S-1 plus oxaliplatin versus capecitabine plus oxaliplatin for first-line treatment of patients with metastatic colorectal cancer: a randomised, non-inferiority phase 3 trial

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Summary

Background Capecitabine plus oxaliplatin (CapeOX) is one of the reference doublet cytotoxic chemotherapy treatments for patients with metastatic colorectal cancer. We aimed to compare the efficacy and safety of CapeOX with that of S-1 plus oxaliplatin (SOX), a promising alternative treatment for patients with metastatic colorectal cancer.

Methods In this open-label, multicentre, randomised phase 3 trial, we randomly assigned patients (1:1) from 11 institutions in South Korea to receive either CapeOX (capecitabine 1000 mg/m² twice daily on days 1–14 and oxaliplatin 130 mg/m² on day 1) or SOX (S-1 40 mg/m² twice daily on days 1–14 and oxaliplatin 130 mg/m² on day 1). Treatment was repeated every 3 weeks and continued for as many as nine cycles of oxaliplatin-containing chemotherapy, except in instances of disease progression, unacceptable toxicity, or a patient's refusal. Maintenance chemotherapy with S-1 or capecitabine was allowed after discontinuation of oxaliplatin. Randomisation was done with a computer-generated sequence (stratified by primary sites, previous adjuvant or neoadjuvant treatment, and the presence of measurable lesions). The primary endpoint was to show non-inferiority of SOX relative to CapeOX in terms of progression-free survival (PFS). The primary analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00677443.

Findings Between May 14, 2008, and Sept 23, 2009, we randomly assigned 168 patients to receive SOX and 172 to receive CapeOX. Median PFS was 8·5 months (95% CI 7·6–9·3) in the SOX group and 6·7 months (6·2–7·1) in the CapeOX group (hazard ratio, 0·79 [95% CI 0·60–1·04]; $p_{non\text{-}inferiority}<0·0001$, $p_{log\text{-}rank}=0·09$). The upper limit of the CI was below the predefined margin of 1·43, showing the non-inferiority of SOX to CapeOX. We recorded a higher incidence of grade 3–4 neutropenia (49 [29%] *vs* 24 [15%]), thrombocytopenia (37 [22%] *vs* 11 [71%]), and diarrhoea (16 [10%] *vs* seven [4%]) in the SOX group than in the CapeOX group. The frequency of any grade of hand-foot syndrome was greater in the CapeOX group than it was in the SOX group (51 [31%] *vs* 23 [14%]).

Interpretation The SOX regimen could be an alternative first-line doublet chemotherapy strategy for patients with metastatic colorectal cancer. Further investigation is needed to explore its potential when used together with other targeted agents or as adjuvant chemotherapy.

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Introduction

Doublet combination chemotherapy plus targeted agents is a widely used treatment strategy for the first-line treatment of patients with metastatic colorectal cancer, and oxaliplatin plus either fluorouracil or capecitabine is one of the reference doublet cytotoxic chemotherapy strategies.[1,2] Capecitabine, an oral fluoropyrimidine, which is at least equivalent to fluorouracil in terms of safety and efficacy, can be used as a substitute for fluorouracil.[3,4] In addition to capecitabine's non-inferiority to fluorouracil when used alone, the doublet combination of capecitabine plus oxaliplatin (CapeOX) has been shown to be non-inferior to FOLFOX (oxaliplatin plus infusional fluorouracil and leucovorin) in both first-line and second-line chemotherapy,[1,3,5,6] and has become one of the reference cytotoxic chemotherapy strategies for patients with metastatic colorectal cancer. Although statistical non-inferiorities have been reported, efficacy outcomes and toxicity profiles of CapeOX have suggested that CapeOX might be slightly inferior to FOLFOX in both respects.[6,7] A need therefore exists for another fluoropyrimidine to substitute for capecitabine.

Another oral fluoropyrimidine, S-1, consists of tegafur, 5-chloro-2,4-dihydroxypyridine (CDHP), and potassium oxonate, in the molar ratio one to 0·4 to one. The antitumour activity of S-1 has been shown in patients with various gastrointestinal cancers, including metastatic colorectal cancer, when given as either monotherapy or in combination chemotherapy.[8–11] Moreover, S-1 plus irinotecan has been shown to be non-inferior to infusional fluorouracil plus irinotecan when given as a second-line chemotherapy.[12]

S-1 could have advantages over capecitabine in terms of reducing the frequency of toxicities such as hand-foot

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syndrome (HFS).[9] Several trials have shown the feasibility and efficacy of S-1 plus oxaliplatin as an upfront chemotherapy for metastatic colorectal cancer.[10,11] However, to our knowledge, S-1 and capecitabine have not been directly compared when either is combined with oxaliplatin.

