Table 1. Patients' profile (n = 51)

Characteristic	No. of patients	%
Median age, years (range)	63 (30–77)	
Sex		
Male	34	67
Female	17	33
ECOG PS		
0	32	63
1	18	35
2	1	2
Disease status		
Advanced	47	92
Recurrent	4	8
Primary tumor		
No	12	24
Yes	39	77
Prior adjuvant chemotherapy		
No	50	98
Yes	1	2
Histology		
Diffuse	35	69
Intestinal	16	31
Sites of metastasis		
Lymph nodes	41	80
Liver	23	45
Lung	9	18
Peritoneum	7	14
Other	9	18
No. of metastases		
1	22	43
≥2	29	57

ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 2. Objective response to treatment (n = 51)

Response	No. of patients	% (95% CI)
CR	0	0
PR	30	59
SD	13	26
PD	5	10
Not evaluable	3	6
Overall response rate	30	59 (44.2–72.4)
Disease control rate (CR + PR + SD)	43	84 (71.4–93.0)

CI, confidence interval; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

patients in the efficacy analysis set (three were not assessable). The RR was 59% (95% CI 44.2% to 72.4%) and the disease control rate (CR + PR + SD) was 84% (95% CI 71.4% to 93.0%) (Table 2).

The median follow-up period was 16.5 months as of 13 July 2009. The median survival time (MST) was 16.5 months (95% CI 13.2–22.3 months) (Figure 1), median PFS was 6.5 months (95% CI 4.8–11.2 months) (Figure 2), and median TTF was 4.8 months (95% CI 4.0–5.6 months). The patients who received

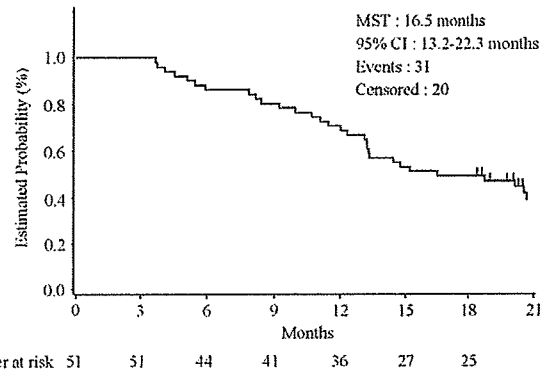

Figure 1. Kaplan–Meier estimates of overall survival (n = 51).

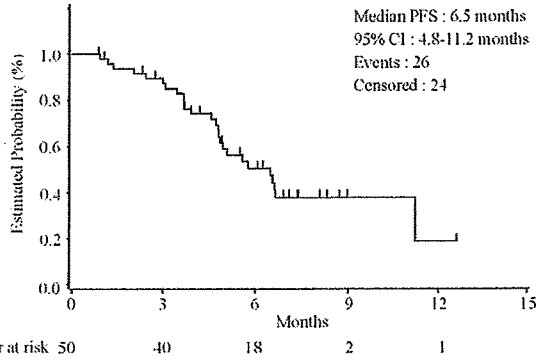

Figure 2. Kaplan–Meier estimates of progression-free survival (n = 50).

the second-line chemotherapy without PD were censored at the date of image examination immediately before the second-line chemotherapy in PFS analysis. The 1-year survival rate was 70.6% (95% CI 58.1% to 83.1%).

Forty-one of the 46 patients (89%) who discontinued treatment received second-line chemotherapy. One patient (2%) with PR underwent surgery and pathological CR was observed.

safety assessment

Grade 3/4 toxicity occurred in 33 of the 54 patients (61%) in the safety analysis set. Grade 3/4 leukopenia, neutropenia, thrombocytopenia, anemia, anorexia, and fatigue were noted in 2 (4%), 12 (22%), 7 (13%), 5 (9%), 3 (6%), and 3 patients (6%), respectively (Table 3). The median onset of thrombocytopenia in all grades was after 42 days and the nadir platelet count was seen at 113 days. The median time from the nadir to grade 0 or platelet count of treatment initiation was 15 days and the duration of thrombocytopenia in all grades was 21 days. Sensory neuropathy was observed in 48 patients (89%), but grade 3/4 neuropathy occurred only in two patients (4%). The median cumulative dose of oxaliplatin associated with sensory neuropathy of any grade was 150 mg/m^2 (grade 1: 150 mg/m^2, grade 2: 900 mg/m^2). There were no treatment-related deaths.

Table 3. Toxicity of therapy (n = 54)

Toxicity (CTCAE)	No. of patients (%)					
	Grade 1	Grade 2	Grade 3	Grade 4	All grades	Grade 3/4
Hematological						
Leukopenia	15 (28)	16 (30)	2 (4)	0	33 (61)	2 (4)
Neutropenia	3 (6)	15 (28)	12 (22)	0	30 (56)	12 (22)
Thrombocytopenia	25 (46)	9 (17)	7 (13)	0	41 (76)	7 (13)
Anemia	14 (26)	14 (26)	4 (7)	1 (2)	33 (61)	5 (9)
Non-hematological						
Nausea	27 (50)	10 (19)	1 (2)	0	38 (70)	1 (2)
Vomiting	15 (28)	4 (7)	0	0	19 (35)	0
Diarrhea	17 (32)	4 (7)	1 (2)	0	22 (41)	1 (2)
Anorexia	21 (39)	16 (30)	2 (4)	1 (2)	40 (74)	3 (6)
Fatigue	24 (44)	14 (26)	2 (4)	1 (2)	41 (76)	3 (6)
Rash	13 (24)	2 (4)	0	0	15 (28)	0
Pigmentation	20 (37)	2 (4)	0	0	22 (41)	0
Hand–foot syndrome	12 (22)	2 (4)	0	0	14 (26)	0
Stomatitis	20 (37)	1 (2)	0	0	21 (39)	0
Increased creatinine	3 (6)	0	0	0	3 (6)	0
Febrile neutropenia	0	0	1 (2)	0	1 (2)	1 (2)
Sensory neuropathy	35 (65)	11 (20)	2 (4)	0	48 (89)	2 (4)

CTCAE, Common Terminology Criteria for Adverse Events V3.0.

discussion

Advanced gastric cancer is usually treated by combination chemotherapy with fluoropyrimidine derivatives and platinum compounds. Several recent large-scale phase III studies have shown that the RR ranges from 25% to 54%, median PFS from 2.9 to 7 months, and MST from 8.6 to 13 months [5, 6, 8, 9, 11, 14]. Unfortunately, these results are not satisfactory. In Japan, S-1 plus cisplatin is considered to be the standard treatment for advanced gastric cancer on the basis of the results of two phase III studies: the JCOG9912 study demonstrated non-inferiority of S-1 to i.v. infusion of 5-FU [14] and the SPIRITS study showed that S-1 plus cisplatin was superior to S-1 alone [11]. In the SPIRITS study, the RR, median PFS, and MST achieved with S-1 plus cisplatin were 54%, 6.0 months, and 13 months, respectively. However, more frequent incidences of grade 3/4 adverse events were reported as compared with S-1-alone group, and the combination regimens with improved safety are expected.

