becoming increasingly relevant given recent data that show a benefit for the continuous use of capecitabine in mCRC patients [4]. This implies that patients may be exposed to capecitabine for prolonged periods of time, during which the presence of even low-grade HFS may become problematic.

S-1 is an oral fluoropyrimidine that combines the 5-FU prodrug tegafur with gimeracil and oteracil. Gimeracil raises the levels of 5-FU in tumour tissue and blood serum by inhibiting dehydroxymethylpyrimidine 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 [5]. S-1 has shown comparable efficacy results compared to 5-FU and capecitabine in mCRC [6–8], but is associated with a lower incidence of HFS compared with capecitabine [7]. However, most studies on S-1 have been performed in Asian populations, who have a markedly different metabolism and toxicity profile compared to Western populations [9]. The maximal tolerated daily dose of S-1 is different in Asian versus Western patients, with 40 mg/m² twice daily and 30 mg/m² twice daily, respectively [9]. Given the paucity of data on S-1 in Western patients, we prospectively compared the safety of S-1 with capecitabine, with the addition of bevacizumab to each drug as an option, as first-line treatment in Western patients with mCRC, with particular attention to HFS.

Methods

Study design

This open-label, randomized phase 3 trial was conducted and sponsored by the Dutch Colorectal Cancer Group in 27 hospitals in the Netherlands. The study was conducted in accordance to the standards of Good Clinical Practice, in agreement with the Declaration of Helsinki. The study was approved centrally by the Ethics Review Committee of the Academic Medical Center, Amsterdam, and by the local institutional review boards. Written informed consent was obtained from all patients before study entry.

Patients were randomly assigned (1 : 1) to either capecitabine or S-1 with the use of TENALEA (an online, central randomization service). Minimization techniques were used with stratification for the planned use of bevacizumab (yes versus no), WHO performance status (0–1 versus 2), serum LDH (normal versus abnormal) and institution.

The primary endpoint was the incidence of any grade HFS as assessed by the local investigators using the National Cancer Institute Common Toxicity Criteria (NCI CTC), version 4.0. Secondary endpoints included the incidence of grade 3 HFS, any grade and grade 3 HFS as assessed by patients, other toxicities, progression-free survival (PFS), response rate (RR), overall survival (OS) and relative dose intensity (RDI). Patient-reported HFS-related symptoms were collected in a diary, which was designed specifically for this trial (supplementary Appendix SA1, available at Annals of Oncology online). These symptoms were graded centrally according to the NCI CTC by an investigator who was unaware of treatment.

Patients

The main eligibility criteria were age ≥18 years, histologically proved CRC with distant metastases, WHO performance status of 0–2, adequate bone marrow, liver and renal function, and planned first-line treatment with fluoropyrimidine monochemotherapy with or without bevacizumab. Patients were excluded if they had prior adjuvant treatment completed within 6 months prior to randomization, planned radical resection of metastatic disease after downsizing by systemic treatment, history of a second malignancy in the past 5 years, previous intolerance of capecitabine, known DPD deficiency, any significant cardiovascular disease within 1 year before randomization, or concomitant administration of any other experimental or anti-cancer therapy.

Treatment

Capecitabine was orally administered twice daily on days 1–14 at a dose of 1250 mg/m² for patients <70 years or 1000 mg/m² for patients ≥70 years of age. S-1 was administered twice daily on days 1–14 at a dose of 30 mg/m², irrespective of age. Co-treatment with bevacizumab, 7.5 mg/kg intravenously on day 1, was left to the discretion of the local investigator. Cycles were repeated every 3 weeks. Details of dose modifications and supportive measures in case of toxicities are presented in supplementary Appendix SA2, available at Annals of Oncology online. Treatment in both arms was continued until disease progression, unacceptable toxicity or patient refusal.