To address this need, we did a randomised phase 3 study to test the non-inferiority of S-1 plus oxaliplatin (SOX) compared with CapeOX as first-line chemotherapy in patients with metastatic colorectal cancer.

Methods

Study design and participants

This was a randomised, open-labelled, multicentre phase 3 study. We recruited patients from 11 institutions in South Korea. To be eligible, patients with metastatic colorectal cancer were required to have histologically confirmed adenocarcinoma, have measurable or assessable lesions, have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2, be aged 18 years or older, have had no previous chemotherapy or immunotherapy in the metastatic setting, and have adequate haematological, hepatic, and renal functions. Adjuvant chemotherapy or radiotherapy was allowed if it had been completed at least 6 months before enrolment. All patients provided written informed consent before study entry, and the study protocol was approved by the institutional review boards of all participating institutions.

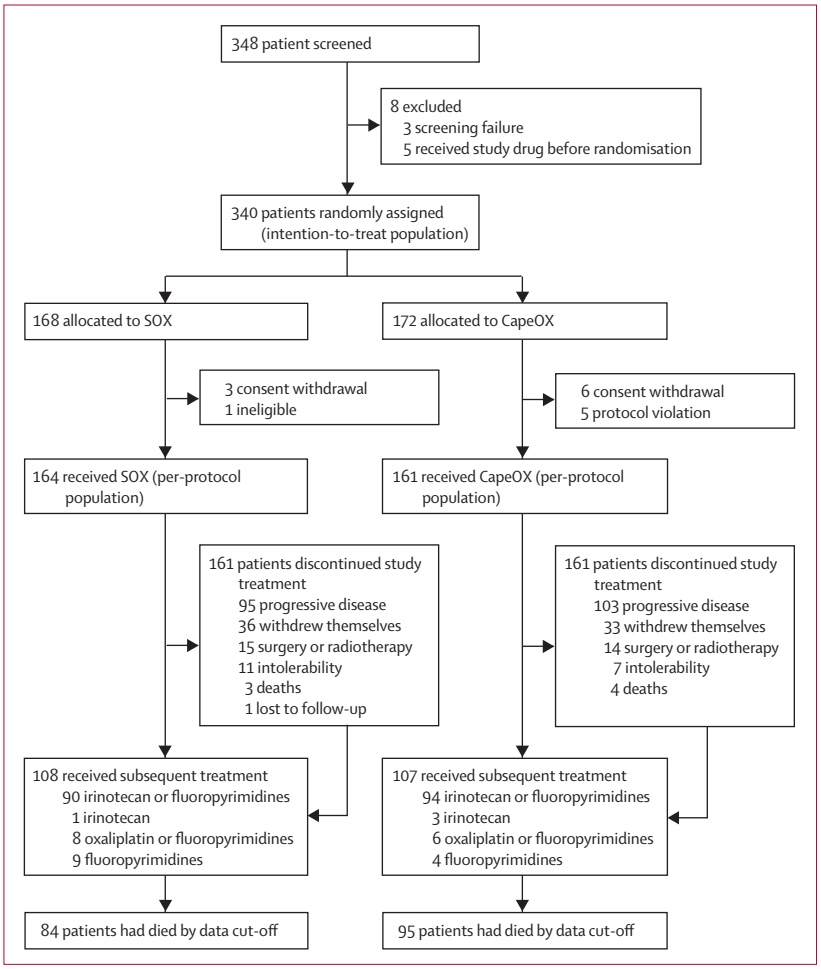

Figure 1: **Trial profile**
SOX=S-1 plus oxaliplatin. CapeOX=capecitabine plus oxaliplatin.

Randomisation and masking

We randomly assigned eligible patients to either CapeOX or SOX in a one-to-one ratio. Randomisation was done centrally with a computer-generated sequence and a permutation block technique that ensured equal distribution of patients on the basis of primary tumour sites (colon *vs* rectum), history of previous adjuvant or neoadjuvant treatment, and the presence of measurable lesions. Investigators or research coordinators sent the randomisation form by fax to the Clinical Research Coordination Centre of the National Cancer Centre, South Korea. After checking the inclusion criteria, the study coordinator sent the allocated treatment back to the investigator by fax. We used a web-based clinical research management platform (Velos Inc, Fremont, CA, USA) for randomisation. Investigators who assessed the response to the treatment were not masked to group assignment.