With the present SOX regimen, the RR was 59%, median PFS was 6.5 months, 1-year survival was 70.6%, and MST was 16.5 months, indicating similar efficacy to that of S-1 plus cisplatin. The excellent result of our SOX regimen in MST may be explicable by good PFS and feasible safety profile, which enabled patients to receive the second-line chemotherapy in the high proportion (89%). The efficacy of SOX regimen was also comparable with epirubicin and oxaliplatin plus capecitabine in the REAL-2 study (1-year survival rate of 47% and MST of 11.2 months) [8], which demonstrated that oxaliplatin was as effective as cisplatin combined with epirubicin and 5-FU or capecitabine.

Comparison of safety between the present SOX regimen and S-1 plus cisplatin that were reported previously [11] indicates a lower incidence of grade 3/4 toxicity with SOX regimen than S-1 plus cisplatin for leucopenia (4% versus 11%), neutropenia (22% versus 40%), anemia (9% versus 26%), anorexia (6% versus 30%), and nausea (2% versus 11%). The incidence of grade 3/4 thrombocytopenia was higher with SOX regimen (13% versus 5%). Sensory neuropathy is a characteristic toxicity of oxaliplatin, and 89% of the patients receiving SOX regimen had neuropathy, but only 4% had severe (grade 3/4) neuropathy. These results indicate that SOX regimen is more tolerable and tends to be superior to S-1 plus cisplatin in terms of safety.

Yamada et al. [15] reported that the treatment was discontinued at high frequency (28%) due to prolonged thrombocytopenia when metastatic colorectal cancer patients were treated with S-1 plus 130 mg/m^2 of oxaliplatin. This discontinuation was supposed to be caused by the geniality of dose reduction criteria which allowed the reduction of oxaliplatin only in case of occurrence of grade 3 or more toxicity in terms of thrombocytopenia. The incidence of thrombocytopenia was 93% in all grades and 28% in grade 3/4, resulting in low median relative dose intensity of S-1 74.6% and that of oxaliplatin 82.8%. Zang et al. [16] also reported the study of SOX regimen with 130 mg/m^2 of oxaliplatin in patients with metastatic colorectal cancer. In their study, the treatment was interrupted in cases of grade 2 or higher toxicity until the recovery to grade 0 or 1, and the doses of oxaliplatin and S-1 were reduced after a second occurrence of grade 2 toxicity. As a result, the incidence of thrombocytopenia was 13% in grade 3/4, and the median relative dose intensity of oxaliplatin and S-1 was 82% and 82%, respectively. In this study, we used 100 mg/m^2 dose of oxaliplatin as SOX regimen for advanced gastric cancer to decrease the incidence of thrombocytopenia considering the possible bleeding from the primary tumor and to maintain the dose intensity of S-1, which have been demonstrated to a key drug against advanced gastric cancer as a single agent. In this new regimen, the incidence of

thrombocytopenia was 13% in grade 3/4 without reducing the antitumor activity. The median relative dose intensity of oxaliplatin and S-1 was 87.5% and 85.7%, respectively, indicating that the treatment was carried out as scheduled in most of patients in this study.

In conclusion, SOX regimen with oxaliplatin at a dose of 100 mg/m^2 was effective and well tolerated in patients with advanced gastric cancer. SOX regimen has the potential to replace current regimens such as S-1 plus cisplatin or 5-FU plus cisplatin because of similar efficacy with less toxicity and more convenient treatment. Further investigation of this SOX regimen is expected.

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disclosure

All authors declared no conflicts of interest.

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Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomised phase 3 study

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Summary

Background The best chemotherapy regimen for metastatic gastric cancer is uncertain, but promising findings have been reported with irinotecan plus cisplatin and S-1 (tegafur, 5-chloro-2,4-dihydropyrimidine, and potassium oxonate). We aimed to investigate the superiority of irinotecan plus cisplatin and non-inferiority of S-1 compared with fluorouracil, with respect to overall survival, in patients with metastatic gastric cancer.

Methods We undertook a phase 3 open label randomised trial in 34 institutions in Japan. We enrolled patients aged 20–75 years or younger, who had histologically proven gastric adenocarcinoma, and randomly assigned them by minimisation to receive either: a continuous infusion of fluorouracil (800 mg/m² per day, on days 1–5) every 4 weeks (n=234); intravenous irinotecan (70 mg/m², on days 1 and 15) and cisplatin (80 mg/m², on day 1) every 4 weeks (n=236); or oral S-1 (40 mg/m², twice a day, on days 1–28) every 6 weeks (n=234). The primary endpoint was overall survival. Analyses were done by intention to treat. This study is registered with Clinicaltrials.gov, number NCT00142350, and with UMIN-CTR, number C000000062.

Findings All randomised patients were included in the primary analysis. Median overall survival was 10·8 months (IQR 5·7–17·8) for individuals assigned fluorouracil, 12·3 months (8·1–19·5) for those allocated irinotecan plus cisplatin (hazard ratio 0·85 [95% CI 0·70–1·04]; p=0·0552), and 11·4 months (6·4–21·3) for those assigned S-1 (0·83 [0·68–1·01]; p=0·0005 for non-inferiority). Three treatment-related deaths occurred in the irinotecan plus cisplatin group and one was recorded in the S-1 group.

Interpretation S-1 is non-inferior to fluorouracil and, in view of the convenience of an oral administration, could replace intravenous fluorouracil for treatment of unresectable or recurrent gastric cancer, at least in Asia. Irinotecan plus cisplatin is not superior to fluorouracil in this setting.

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Introduction

Gastric cancer is the second leading cause of death from malignant disease worldwide.[1] The prognosis of unresectable or recurrent tumours is dismal: with best supportive care, median survival is about 4 months, and with chemotherapy it is around 8 months.[2–4]

During the early 1990s, several randomised trials for gastric cancer were undertaken of anthracyclines, mitomycin C, fluorouracil, methotrexate, and cisplatin.[5–13] At that time, the standard treatment for this malignant disease had not been established. When planning our current trial, no meta-analysis had been published of chemotherapy for advanced gastric cancer. Data from three phase 3 trials did not show a survival benefit of fluorouracil plus cisplatin over fluorouracil alone.[11–13] We reported previously that fluorouracil plus cisplatin caused more toxic effects and did not extend survival compared with continuous infusion of fluorouracil alone, despite a higher response rate and longer progression-free survival.[13] We concluded that continuous infusion of fluorouracil would be a standard arm in any subsequent phase 3 study.

In the late 1990s, new antitumour agents were developed for gastric cancer. In a phase 2 trial, combination chemotherapy with irinotecan plus cisplatin showed a response rate of 59% and median survival time of 322 days with grade 4 neutropenia (57%) and grade 3 or 4 diarrhoea (20%).[14] These efficacy measures were the best compared with those of other phase 2 trials. Although this regimen showed substantial toxic effects, they were deemed manageable, with dose reduction in some patients.