Assessment

Patients in both study groups were evaluated every 3 weeks for toxicity by NCI CTC and every 9 weeks for disease status by CT-scan according to the Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 criteria. Patients were asked to score symptoms associated with HFS in a diary at the end of each cycle. Diaries were collected at the end of study treatment, and scores were unknown to local investigators. After discontinuation of treatment for reasons other than disease progression, patients were followed every 3 months until progression or death.

Statistical analysis

The primary objective was to show an improvement of the incidence of HFS of at least 20%—from 30% for capecitabine to 10% for S-1—based on a previous Asian study [7]. The study required 150 patients to detect this difference with 90% power (two-sided α = 0.05). The intention-to-treat population was defined as all randomized patients and the safety population as all patients who received at least one dose of study medication.

The frequency of HFS and other adverse events were compared with Fisher’s exact test in the safety population. The cumulative incidence of grades 2 and 3 HFS was calculated by censoring patients without grades 2 and 3 HFS and treating death and progression as a competing risk. We used logistic regression for pre-planned subgroup analyses of co-treatment with bevacizumab (yes versus no), WHO performance score (0–1 versus 2), serum LDH (normal versus abnormal), sex (male versus female) and age (<70 versus ≥70 years), and for exploratory analyses of prior adjuvant therapy (yes versus no), and localization of metastasis (liver only versus extraregional). PFS and OS were calculated from randomization in the intention-to-treat population and compared with Cox
Results

Between January 2014 and July 2015, we randomly assigned 161 patients from 27 Dutch hospitals in either the capecitabine group (n = 81) or S-1 group (n = 80). Median age was 73 years (range 50–86). Co-treatment with bevacizumab was administered in 59% of patients (n = 47 for capecitabine, n = 48 for S-1). Baseline characteristics are listed in Table 1. Supplementary Figure S1, available at *Annals of Oncology* online shows the flow diagram of the study population.

The median number of cycles in the capecitabine group was 8 [interquartile range (IQR) 4–12] and in the S-1 group (IQR 3–13). The incidence of any grade HFS as assessed by local investigators was 73% in the capecitabine group and 45% in the S-1 group (n = 42 versus 33, OR 0.26 (95% CI 0.10–0.64), P = 0.004). The incidence of grade 3 HFS as assessed by patients was 8% in the capecitabine group and 58% in the S-1 group (n = 42 versus 33, OR 0.26 (95% CI 0.10–0.64), P = 0.004).

Supplementary Tables S1 and S2, available at *Annals of Oncology* online show the distribution of HFS among both treatment groups. Especially grades 2 and 3 HFS occurred more frequently upon the use of capecitabine. In patients developing grades 2 and 3 HFS, the median time to first occurrence was 2 months (IQR 1–4) in the capecitabine group (n = 41) and 3 months (IQR 1–7) in the S-1 group (n = 14; P = 0.13) (Figure 1). A lower incidence of any grade HFS and grade 3 HFS favouring S-1 was observed in all pre-planned subgroup analyses. Co-treatment with bevacizumab in the capecitabine group was associated with a higher incidence of any grade and grade 3 HFS, although not statistically significant. This trend was not observed in the S-1 group (supplementary Table S3, available at *Annals of Oncology* online).

Other adverse events are listed in Table 2. Any grade diarrhoea (P = 0.01) and grade 3 anorexia (P = 0.03) occurred more frequently in the S-1 group. One patient in the S-1 group died due to bevacizumab-related bowel perforation and one patient in the capecitabine group died due to sepsis which was possibly related to treatment. Three patients in the S-1 group and two patients in the capecitabine group were hospitalized due to treatment-related adverse events.

Significantly more patients required a dose reduction in the capecitabine group [n = 53 (66%) for capecitabine, n = 81) or S-1 group (n = 80). Median age was 73 years (range 50–86). Co-treatment with bevacizumab was administered in 59% of patients (n = 47 for capecitabine, n = 48 for S-1). Baseline characteristics are listed in Table 1. Supplementary Figure S1, available at *Annals of Oncology* online shows the flow diagram of the study population.