Procedures

All treatment cycles were administered every 3 weeks. We administered oral S-1 (40 mg/m²) twice a day on days 1–14, oral capecitabine (1000 mg/m²) twice a day on days 1–14, and oxaliplatin (130 mg/m²) on day 1 as a 2-h intravenous infusion. Treatment was continued for as many as nine cycles of oxaliplatin-containing chemotherapy, except in instances of disease progression, unacceptable toxicity, or a patient's refusal. Maintenance chemotherapy with S-1 or capecitabine was allowed after discontinuation of oxaliplatin.

Treatment responses were assessed every three cycles (9 weeks) during study treatments or sooner if needed for documentation of disease progression. Objective tumour responses were independently reviewed according to the Response Evaluation Criteria In Solid Tumors (RECIST; version 1.0). Clinical and laboratory toxicities were monitored according to the National Cancer Institute Common Terminology Criteria (NCI-CTC) for Adverse Events (version 3.0). Quality of life (QOL) was assessed before treatment and at every point of response assessments with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ C30; Korean version).[13]

The primary endpoint was progression-free survival (PFS), and secondary endpoints were response rate, time to treatment failure (TTF), overall survival, toxicity, and QoL. Data collection was done by the Velos system of the National Cancer Centre, South Korea.

Statistical analyses

For the primary efficacy analysis, in which we aimed to assess the non-inferiority of SOX to CapeOX in terms of PFS, we assessed all patients allocated to treatment (intention-to-treat population), and we also did a per-protocol analysis in those who received protocol treatments without major violations. For the safety analysis, we assessed data for all patients who received at least one dose of study treatment. PFS at 15 months in both groups was assumed to be 38%, and the lower non-inferiority limit was set as –13%, corresponding to a hazard ratio (HR) of 1·43. On the basis of these conditions, 192 events were needed for a one-sided type-I error of 5% and a power of 80%. Assuming a 10% loss, we needed 344 patients (172 per treatment group). The protocol was amended on Jan 28, 2009: initially, we had targeted 165 events and accrual of 298 patients (149 per treatment group) of which the upper limit of non-inferiority margin was 1·31. Overall survival (time to death), PFS (time to progression or death), and TTF (time to treatment discontinuation from any cause including disease progression, patients' refusal, lost to follow-up, chemotherapy-free interval after completion of planned nine cycles of study treatment even without evidence of disease progression, and intolerability from adverse events), along with 95% CI for median time to event, were assessed with the Kaplan-Meier method. Patients who entered into a chemotherapy-free interval after completion of planned treatment were censored for the PFS estimations. We estimated the hazard ratio (HR) and corresponding 95% CI using the Cox proportional hazard regression model. We calculated the dose intensity as the ratio of the total dose divided by the total treatment duration. We compared the EORTC QLQ C30 score changes from baseline between treatment groups using the Wilcoxon rank sum test. We used SAS (version 9.1) and SPSS (version 20.0) for all statistical analyses. This study is registered with ClinicalTrials.gov, number NCT00677443.

	SOX (n=168)	CapeOX (n=172)
Primary site		
Colon	109 (65%)	108 (63%)
Rectum	59 (35%)	64 (37%)
Sex		
Male	109 (65%)	102 (59%)
Female	59 (35%)	70 (41%)
Age in years (median [IQR])	61 (53–66)	60 (52–66)
≤65 years	121 (72%)	126 (73%)
>65 years	47 (28%)	46 (27%)
ECOG performance status		
0–1	164 (98%)	168 (98%)
2	4 (2%)	4 (2%)
Previous (neo)adjuvant therapy		
Yes	37 (22%)	38 (22%)
No	131 (78%)	134 (78%)
Tumour differentiation		
Well-differentiated	35 (21%)	29 (17%)
Moderately differentiated	116 (69%)	120 (70%)
Poorly differentiated	13 (8%)	19 (11%)
Mucinous or signet ring cell	1 (1%)	3 (2%)
Undetermined	3 (2%)	1 (1%)
Site of metastasis		
Liver	105 (63%)	111 (65%)
Lymph node	81 (48%)	100 (58%)
Lung	66 (39%)	79 (46%)
Peritoneum	40 (24%)	33 (19%)
Bone	4 (2%)	9 (5%)
Number of metastatic organs		
One organ	65 (39%)	49 (29%)
Two organs	61 (36%)	70 (41%)
Three or more organs	42 (25%)	53 (31%)
Measurability		
Measurable lesions	155 (92%)	155 (90%)
Assessable lesions only	13 (8%)	17 (10%)

Data are n (%), unless stated otherwise. SOX=S-1 plus oxaliplatin. CapeOX=capecitabine plus oxaliplatin. ECOG=Eastern Cooperative Oncology Group.

Table 1: **Baseline characteristics (intention-to-treat population)**

Role of the funding source

The study sponsor had no role in the study design, data collection, analysis, interpretation, writing, or the decision to submit for publication. YSH, SJJ, and JWL access to the raw data. The corresponding author had full access to all study data and final responsibility for the decision to submit for publication.