S-1 is a new oral fluoropyrimidine, consisting of tegafur, 5-chloro-2,4-dihydropyrimidine, and potassium oxonate. Data of two phase 2 studies of S-1 alone[15,16] showed a response rate of 45% and 2-year survival of 17%, in association with 5% or lower frequencies of grade 3 or 4 toxic effects. Furthermore, treatment could be administered on an outpatient basis.

With these findings in mind, we planned a three-arm phase 3 study of two pair-comparisons. On behalf of the gastrointestinal oncology study group of Japan Clinical Oncology Group (GIOSG/JCOG), we aimed to investigate

superiority of irinotecan plus cisplatin, and non-inferiority of S-1, compared with continuous infusion of fluorouracil for metastatic gastric cancer.

Methods

Patients

We undertook a three-arm, phase 3, randomised trial in 34 institutions in Japan. We used the following eligibility criteria to screen patients for inclusion: histologically proven gastric adenocarcinoma; unresectable or recurrent disease; adequate self-supported nutritional intake; age-range 20–75 years; Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less; no history of chemotherapy, radiation therapy, or both (however, adjuvant chemotherapy with an oral fluoropyrimidine other than S-1, not exceeding 1-year duration, completed more than 6 months before entry, was allowed); preserved organ functions; white-blood-cell count of 3·0–12·0×10⁹/L; number of platelets 100×10⁹/L or more; aspartate aminotransferase and alanine aminotransferase concentrations of 99 U/L or less; total bilirubin 25·65 μmol/L or lower; creatinine concentration 132·6 μmol/L or less; and creatinine clearance of 50 mL/min or faster. Having a target lesion or lesions according to response evaluation criteria in solid tumours was not mandatory. We excluded patients with severe peritoneal metastasis such as ileus or sub-ileus, ascites beyond the pelvic cavity, or narrowing of the colon detected by barium enema.

All eligible patients provided written informed consent to participate. The study was approved by the institutional review board of every participating institution. The JCOG data and safety monitoring committee (standing committee) monitored patients' safety, adverse events, and progress of the trial.

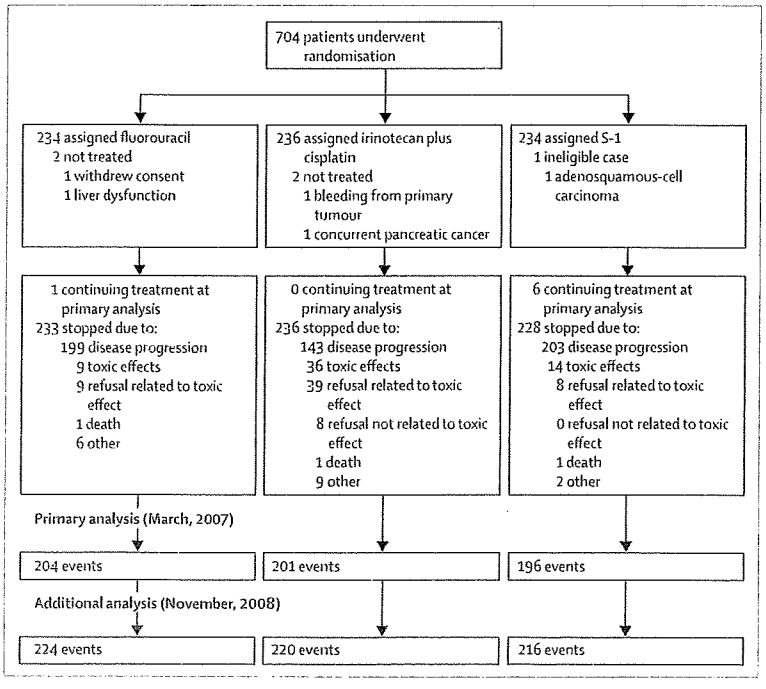

Figure 1: Trial profile

Randomisation and masking

We communicated patient's details to the data centre by fax or telephone. Staff in data centre entered these details into the computer to check eligibility, complete registration if appropriate, and randomly allocate the patient to a treatment group. Staff at the JCOG data centre randomly assigned every patient to either continuous infusion of fluorouracil, irinotecan plus cisplatin, or S-1, using the minimisation method,[17] with an algorithm (concealed to the investigators) that balanced institution, ECOG performance status (0, 1, or 2), and previous treatment (none, curative surgery alone, curative surgery and adjuvant chemotherapy). The treatment allocation was then communicated to the appropriate investigator by fax or telephone. The investigators participating in this trial treated their patients and took care of them all through the clinical course. Because the three treatment methods studied were quite different, the treatment allocation could not be masked from the investigators or patients. All data in case-report forms were sent to the JCOG data centre and checked by central data managers.

Procedures

Patients assigned fluorouracil received 800 mg/m² daily as a continuous infusion for 5 days, repeated every 4 weeks. Those assigned irinotecan plus cisplatin received an infusion of 70 mg/m² irinotecan on days 1 and 15 and 80 mg/m² cisplatin as a drip infusion on day 1 with adequate hydration, repeated every 4 weeks. After six cycles, the same dose of irinotecan alone was continued every 2 weeks. Individuals assigned S-1 received 40 mg/m² twice a day orally for 4 weeks, followed by a 2-week rest.

We delayed every treatment cycle until non-haematological toxic effects had recovered to grade 1 or lower, body temperature was 38°C or less, white-blood-cell count was 3·0–12·0×10⁹/L, platelets were 100×10⁹/L or more, aspartate aminotransferase and alanine aminotransferase concentrations were 99 U/L or less, total bilirubin was 25·65 μmol/L or lower, and creatinine concentration was 132·6 μmol/L or less. We reduced the treatment dose if, during the previous cycle, one of the following events had arisen: grade 4 leucopenia (less than 1·0×10⁹/L); thrombocytopenia (less than 10·0×10⁹/L); haemoglobin (less than 65g/L); grade 3 or higher non-haematological toxic effect; irinotecan not given on day 15; or S-1 or fluorouracil administration was suspended. The dose of cisplatin was reduced if the amount of creatinine was 106·1–132·6 μmol/L. We discontinued treatment if disease progression was diagnosed clinically or by imaging, if a serious adverse

event arose, if a treatment cycle was delayed due to an adverse event continuing for longer than 2 weeks, if an adverse event meant a subsequent dose reduction was needed after the first reduction, if the patient refused treatment, or if judged necessary by the treating doctor for other reasons.

We did physical examinations and laboratory tests at least once every 2 weeks, and we assessed all adverse events according to the National Cancer Institute's common toxicity criteria (version 2.0). The JCOG data and safety monitoring committee reviewed serious adverse events and judged whether an adverse event was attributable to treatment. We assessed tumour response every 2 months according to RECIST (version 1.0). CT and endoscopic images of responders taken every 2 months independently of the treatment schedule were reviewed centrally at a trial group meeting; reviewers were unaware of treatment allocations at this time. We calculated response rates without interval confirmation.