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A total of 71 dose reductions were applied in the capecitabine group, compared with 42 in the S-1 group \( (P = 0.0015) \). The median RDI for capecitabine was 88\% (IQR 76–99) and for S-1 95\% (IQR 83–100) \( (P = 0.026) \). Seven patients, all treated with capecitabine, discontinued treatment due to HFS \( (10\% \text{ versus } 0\%, \ P = 0.013) \). After a median follow-up duration of 20.2 months (IQR 17.0–23.5), 73 (90\%) patients in the capecitabine group and 70 (88\%) patients in the S-1 group had progressed or died. Median PFS was 8.2 months (95\% CI 6.4–10.3) in the capecitabine group and 8.4 months (6.4–10.6) in the S-1 group \( [\text{hazard ratio (HR)} 0.99, 95\% \text{ CI } 0.71–1.37, \ P = 0.93, \text{Figure 2}] \). The addition of bevacizumab to capecitabine/S-1 was associated with an improved PFS \( [8.7 \text{ months (7.8–10.8) with bevacizumab (} n = 95 \text{) versus } 6.6 \text{ months (5.3–8.5) without bevacizumab (} n = 66 \text{), HR 0.74, } 95\% \text{ CI 0.53–1.03, } P = 0.08, \text{ supplementary Figure S2, available at Annals of Oncology online}] \). There was a statistically significant difference in median PFS between capecitabine \( (n = 34) \) and capecitabine plus bevacizumab \( (n = 47) \) \( [6.6 \text{ months (5.5–8.5) versus } 9.2 \text{ months (6.6–13.8); } HR 0.61, 95\% \text{ CI } 0.38–0.97; \ P = 0.04] \). Median PFS for S-1 alone \( (n = 32) \) and S-1 plus bevacizumab \( (n = 48) \) was 6.4 months (4.3–12.8) and 8.7 months (6.7–10.6), respectively \( (HR 0.91, 95\% \text{ CI } 0.56–1.47; \ P = 0.69) \).

OS at 12 and 18 months was 67\% (95\% CI 57–78) and 50\% (40–63), respectively, in the capecitabine group, compared with 62\% (53–74) and 41\% (30–54) in the S-1 group \( (HR 1.23, 95\% \text{ CI } 0.82–1.86, \ P = 0.32) \).

The overall objective RR in 146 evaluable patients was 47\% in the capecitabine group and 32\% in the S-1 group \( (n = 35 \text{ versus } 23, \ P = 0.09) \). Disease control was observed in 95\% of the patients in the capecitabine group and 89\% in the S-1 group \( (n = 71 \text{ versus } 63, \ P = 0.24) \) (supplementary Table S4, available at Annals of Oncology online).

Subsequent treatments are listed in supplementary Figure S1, available at Annals of Oncology online. Patients in the capecitabine group received more subsequent lines of treatment than patients in the S-1 group, although not statistically significant \( (P = 0.30) \).

### Discussion

Our results show that treatment with S-1 is associated with a statistically significant and clinically relevant lower incidence of HFS compared with capecitabine in Western mCRC patients, without compromising efficacy. This especially concerned grades 2 and 3 HFS.

S-1-related HFS occurred later in time compared with capecitabine-related HFS. Although the overall incidence of grade ≥3 toxicities did not significantly differ between the two treatment...
groups, patients in the S-1 group experienced a significantly lower rate of dose reductions and higher RDI. The only grade 3 toxicity that was more common in patients treated with S-1 was anorexia. Although the assessment of adverse events may be subjective and potential differences in the use of supportive measures may exist, these findings suggest that S-1 is better tolerated than capecitabine.

It has been suggested that fluoropyrimidine-induced HFS is elicited by 5-FU catabolites. This theory is based on the rarity of HFS in patients with a DPD-deficiency and a lower incidence of HFS when DPD-inhibitors are added to fluoropyrimidines [10]. S-1 contains the DPD-inhibitor gimeracil and indeed the concentration of the S-1 catabolite α-fluoro-β-alanine (FBAL) was shown to be 18-fold lower after the administration of S-1 compared with capecitabine [11, 12].