Results

Between May 14, 2008, and Sept 23, 2009, we enrolled 348 patients from 11 institutions. We randomly assigned 340 patients who met the eligibility criteria to treatment:

	SOX (N=164)	CapeOX (N=161)	p value
Total number of cycles of S-1 or capecitabine administered (median [IQR])*	1520 (9 [5–10·5])	1206 (6 [5–9])	
Total number of cycles of oxaliplatin administered (median [IQR])	1194 (8 [4·5–9])	1084 (6 [5–9])	
Cycles with delayed schedule	313 (21%)	188 (16%)	0·004
Because of neutropenia	85 (27%)	36 (19%)	
Because of thrombocytopenia	82 (26%)	24 (13%)	
Cycles with dose modification	169 (11%)	105 (9%)	0·038
Because of neutropenia	49 (29%)	45 (43%)	
Because of thrombocytopenia	57 (34%)	29 (28%)	
Relative dose intensity			
Oxaliplatin (median [%])	114·3 (88%)	125·0 (96%)	<0·0001
S-1 or capecitabine (median [%])	74·3 (93%)	1916·7 (96%)	

Data are n (%), unless stated otherwise. SOX=S-1 plus oxaliplatin. CapeOX=capecitabine plus oxaliplatin. *S-1 given to individuals in the SOX group and capecitabine given to those in the CapeOX group (includes maintenance schedules [either S-1 or capecitabine monotherapy] as chemotherapy cycles).

Table 2: **Treatment exposure (per-protocol population)**

168 to the SOX group and 172 to the CapeOX group (intent-to-treat population; figure 1). Baseline characteristics were much the same between the two groups (table 1).

We recorded no statistical difference in the median number of oxaliplatin cycles between the two groups (p=0·16). 31 patients in the SOX group entered into maintenance chemotherapy (median duration of maintenance 3·7 months, IQR 1·4–6·9 [S-1 alone for eight cycles]) and 20 patients in the CapeOX group entered into maintenance chemotherapy (2·3 months, 0·5–4·8 [capecitabine alone for five cycles]). The median relative dose intensity was greater in the CapeOX group than it was in the SOX group (table 2).

See Online for appendix

1520 cycles of chemotherapy (of which 1194 cycles contained oxaliplatin) were given to 164 patients in the SOX group (table 2), and the most common cause for discontinuation of treatment was disease progression (figure 1). In the SOX group, treatment delays were made in 313 cycles (21%) for 120 (73%) patients; modifications of oxaliplatin were made for 117 (71%) patients and modifications of S-1 were made for 113 (69%) patients.

In the CapeOX group, 1206 cycles of chemotherapy (of which 1084 cycles contained oxaliplatin) were given to 161 patients (table 2), and the most common cause for discontinuation of treatment was disease progression (figure 1). Treatment delays in this group were made in 188 cycles (16%) for 93 (58%) patients; modifications of oxaliplatin were made in 89 (55%) patients and modifications of capecitabine were made in 86 (53%) patients.

At the cut-off date for data collection (Aug 31, 2011), study treatments had been discontinued in 161 patients in the SOX group and 161 patients in the CapeOX group; median follow-up was 20·6 months (IQR 12·0–29·4). In the SOX group, PFS at 15 months was 38·7% (95% CI 31·3–46·1) and the median PFS was 8·5 months (7·6–9·3); the corresponding values in the CapeOX group were 32·2% (25·2–39·2) and 6·7 months (6·2–7·1; intention-to-treat analysis; table 3 and figure 2). The HR comparing PFS between the two groups was 0·79 (95% CI 0·60–1·04, $p_{non\text{-}inferiority}<0·0001$, $p_{log\text{-}rank}=0·09$), and the upper limit of the CI was below the predefined margin of 1·43—our data therefore show non-inferiority of the SOX regimen compared with the CapeOX regimen. We also recorded non-inferiority in the per-protocol analysis (table 3).

In both the intention-to-treat population and per-protocol population, median TTF was statistically significantly longer in the SOX group than it was in the CapeOX group, but we recorded no statistically significant difference between groups when comparing overall survival (table 3 and figure 2).

Of 340 randomized patients, 310 patients with measurable lesion(s) were included in the assessment of objective responses. Overall objective response in both the intention-to-treat and per-protocol population was greater in the SOX group than it was in the CapeOX group (table 3). We recorded no statistically significant difference in disease control rate in either the intention-to-treat or per-protocol population (table 3).