The primary endpoint was overall survival. Secondary endpoints were time to treatment failure, non-hospitalised survival, adverse events, and response rate in patients with target lesions. We measured overall survival from the date of randomisation to the date of death and censored at the date of last contact for a surviving patient. We calculated progression-free survival to the date disease progression was detected, or death, and censored at the date on which progression-free status was verified. We deemed time to treatment failure to be the date when the doctor decided to discontinue treatment for any reason, and we censored at the date of last contact. We calculated non-hospitalised survival by subtracting the sum of all days in hospital from overall survival.

Statistical analysis

We estimated 6-month and 1-year survival with a continuous infusion of fluorouracil as 50% and 30%. The initial sample size was 450 in total, which allowed detection of a 10% increase in overall survival for irinotecan plus cisplatin and a 5% margin of non-inferiority for S-1, with a study-wide one-sided α level of 0·05 and a power of 70% for each pair comparison. Non-inferiority with a 5% margin corresponds to a hazard ratio of 1·16. We adjusted for multiplicity due to two pair-comparisons with the Bonferroni method, with a one-sided α level of 0·025 for each comparison keeping a study-wide α error of 0·05. We planned an interim analysis when 300 patients had been accrued, using the O'Brien and Fleming type α spending function.

We calculated 1-year survival for all randomised patients when initial accrual was almost complete and it was much higher than anticipated. Therefore, in March, 2005, we recalculated the sample size along with an increase of power from 70% to 80%, and the final sample size was 690. To raise statistical efficiency, we amended the method for adjustment of multiplicity in February, 2007, to that of Holm.[18] According to Holm's method, the pair with the largest difference is compared at first with an α of 0·025 and, if significant, then the other is compared with an α of 0·05. If non-inferiority of S-1 is confirmed, superiority is tested with the same significance level. We planned these amendments in a masked way and they were approved by the data and safety monitoring committee before the primary analysis.

We did the primary analysis in March, 2007, of all randomised patients, based on data up to 1 year after the last patient was enrolled. We analysed overall survival with the stratified log-rank test, and we estimated every hazard ratio (HR) with stratified Cox's proportional-hazards model. We did these stratified analyses with the balancing factors used for randomisation, except for institution. For analyses of progression-free survival, time to treatment failure, and non-hospitalised survival, and for subgroup analyses, we used the log-rank test and estimated the hazard ratio with the Cox model, assuming a common baseline hazard without balancing factors. All subgroup analyses were exploratory and details were not prespecified in the protocol. We revised the protocol to undertake additional analyses of overall survival, progression-free survival, and non-hospitalised survival after 2 years of follow-up, in November, 2008.

	Fluorouracil (n=234)	Irinotecan plus cisplatin (n=236)	S-1 (n=234)
Age (years)	63·5 (57–69)	63 (59–68)	64 (58–69)
Sex (male)	176	180	175
ECOG performance status			
0	152	151	151
1	79*	81	80
2	3	4	3
Surgery			
Unresectable	189	190	188
Recurrent	45	46	46
Previous adjuvant chemotherapy	1	1	1
Macroscopic type†			
0	5	5	5
1, 2	63	73	68
3, 4, 5	164	155	161
Histological type‡			
Intestinal	111	102	110
Diffuse	121	134	124
Target lesions§	175	181	175
Metastatic sites			
0, 1	103	100	102
≥2	131	136	132
Peritoneal metastasis	87	76	69

Data are median (range) or number of patients, with the exception of age (median; IQR). *Includes one patient who underwent random allocation as ECOG performance status 1, but was later found to be 0. This patient was treated as performance status 1 in all analyses. †Japanese classification of gastric carcinoma; no data available for two patients assigned fluorouracil and three assigned irinotecan plus cisplatin. ‡Assessed with Lauren classification; no data available for two patients assigned fluorouracil and for one in the S-1 arm with adenosquamous-type cancer. §Assessed with the RECIST; target lesions larger than double the size of a CT slice.

Table 1: **Baseline characteristics**

We did all analyses by intention to treat using SAS version 9.1. Unless otherwise specified, we present one-sided p values for superiority. This study is registered with ClinicalTrials.gov, number NCT00142350, and UMIN-CTR, number C000000062.

For UMIN-CTR see http://www.umin.ac.jp/ctr

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Nov 13, 2000, and Jan 20, 2006, 704 patients underwent randomisation: 234 were allocated continuous infusion of fluorouracil, 236 irinotecan plus cisplatin, and 234 S-1 (figure 1). Baseline characteristics were well balanced between the three treatment groups (table 1). Nearly all individuals had an ECOG performance status of 0 or 1. Only one patient in every group had received previous adjuvant chemotherapy. About 75% (531/704) of participants had a target lesion or lesions.

Table 2 shows adverse events recorded within 6 months. For patients assigned continuous infusion of fluorouracil, grade 3 or 4 adverse events with frequencies greater than 10% were haemoglobin (<80 g/L) and anorexia. For individuals assigned irinotecan plus cisplatin, grade 3 or 4 leucopenia and neutropenia had the highest frequencies and were associated with febrile neutropenia and infection with neutropenia. Frequencies of grade 3 or 4 adverse events in patients assigned S-1 were similar to those seen with continuous infusion of fluorouracil, except for a higher rate of diarrhoea. Three treatment-related deaths were reported in the group assigned irinotecan plus cisplatin and one in the S-1 group.

	Fluorouracil (n=232)*	Irinotecan plus cisplatin (n=234)*	S-1 (n=234)
Leucocytes (<2·0×10⁹/L)	0	97 (41)	2 (1)
Neutrophils (<1·0×10⁹/L)	3 (1)†	152 (65)	13 (6)
Haemoglobin (<80 g/L)	36 (16)	92 (39)	30 (13)
Febrile neutropenia	0	22 (9)	0
Infection with neutropenia	0	18 (8)	1 (<1)
Infection without neutropenia	9 (4)	9 (4)	13 (6)
Aspartate aminotransferase (≤99 U/L)	11 (5)	6 (3)	11 (5)
Alanine aminotransferase (≤99 U/L)	8 (3)	6 (3)	8 (3)
Bilirubin (≤25·65 μmol/L)	7 (3)	3 (1)	10 (4)
Creatinine (≤132·6 μmol/L)	0	5 (2)	2 (1)
Hyponatraemia	15 (6)‡	53 (23)	12 (5)‡
Fatigue	4 (2)	24 (10)	12 (5)
Anorexia	29 (13)	77 (33)	29 (12)
Diarrhoea	1 (<1)	21 (9)	18 (8)
Nausea	16 (7)	48 (21)	13 (6)
Stomatitis	7 (3)	0	4 (2)
Hand-foot syndrome	0	0	3 (1)
Neuropathy—motor	0	1 (<1)	2 (1)
Neuropathy—sensory	0	1 (<1)	0
Treatment-related death§	0	3 (1)	1 (<1)

Data are number of patients (%). *Two patients were not treated in each group. †Data for one patient not available. ‡Data for two patients not available. §Judged by data and safety monitoring committee.