The reported incidence of capecitabine-induced all grade HFS in Western patients varies from 29% to 77% [3, 13]. Our investigator-assessed incidence of 73% is at the upper limit of this range. This variation may be caused by the fact that the scoring of HFS is at least partly subjective, and depends on the carefulness by which this event is being scored. The reported incidence of S-1-induced HFS in Asian patients is substantially lower and ranges from 12% to 16% [7, 8, 14]. Inter-ethnic variability in the pharmacokinetics and pharmacodynamics of S-1 may contribute to this disparity. A lower maximum concentration and area under the curve of FBAL has been observed in Asian compared with Caucasian patients upon administration of S-1 [15]. Data on the incidence of S-1-induced HFS in Western patients are scarce and range from 5% to 13% [16–18], which is lower compared with our findings. This may at least partly be explained by the fact that investigators of our study may have been more perceptive to HFS as it was the primary endpoint. The fact that our data on patient-assessed incidence of HFS are comparable to the findings of the local investigators supports that our findings more accurately represent the incidence of both S-1 and capecitabine-induced HFS in Western patients.

Earlier studies have shown that the addition of bevacizumab to capecitabine monotherapy increases the incidence of HFS, for reasons that are yet unknown [3, 19]. Interestingly, we observed a similar trend in the capecitabine group, but not in the S-1 group.

Our results are supported by our retrospective analysis of 52 patients who switched from capecitabine to S-1 because of severe HFS [20]. A decrease in HFS-related symptoms was observed in 94% of patients with 56% of patients even showing a complete resolution of symptoms, despite the fact that S-1 was initiated at full dose without waiting for capecitabine-related symptoms to ameliorate in 63% of patients.

Our study was not sufficiently powered for clinical efficacy endpoints. However, no significant differences in the secondary endpoints of clinical efficacy between the treatment groups were observed, with a median PFS that was highly similar between capecitabine and S-1. Although the objective RR was numerically lower in patients treated with S-1, the disease control rate was comparable in both study arms. Also, the non-significantly higher 12- and 18-month OS rates numerically favoured the capecitabine arm, which may be explained by the higher number of subsequent treatments in this arm. Whether this latter finding may have an inherent relation to the fluoropyrimidine administered in first line or just occurred by chance cannot be concluded from our study. We left the decision to add bevacizumab to S-1 or capecitabine to the local investigator, since several Dutch hospitals were known to have financial restrictions for its use. Indeed, the use of bevacizumab strongly correlated to institutions. Although the addition of bevacizumab to both S-1 and capecitabine resulted in a numerical increase in median PFS and OS, our study was not powered for this subgroup analysis.

Sequential treatment starting with fluoropyrimidine monotherapy has been shown a valid alternative to combination chemotherapy in selected patients [21], and is often used in elderly or frail patients. This is reflected in our study population, with a relatively high median age and low number of subsequent treatments. Therefore, our results on efficacy outcomes should not be compared with the results in the general population of mCRC patients. Only a minority of patients received subsequent treatment with an anti-EGFR antibody. Although we have no data on the RAS mutation status of the tumours from included patients, this may be explained by the fact that EGFR antibody treatment in the Netherlands is usually given as monotherapy in third or later line treatment. The number of patients that discontinued treatment due to adverse events was equivalent in both groups and is comparable with data from previous studies on S-1 or capecitabine in combination with bevacizumab in elderly populations [19, 22].

In conclusion, our data demonstrate that S-1 has a lower incidence and severity of HFS compared to capecitabine, and is therefore a useful alternative in Western cancer patients.

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Disclosure

CJAP has acted in an advisory role for Servier and Nordic Pharma. JJMK has received an honorarium by Nordic Pharma. TvV has received grants from Astellas, Roche, and Pfizer, and expert testimony fees from Ipsen. All remaining authors have declared no conflicts of interest.

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