The safety population included 335 patients who were treated with at least one cycle of their allocated study

	Intention-to-treat population			Per-protocol population		
	SOX	CapeOX	Effect size (95% CI); p value	SOX	CapeOX	Effect size (95% CI); p value
Number of patients	168	172		164	161	
Primary endpoint						
PFS at 15 months	38·7 (31·3–46·1)	32·2 (25·2–39·2)		38·7 (31·2–46·2)	31·9 (24·7–39·1)	
Median PFS (95% CI)*	8·5 (7·6–9·3)	6·7 (6·2–7·1)	0·79 (0·60–1·04); $p_{non\text{-}inferiority}<0·0001$	8·5 (7·6–9·3)	6·6 (6·0–7·0)	0·78 (0·60–1·03); $p_{non\text{-}inferiority}<0·0001$
Secondary endpoints						
Median TTF (95% CI)*	6·9 (6·1–7·8)	5·6 (4·7–6·4)	0·78 (0·62–0·99); $p_{log\text{-}rank}=0·036$	6·9 (6·1–7·8)	5·6 (4·7–6·4)	0·79 (0·63–0·99); $p_{log\text{-}rank}=0·042$
Median overall survival (95% CI)*	21·2 (16·2–26·2)	20·5 (18·2–22·9)	0·82 (0·61–1·10); $p_{log\text{-}rank}=0·18$	21·2 (16·2–26·2)	20·3 (18·6–21·9)	0·80 (0·60–1·08); $p_{log\text{-}rank}=0·15$
Number of patients with measurable disease	155	155		153	148	
Response rates						
Complete response	1 (1%)	1 (1%)		1 (1%)	1 (1%)	
Partial response	72 (47%)	54 (35%)		72 (47%)	54 (37%)	
Stable disease	53 (34%)	70 (45%)		53 (35%)	67 (45%)	
Progressive disease	18 (12%)	20 (13%)		18 (12%)	20 (14%)	
Not determinable	11 (7%)	10 (7%)		9 (6%)	6 (4%)	
Objective response†	73 (47%)	55 (36%)	1·68 (1·05–2·69); p=0·029	73 (48%)	55 (37%)	1·63 (1·02–2·60); p=0·042
Disease control†	126 (81%)	125 (81%)	1·12 (0·57–2·22); p=0·75	126 (82%)	122 (82%)	1·15 (0·58–2·27); p=0·69

Data are n (%), time in months (95% CI), or effect size (95% CI). SOX=S-1 plus oxaliplatin. CapeOX=capecitabine plus oxaliplatin. PFS=progression-free survival. TTF=time to treatment failure. HR=hazard ratio. OR=odds ratio. *Effect size given as hazard ratio. †Effect size given as odds ratio.

Table 3: **Efficacy outcomes**

treatment. Grade 3 or grade 4 neutropenia, thrombocytopenia, and diarrhoea were more common in the SOX group (table 4) Any grade thrombocytopenia, jaundice, anorexia, diarrhoea, and stomatitis were more common in the SOX group, and any grade hand-foot syndrome was more common in the CapeOX group (table 4).

Overall completion of the quality-of-life questionnaire for comparisons between baseline and final visits were satisfactory (>80%) for both groups (appendix). We recorded no statistically significant differences between the two groups with respect to changes in global health status or functioning and symptom scales (appendix). Some scores differed significantly between baseline and final visits, although the changes in the score were not clinically relevant because, with the exception of role functioning scores, they were less than 10. The role functioning scores in both groups by more than 10 points and we recorded no statistically significant difference between the two groups.

Of 325 patients, 215 (66%) received further treatment after SOX or CapeOX (figure 1). We recorded no statistically significant differences between the SOX group and the CapeOx group in terms of the proportion of patients who received all three cytotoxic agents (irinotecan, oxaliplatin, and S-1 or capecitabine) during the whole treatment period (98 [60%] of 164 patients *vs* 104 [65%] of 161 patients), or in terms of those subsequently given bevacizumab (10 [6%] of 164 patients *vs* eight [5%] of 161 patients) or cetuximab (27 [17%] of 164 patients *vs* 32 [20%] of 161 patients).

Discussion

Our findings suggest that SOX is non-inferior to CapeOX when given as first-line chemotherapy to patients with metastatic colorectal cancer in terms of our primary endpoint, PFS. Furthermore, patients in the SOX group had a better outcome than did those in the CapeOX group in terms of two of our secondary endpoints, response rate and TTF.