Table 2: Adverse events (grade 3 or higher) recorded within 6 months

At the time of the primary analysis (March, 2007), 601 (85%) events had been recorded (figure 1). Median overall survival in patients assigned continuous infusion of fluorouracil was 10·8 (IQR 5·7–17·8) months, in individuals allocated irinotecan plus cisplatin it was 12·3 (8·1–19·5) months, and in those assigned S-1 it was 11·4 (6·4–21·3) months. Irinotecan plus cisplatin was not superior to continuous infusion of fluorouracil (HR 0·85 [95% CI 0·70–1·04]; p=0·0552). Non-inferiority of S-1 to a continuous infusion of fluorouracil was confirmed (0·83 [0·68–1·01]; p=0·0005), but S-1 was not superior to fluorouracil (p=0·0336; one-sided α=0·025).

At the time of the additional analysis (November, 2008), the number of events had risen to 660 (94%; figure 1). Actual 2-year overall survival was 14% in patients assigned continuous infusion of fluorouracil, 18% in individuals allocated irinotecan plus cisplatin, and 21% in those assigned S-1 (figure 2). Irinotecan plus cisplatin was not superior to continuous infusion of fluorouracil (HR 0·82 [95% CI 0·68–0·99]; p=0·0194), whereas S-1 was non-inferior to fluorouracil (0·83 [0·68–1·00]; p=0·0002 for non-inferiority, p=0·0233 for superiority). All HR calculated by multivariate analyses with baseline factors were essentially the same as those measured by univariate analyses (data not shown).

The median time to treatment failure was 2·3 (IQR 1·4–5·4) months for patients assigned continuous infusion of fluorouracil, 3·7 (1·9–5·6) months for those allocated irinotecan plus cisplatin (HR 0·85 [95% CI 0·71–1·02]; p=0·0430), and 4·0 (2·0–6·3) months for individuals assigned S-1 (0·73 [0·61–0·88]; p=0·0004). More than 85% of patients who were allocated either continuous infusion of fluorouracil or S-1 discontinued treatment because of disease progression; a third of those allocated irinotecan plus cisplatin stopped because of toxic effects (figure 1). Median non-hospitalised survival was 7·2 (IQR 2·7–13·3) months for individuals assigned continuous infusion of fluorouracil, 9·5 (4·9–15·7) months for those allocated irinotecan plus cisplatin (0·81 [0·67–0·97]; p=0·0115), and 9·3 (4·2–18·0) months for those assigned S-1 (0·77 [0·63–0·92]; p=0·0025).

Second-line chemotherapy was given to 194 (83%) patients assigned continuous infusion of fluorouracil, 183 (78%) allocated irinotecan and cisplatin, and 173 (74%) assigned S-1 (data not available for 31 individuals). Of those assigned continuous infusion of fluorouracil, 70 crossed over to irinotecan plus cisplatin and 20 moved to S-1. Of those allocated irinotecan plus cisplatin,

127 moved to S-1 and seven to continuous infusion of fluorouracil. Finally, of those in the S-1 arm, two patients crossed over to continuous infusion of fluorouracil and 68 moved to irinotecan plus cisplatin.

Median progression-free survival was 2·9 (IQR 1·7–5·7) months for patients assigned continuous infusion of fluorouracil, 4·8 (2·3–8·2) months for those allocated irinotecan plus cisplatin (HR 0·69 [95% CI 0·58–0·83]; p<0·0001), and 4·2 (2·2–7·1) months for individuals assigned S-1 (0·77 [0·64–0·93]; p=0·0027; figure 2). In patients with a target lesion or lesions, response rates were 9% (15/175) for those assigned continuous infusion of fluorouracil, 38% (68/181) for those allocated irinotecan plus cisplatin, and 28% (49/174, data not available for one patient) for individuals assigned S-1. In this subgroup, median progression-free survival was 2·2 (1·4–5·3) months for patients assigned continuous infusion of fluorouracil, 4·8 (2·3–8·1) months for those allocated irinotecan plus cisplatin (0·56 [0·45–0·69]; p<0·0001) and 3·8 (2·0–5·6) months for those assigned S-1 (0·80 [0·65–0·98]; p=0·0174).

Findings of exploratory subgroup analyses of overall survival (figure 3) showed favourable results for S-1 compared with continuous infusion of fluorouracil for all subgroups except recurrent cases. In the subgroup with target lesions, median survival was 9·0 (IQR 5·4–15·2) months for patients assigned continuous infusion of fluorouracil (n=175), 12·1 (8·1–19·0) months for those allocated irinotecan plus cisplatin (n=181; HR 0·73 [0·59–0·91]; p=0·0022), and 10·5 (5·6–19·2) months for those assigned S-1 (n=175; 0·84 [0·68–1·05]; p=0·0590). In the subgroup without target lesions, median survival was 13·5 (7·9–23·4) months for patients assigned continuous infusion of fluorouracil (n=59), 14·4 (9·0–20·7) months for those allocated irinotecan plus cisplatin (n=55; 1·12 [0·76–1·65]; p=0·7219), and 18·1 (10·5–26·6) months for those assigned S-1 (n=59; 0·79 [0·53–1·16]; p=0·1101).

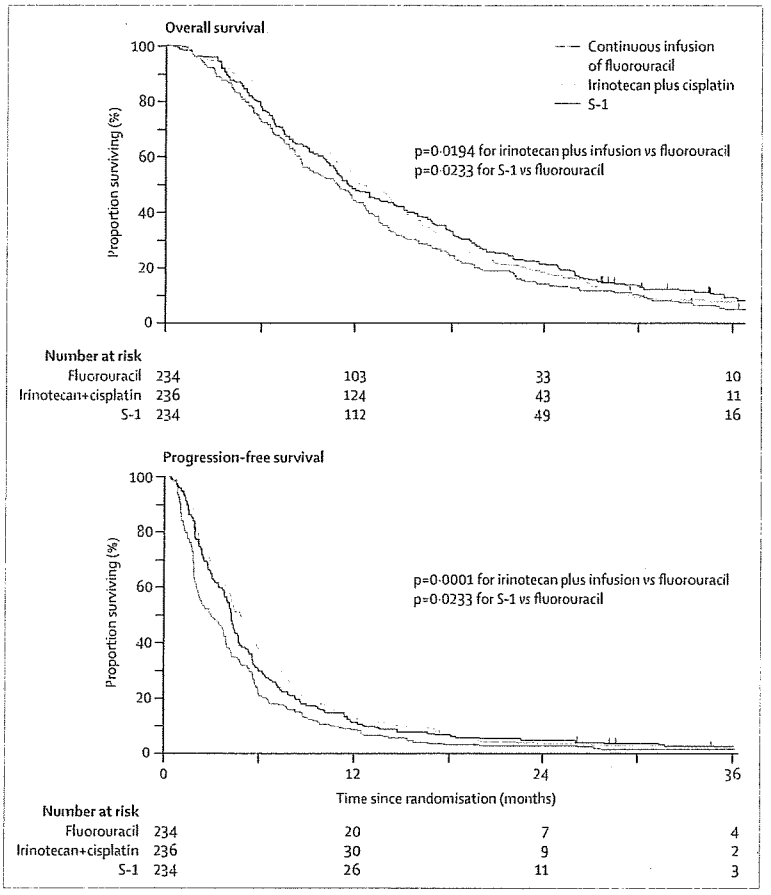

Figure 2: Survival curves of all randomised patients (November, 2008)