Patients in the CapeOX group in this study had a response rate of 36% and a PFS of 6·7 months, which are similar values to those reported in previous trials.[1,3,5,6] Similarly, the SOX group in our study showed promising results, similar to values recorded for FOLFOX in previous studies.[6] The incidence of grade 3 or grade 4 diarrhoea (4%) and HFS (2%) in the CapeOX group in our study were lower than those reported in previous studies of CapeOX (20–31%[3,5,7] and 6–19%,[3,5,7] respectively). Some investigators have suggested that a reduced dose of capecitabine should be combined with oxaliplatin to improve tolerability and efficacy outcomes with CapeOX.[3,7] However, in view of the fact that the median relative dose intensity of capecitabine was 96%

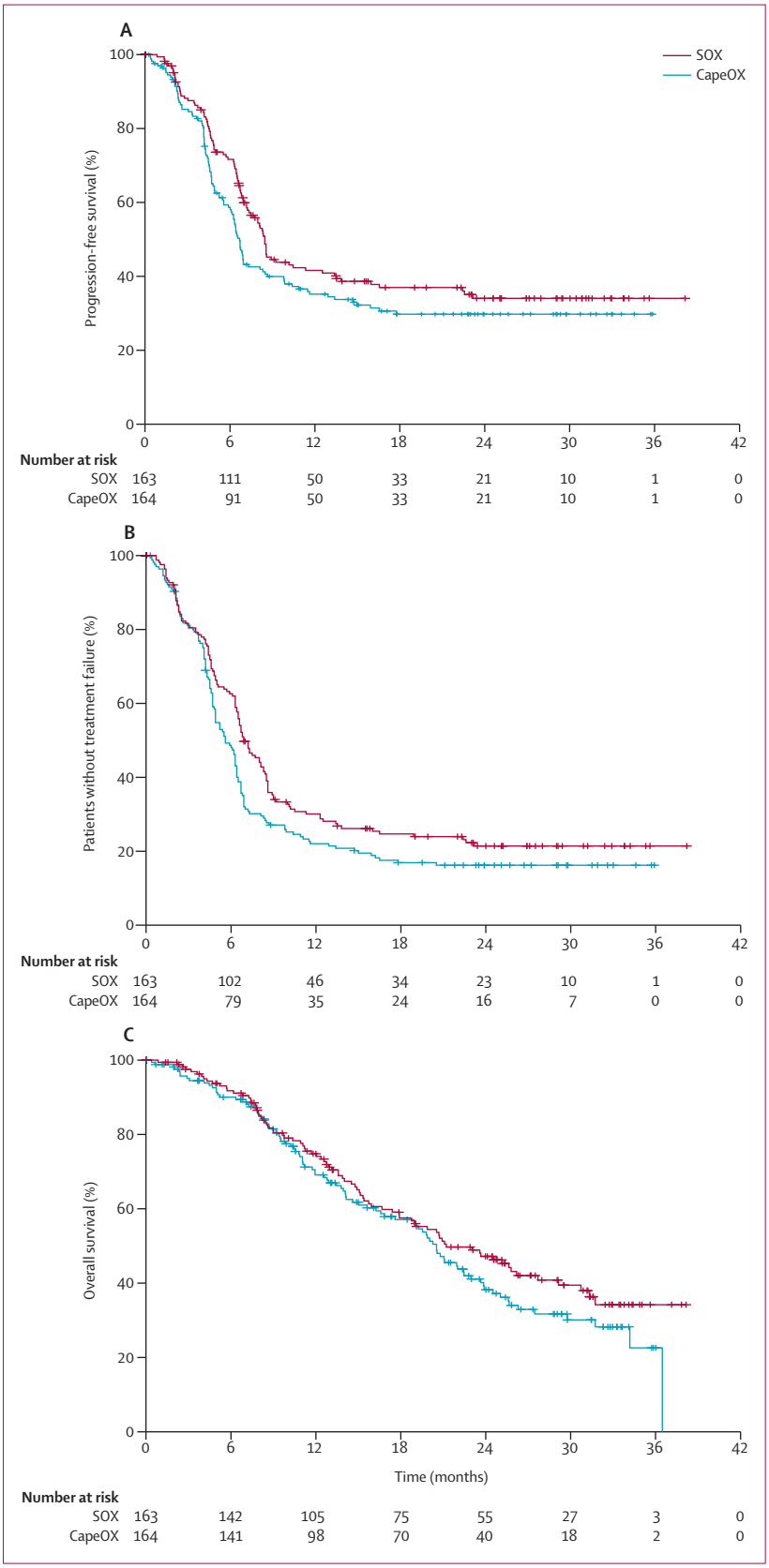

Figure 2: **Kaplan Meier curves of progression-free survival (A), time to treatment failure (B), and overall survival (B)**
SOX=S-1 plus oxaliplatin. CapeOX=capecitabine plus oxaliplatin.