Discussion

Our findings show that S-1 is non-inferior to continuous infusion of fluorouracil with respect to overall survival. Although S-1 was not superior with respect to overall survival at the primary analysis, patients assigned S-1 had a 7% higher 2-year overall survival rate than those allocated a continuous infusion of fluorouracil. Furthermore, other measures of effectiveness of S-1, such as response rate and progression-free survival, were better than those obtained with continuous infusion of fluorouracil. These findings for S-1 are consistent with those reported in two phase 3 trials containing an S-1 alone arm.[19,20] Drug development for gastric cancer has been focused on replacement of intravenous fluorouracil with oral agents.[11,12] Taken together with our findings, S-1 might have some advantages over continuous infusion of fluorouracil.

Any new treatment, even if non-inferior to standard treatment, should have some benefits, such as for quality of life, cost, or safety. In our study, compared with continuous infusion of fluorouracil, S-1 was associated with almost equivalent safety and longer non-hospitalised survival. Additionally, in Japan, the cost of S-1 (about ¥76 000 per month [about US$834]) is cheaper than that of continuous infusion of fluorouracil (about ¥140 000 per month [US$1537]). In view of the effectiveness, safety, convenience, and cost, continuous infusion of fluorouracil could be replaced by S-1 for first-line chemotherapy of metastatic gastric cancer.

Findings of a meta-analysis of chemotherapy for advanced gastric cancer[21] indicated that survival was slightly better with combination chemotherapy than with a single agent. In the SPIRITS trial,[19] in which S-1 plus cisplatin was compared with S-1 alone for recurrent or unresectable gastric cancer, the combination showed a survival benefit over S-1 alone. In a previous study by us,[13] fluorouracil plus cisplatin could not prolong survival compared with a continuous infusion of fluorouracil, and our findings in this current study suggest that S-1 is non-inferior to continuous infusion of fluorouracil. Therefore, these data support the rationale for S-1 to be a control arm in the SPIRITS trial.[19] Several studies of

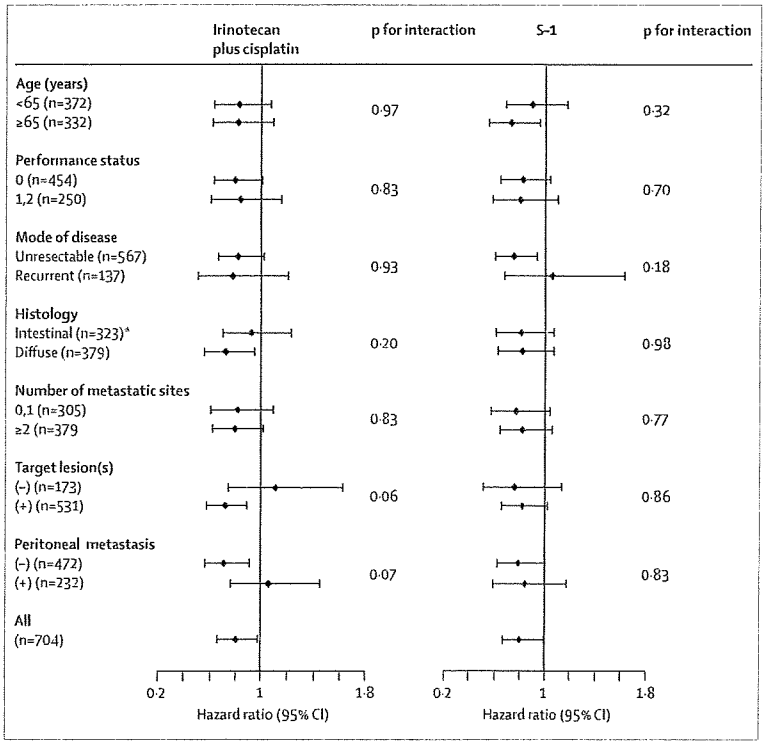

Figure 3: **Forest plot of subgroup analyses**
For every analysis, continuous infusion of fluorouracil is compared with irinotecan plus cisplatin (left) and S-1 (right). *Unknown types were excluded from the analysis.

combination chemotherapy based on S-1 plus cisplatin, including molecular target agents, are ongoing.

Toxic effects of S-1 have been reported to be more severe in individuals from the USA than in Asian patients, resulting in different recommended doses in these populations.[24,25] Since similar discrepancies in toxic effects have been noted with tegafur and uracil,[26] ethnic variations would seem to be a factor with these dihydropyrimidine dehydrogenase inhibitory fluoropyrimidines. In a trial from China,[27] S-1 plus cisplatin was superior to continuous infusion of fluorouracil plus cisplatin. Outside Asia,[28] despite differences in dose and schedule of S-1 from Asian trials, S-1 plus cisplatin was associated with fewer toxic effects, had slightly better survival, and showed non-inferiority compared with fluorouracil plus cisplatin. S-1 plus cisplatin, with an equitoxic dose to fluorouracil plus cisplatin, should be investigated in European and North American populations.

The toxic effects of irinotecan plus cisplatin were the most severe of the three treatment groups in our study, and the rate of treatment failure due to toxic effects was the highest, resulting in a shorter time to treatment failure than that obtained with S-1. In the subgroup with target lesions, of the three treatment groups, irinotecan plus cisplatin showed the best response rate, progression-free survival, survival within 1 year, and overall survival. In North America, divided doses of irinotecan and cisplatin have been investigated,[29] which are associated with a similar response rate to, and fewer toxic effects than, the regimen in our study. Since control of toxic effects of irinotecan plus cisplatin is a big problem, divided doses of irinotecan and cisplatin should be investigated in future phase 3 trials.

Some chemosensitivity-related markers have been suggested to be prognostic factors for irinotecan plus cisplatin treatment.[30] Expression of specific chemosensitivity-related genes is currently being investigated in patients enrolled in our study, and preliminary data suggest that dihydropyrimidine dehydrogenase expression could be a predictive marker for whether irinotecan plus cisplatin or S-1 (plus cisplatin) would be the better treatment in a given patient.[31] We postulate that some populations would benefit from irinotecan plus cisplatin even though chemotherapy regimens containing irinotecan have not shown a survival benefit in phase 3 trials.[20,17] Because clinical behaviour and pathogenesis of gastric cancer are heterogeneous, treatment strategies tailored for optimum chemotherapy according to a patient's clinical and genetic background should be established in the near future, and irinotecan plus cisplatin could then serve as one of the options.

Although median progression-free survival of S-1 and irinotecan plus cisplatin in our study were similar to those reported in other phase 3 trials, median overall survival was somewhat extended.[21,22,32–34] Moreover, median progression-free survival—both in this study and in our previous phase 3 trial[13]—was 2 months for patients who received continuous infusion of fluorouracil. Overall survival of patients with target lesions in this current study was about 2 months longer than that reported by us previously. The proportion of patients who received second-line chemotherapy in our study was more than 70%, which is higher than in our previous study (53%).[13] Since irinotecan and taxanes were approved in the late 1990s in Japan, available active agents for subsequent chemotherapy differed between this current study and our previous study. We postulate that second-line chemotherapy might have contributed to the favourable overall survival in this study, although a survival benefit of second-line chemotherapy has not yet been clarified.

Contributors
NB, HF, and SY wrote the protocol and designed the trial based on discussion with, and agreement from, all authors. All authors (except SY and HF) recruited patients to the study. HF directed the data centre. SY and HF did the statistical analysis. NB wrote the report with revisions from all other authors.

Conflicts of interest
The authors declared no conflicts of interest.

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Short Communication

Activity of S-1 in Advanced or Recurrent Gastric Cancer Patients after Failure of Prior Chemotherapy, Including Irinotecan + Cisplatin or Fluorouracil (Except S-1)

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We retrospectively reviewed to investigate the efficacy and toxicity of monotherapy with S-1 in patients with advanced or recurrent gastric cancer after failure of first-line chemotherapy. Twenty-one patients were evaluated. The median number of treatment cycles was 2 (range 1–19). There were no cases showing either complete or partial response, and 10 patients (47.6%) showed stable disease. The median progression-free survival was 89 days. Sixteen patients (76%) received third-line chemotherapy. The median survival time was 271 days after the initiation of S-1, with a 1-year survival rate of 32%. Hematological toxicities were Grade 4 anemia (9.5%), Grade 3 or 4 neutropenia (9.5%) and leukopenia (4.7%). As for non-hematological toxicities, Grade 3 or 4 diarrhea and anorexia were noted in 9.5% and 14.2% of the patients, respectively. S-1 was found to show no efficacy and cannot be recommended for second-line chemotherapy against gastric cancer.

Key words: S-1 – gastric cancer – second-line

INTRODUCTION

In Japan, several randomized trials have been performed during the last decade. The Japan Clinical Oncology Group (JCOG) conducted a Phase III trial to compare continuous infusion of 5-fluorouracil (5-FUci), 5-FU + cisplatin (CDDP) (FP) and uracil and tegafur (UFT) + mitomycin (UFTM) in patients with advanced gastric cancer (1). Combined chemotherapy with either FP or UFTM yielded no survival benefit when compared with that obtained with 5-Fuci; furthermore, 5-FUci was associated with significantly lesser toxicity. Thus, 5-FUci was adopted as the control arm for the subsequent Phase III trials.

The endpoint in many clinical studies is the overall survival, even in those evaluating the effects of first-line treatment. On the other hand, with the emergence of many potent antitumor agents, some of them have been used in the second-line setting, after failure of first-line chemotherapy, with disease progression. In a Phase III trial (JCOG9912) comparing S-1 monotherapy and combination chemotherapy with irinotecan (CPT-11) + CDDP to 5-FUci, the activity of S-1 was confirmed in the first-line setting in patients with unresectable advanced gastric cancer. In this study, while the median time-to-treatment failure of 5-FUci, CPT-11 + CDDP and S-1 monotherapy was not so long (2.3, 3.7 and 4.0 months, respectively), the median survival times (MSTs) were 10.8, 12.3 and 11.4 months, respectively. These differences between the time-to-treatment failure and overall survival seemed to be larger than those reported from other recent Phase III trials (2). Moreover, the overall survival times in patients treated with 5-FUci in the JCOG9912 trial was remarkably longer than that in those treated in the JCOG9205 trial. After the completion of the JCOG9205 trial, not a few number of active agents, such as S-1, CPT-11 and taxanes, have been approved and used in clinical practice in Japan. The results of use of these agents suggest that second-line chemotherapy with these newly

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approved agents may improve the survival after failure of first-line chemotherapy in advanced gastric cancer patients.

Several Phase II trials and some retrospective analyses of second-line chemotherapy for gastric cancer have been conducted (3–7). However, there have been no reports of evaluation of the efficacy/tolerability of S-1 monotherapy in the second-line setting for advanced gastric cancer. We retrospectively reviewed to evaluate the activity of S-1 in advanced or recurrent gastric cancer patients with a previous history of chemotherapy, including with CPT-11 + CDDP or regimens containing a fluoropyrimidine other than S-1.

PATIENTS AND METHODS

Subjects

A total of 25 patients with advanced or recurrent gastric cancer were treated with S-1 in the second-line setting at our institution between September 2002 and October 2006. Twenty-one of the 25 patients had a history of failure of first-line chemotherapy with CPT-11 + CDDP or regimens containing a fluoropyrimidine other than S-1. The reasons for the failure of the first-line chemotherapy included disease progression in 17 patients, unacceptable toxicities in 3 patients and refusal to continue treatment in 1 patient. The subjects of this study were these 21 patients who satisfied the following criteria: (i) histologically confirmed adenocarcinoma of the stomach; (ii) 75 years or lower in age; (iii) performance status of 0 or 1 on the ECOG PS; (iv) adequate bone marrow, hepatic and renal functions; and (iv) absence of other serious medical conditions. Two of the four patients excluded had previously been treated with S-1-containing regimens and the remaining two were >75 years old.

Treatment

The treatment schedule comprised oral administration of S-1 twice daily at 40 mg/m^2/day for 28 consecutive days, followed by a 14-day rest. The treatment cycles were repeated until disease progression or the appearance of unacceptable toxicities. The actual doses of S-1 according to the body surface area (BSA) were: BSA < 1.25 m^2, 80 mg/body/day; 1.25 m^2 $\leq$ BSA < 1.5 m^2, 100 mg/body/day; and 1.5 m^2 $\leq$ BSA, 120 mg/body/day. The dose of S-1 was reduced by one level in the event of development of Grade 4 hematological toxicities, febrile neutropenia, Grade 2 liver or renal dysfunction, or of other complicated medical conditions judged as necessitating dose reduction by the attending physician.

Evaluation

Laboratory parameters and symptoms were checked at least every 2 weeks, and adverse events were graded according to the CTCAE ver. 3.0. Tumor responses were evaluated by computed tomography, and endoscopic examination was also conducted where judged necessary. Objective tumor responses were assessed as complete response, partial response, stable disease or progressive disease, according to RECIST guideline.

Statistical Analysis

Overall survival was calculated from the date of initiation of S-1 monotherapy to the date of death. Progression-free survival (PFS) was counted to the earlier date of disease progression or of deciding treatment discontinuation for any reason. Survival curves were estimated by the Kaplan–Meier method.