	Any grade			Grade 3 or grade 4		
	SOX (N=169)	CapeOX (N=166)	p value	SOX (N=169)	CapeOX (N=166)	p value
Haematological						
Leucopenia	2 (1%)	4 (2%)	0·23	1 (1%)	1 (1%)	0·50
Neutropenia	82 (49%)	67 (40%)	0·08	49 (29%)	24 (15%)	0·001
Febrile neutropenia	2 (1%)	2 (1%)	0·38	2 (1%)	2 (1%)	0·38
Thrombocytopenia	84 (50%)	52 (31%)	0·001	37 (22%)	11 (7%)	<0·0001
Anaemia	27 (16%)	17 (10%)	0·08	6 (4%)	3 (2%)	0·26
Non-hematological						
Jaundice	23 (14%)	9 (5%)	0·008	3 (2%)	4 (2%)	0·27
ALP abnormality	3 (2%)	2 (1%)	0·51	0	1 (1%)	0·50
AST or ALT abnormality	21 (12%)	21 (13%)	0·13	3 (2%)	7 (4%)	0·11
Anorexia	120 (71%)	94 (57%)	0·004	11 (7%)	4 (2%)	0·06
Fatigue	77 (46%)	66 (40%)	0·17	10 (6%)	6 (4%)	0·23
Constipation	54 (32%)	50 (30%)	0·40	1 (1%)	0	0·50
Diarrhoea	75 (44%)	57 (34%)	0·038	16 (10%)	7 (4%)	0·045
Stomatitis	64 (38%)	38 (23%)	0·002	1 (1%)	0	0·50
Nausea	95 (56%)	92 (55%)	0·09	5 (3%)	4 (2%)	0·51
Vomiting	62 (37%)	59 (36%)	0·46	3 (2%)	6 (4%)	0·16
Bleeding	28 (17%)	27 (16%)	0·53	2 (1%)	0	0·25
Hand-foot syndrome	23 (14%)	51 (31%)	<0·0001	1 (1%)	3 (2%)	0·25
Sensory neuropathy	133 (79%)	129 (78%)	0·47	14 (8%)	9 (5%)	0·21
Hypersensitivity	10 (6%)	9 (5%)	0·52	2 (1%)	2 (1%)	0·38

Data are n (%). SOX=S-1 plus oxaliplatin. ALP=alkaline phosphatase. ALT=alanine aminotransferase. AST=aspartate aminotransferase. CapeOX=capecitabine plus oxaliplatin.

Table 4: **Adverse events (safety population)**

in our study, the inferior efficacy of CapeOX relative to FOLFOX, as suggested in a previous study,[7] cannot be wholly explained by tolerability and dose of capecitabine used.

We did a non-inferiority trial rather than an equivalence trial because S-1 plus oxaliplatin could be a substitute for CapeOX. Efficacy outcomes in the SOX group were not inferior to those in the CapeOX group, despite the lower dose intensity of oxaliplatin and more frequent cycle delays caused by adverse events. However, because of the need for reduced dose intensity and more frequent cycle delays compared with CapeOX, further studies are needed to determine the optimum dose for SOX. S-1 is used mainly in South Korea and Japan, however, the dose and schedules of S-1 are varied: 50–120 mg per day or 70–90 mg/m² per day with 3-week to 6-week schedules.[8,12,14–17] The dose of S-1 in this study was 80 mg/m² per day, which is higher than those used in the reference trials that combined it with oxaliplatin.[8,10] This fact might explain the high frequency of adverse events and treatment modifications in the SOX group in our trial. Furthermore, differences between different ethnic groupings in the prevalence of CYP2A6 polymorphisms (which are more common in Asian people than they are in white people) have been suggested to effect the efficacy and toxicity from S-1,[14,15,18] which means that the optimum dose of SOX needs to be established for all ethnic groups.

Thrombocytopenia is one of the key haematological toxicities caused by oxaliplatin, and the incidence of grade 3 or grade 4 thrombocytopenia has been reported to range from 2–10% after FOLFOX or CapeOX.[1,3,5,7] The incidence of grade 3 or grade 4 thrombocytopenia in patients treated with CapeOX in this study is similar to those reported in these previous studies. In our trial, the much higher frequency of grade 3 or grade 4 thrombocytopenia in the SOX group suggests that thrombocytopenia might be a serious undesirable side-effect of SOX treatment. However, the serious adverse events caused by thrombocytopenia, such as bleeding, did not differ between the SOX and CapeOX groups. Several studies of S-1 plus oxaliplatin for various cancer types also showed a higher incidence of grade 3 or grade 4 thrombocytopenia (13–28%).[10,11,19] The incidence of thrombocytopenia after S-1 monotherapy in other trials does not seem to differ from that seen with monotherapy with other fluoropyrimidines.[4,8–10,20]

The thrombocytopenia caused by oxaliplatin-based chemotherapy has been suggested to be associated with both bone marrow suppression and liver damage from sinusoidal obstruction syndrome (SOS).[21,22] The rate of any grade of hyperbilirubinemia in our study was higher in the SOX group than it was in the CapeOX group, which might be explained by the association between SOS and thrombocytopenia. There is no definitive evidence that oxaliplatin-induced SOS is augmented by the combination with S-1 rather than with other fluoropyrimidines. However, further investigation of this aspect is needed, using non-invasive methods such as liver-specific imaging to better understand the effects of combined delivery of oxaliplatin and other fluoropyrimidines.[23]

The cumulative dose of oxaliplatin was about 1000 mg/m² after nine cycles of SOX or CapeOX, which is an upper limit causing permanent sensory neuropathy—but the cumulative effects would differ between patients. We planned not to exceed nine cycles of oxaliplatin in this study because the OPTIMOX studies have shown that continuation of oxaliplatin past this point does not improve efficacy.[24,25] We did, however, allow fluoropyrimidine maintenance in patients who completed the planned nine cycles of oxaliplatin without disease progression, which we consider to be an acceptable treatment strategy.

The addition of targeted agents to the first-line chemotherapy have improved survival in patients with metastatic colorectal cancer—previous studies have shown that bevacizumab plus FOLFOX or CapeOX improves PFS;[6] cetuximab plus FOLFIRI improves RR, PFS, and overall survival;[26] and panitumumab plus FOLFOX improves RR and PFS.[27] The combination of cetuximab or panitumumab is used only in patients whose tumours harbour wild-type *KRAS*, and cetuximab

Panel: Research in context

Systematic review

We searched PubMed for published studies, scientific meeting abstracts for any preliminary results, and ClinicalTrials.gov for any additional open or closed phase 2–3 trials of S-1 for patients with metastatic colorectal cancer. We searched for studies published up to Jan 31, 2008. We used search terms including "tegafur", "5-fluorouracil", "colorectal", "chemotherapy", "S-1", and "fluoropyrimidine". We retrieved three preclinical, phase 1–2 studies of S-1 plus oxaliplatin in patients with metastatic colorectal cancer, and one phase 1–2 study in patients with gastric cancer. To the best of our knowledge, no other phase 3 study has compared S-1 plus oxaliplatin to capecitabine plus oxaliplatin in terms of progression-free survival. We therefore undertook this trial to compare SOX and CapeOX.

Interpretation

Our study has shown non-inferiority of S-1 plus oxaliplatin to capecitabine plus oxaliplatin in terms of progression-free survival.These findings suggest that S-1 plus oxaliplatin could be an additional therapeutic option for first-line chemotherapy for patients with metastatic colorectal cancer. This combination of S-1 plus oxaliplatin should be investigated further, either combined with targeted agents or as adjuvant chemotherapy. However, dose modifications regarding the optimum dosage of either S-1 or oxaliplatin should be considered in any further studies, especially for use in non-Asian patients because of differences between different ethnic populations in terms of efficacy and toxicity.

seemed not to have additional benefit combined with oxaliplatin or capecitabine-based chemotherapy.[28,29] The efficacy of bevacizumab, however, has been shown to not be affected by the choice of chemotherapy backbone or *KRAS* status.[6,30,31] A few studies of bevacizumab with S-1 plus oxaliplatin have been reported,[32] thus a phase 3 study comparing SOX with or without bevacizumab is needed.

We could have combined bevacizumab with both SOX and CapeOX in this study, because bevacizumab is often combined with doublet chemotherapy in clinical practice. However, the main purpose of this study was to compare two different oral fluoropyrimidines, S-1 and capecitabine, and CapeOX is still regarded as one of the reference doublet cytotoxic chemotherapy in many countries.

Our findings suggest that that a combination of S-1 and oxaliplatin can be regarded as an alternate doublet chemotherapy strategy to CapeOX. Further investigations are needed to explore its potential when used together with other targeted agents or as adjuvant chemotherapy. The results of this study, if substantiated in further trials, could widen the choice of doublet cytotoxic chemotherapy choices for patients with metastatic colorectal cancer.

Contributors

YSP, HYL, JL, SJJ, and JWL contributed to the study design. YSH, SJJ, and JWL contributed to the data collection and analysis, and YSP led the analysis and interpretation. YSH, YSP, HYL, JL, TWK, and KPK contributed to the writing of the paper. All authors contributed to review of paper and approved the final version.

Conflicts of interest

We declare that we have no conflicts of interest.

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