RESULTS

Patient's Characteristics

Most were male (90%), and the median age was 62 years. Thirteen (62%) and eight (38%) patients showed an ECOG PS 0 and 1, respectively. The number of metastatic sites, including liver, lymph nodes, peritoneum and other sites, was 1 in 11 patients and 2 in the remaining 10 patients. The histological type of the cancer was the intestinal type in 10 patients and the diffuse type in the remaining 11 patients. All the patients had at least one target lesion. In regard to the first-line therapy used, 17 (81%) patients had received chemotherapy with CPT-11 + CDDP and 4 (19%) patients had been treated with a 5-FU-containing regimen. There were no complete and six partial responses to chemotherapy with CPT-11 + CDDP, and one partial response to treatment with a 5-FU-containing regimen (Table 1).

Treatment

The median number of cycles administered was 2 (range 1–5), and dose reduction was required in two patients due to the appearance of Grade 4 hematological toxicity. Monotherapy with S-1 was discontinued due to progressive disease in 18 patients (85%) and due to the appearance of adverse events in 3 patients, including Grade 3 dermatitis in 1, bleeding from the primary lesion in 1 and diarrhea in 1 patient. Third-line chemotherapy was administered with paclitaxel in 13 patients (61.9%), docetaxel in 1 patient (4.7%), CPT-11 + CDDP in 1 patient and hepatoarterial infusion of 5-FU in 1 patient (Table 1).

Efficacy

Of the 21 patients, there were no cases showing complete or partial response, and 10 patients (47%) showed stable disease (Table 1). The median PFS was 91 days, and the MST was 275 days after the initiation of S-1 administration, with a 1-year survival rate of 32% (Fig. 1).

Toxicities

In regard to hematological toxicities, Grade 4 anemia was observed in two patients (9.5%); there were no cases of

Table 1. Patient's characteristics, tumor response and treatment

	Number
Patients	21
Sex: male/female	19/2
Median age (range)	62 (34–75)
ECOG PS: 0/1/2	13/8/0
Metastatic lesion[a]: liver/LN/peritoneum/other	10/11/5/2
No. of metastatic sites: 1/2/3	11/10/0
Histological type: por/tub/pap/sig/muc	7/8/2/3/1
Target lesion: yes/no (the time of administration of S-1)	21/0
Primary lesion: yes/no	11/10
Prior regimen: IP/FU	17/4
Tumor response: PR/SD/PD/NE	0/10/7/4
Median delivery (range)	2 (1–5)
Dose reduction (rate)	2 (9.5%)
Treatment off	21 (100%)
Progressive disease/toxicity	18/3
Post-chemotherapy	16 (76%)
Paclitaxel/docetaxel/IP/HAI	13/1/1/1

ECOG, Eastern Cooperative Oncology Group; PS, performance status; LN, lymph node; por, poorly differentiated adenocarcinoma; tub, tubular adenocarcinoma; pap, papillary; sig, signet-ring cell carcinoma; muc, mucinous adenocarcinoma; IP, cisplatin + irinotecan; FU, fluorouracil (except S-1); PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; HAI, hepatoarterial infusion.
[a]Some patients had metastases at multiple site.

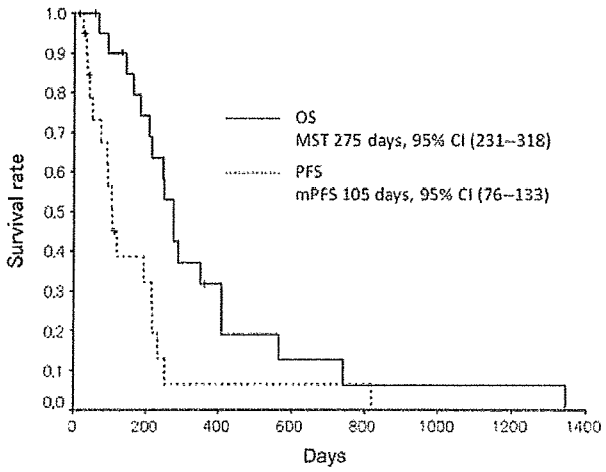

Figure 1. Progression-free survival (PFS) and overall survival (OS) time. Median PFS (mPFS) was 105 days and median survival time (MST) was 275 days. CI, confidence interval.

Grade 4 neutropenia or leukopenia, or of febrile neutropenia. As for non-hematological toxicities, Grade 3 or 4 anorexia was observed in three patients (14.2%), diarrhea in two patients (9.5%) and nausea, vomiting, rush hot flush and fatigue in one patient each. There were no early deaths within 30 days of the last administration of S-1 and no treatment-related deaths.

DISCUSSION

S-1 is a newly developed oral fluoropyrimidine, composed of a mixture of tegafur, 5-chloro-2,4-dehydroxypyridine and potassium oxonate in a molar ratio of 1:0.4:1 (8). The results of a few Phase II trials of monotherapy with S-1 in the first-line setting among Japanese patients with advanced gastric cancer have been encouraging. They reported a response rate (RR) of 44% and 49%, respectively, at the recommended doses, and an MST of 207 and 250 days, respectively. Thus, treatment with S-1 was concluded to be very feasible and convenient in both trials (9,10).

In regard to second-line chemotherapy for gastric cancer, the guideline for the treatment of gastric cancer in Japan (11) does not recommend any particular chemotherapeutic regimen, because none has been demonstrated to yield survival benefit. In practice, there are four active agents, fluoropyrimidine, cisplatin, irinotecan and taxanes, that are available for the treatment of gastric cancer in Japan, and many gastric cancer patients receive second-line chemotherapy with some of these drugs. There have been many reports of second-line chemotherapy after failure of S-1 therapy. Ueda et al. (6) reported a retrospective study, in which 32 patients treated with CPT-11 (70 mg/m^2) + CDDP (80 mg/m^2) repeated every 4 weeks showed an RR of 25%, PFS of 3.4 months and MST of 9.4 months. Hironaka (3) reported that weekly paclitaxel (80 mg/m^2, repeated weekly three times for 4 weeks) yielded an RR of 23%, PFS of 2.1 months and MST of 5 months in 38 patients who were treated with fluorouracil agents, including S-1, CDDP + fluoropyrimidine, or 5-FU + methotrexate. Giuliani et al. (7) reported a Phase II study of CPT-11 + mitomycin C (MMC) administered every 4 weeks in patients who had received CDDP, taxane- or fluoropyrimidine/anthracycline-based regimens, which yielded an RR of 32%, PFS of 4 months and MST of 8 months. It is believed that second-line chemotherapy with irinotecan or taxanes can yield tumor shrinkage in some patients.

In this study, 81% of the subjects had been treated with CPT-11 + CDDP in the first-line setting. S-1 did not show any efficacy in the second-line setting. This result indicates that S-1 does not cause tumor shrinkage. It has been reported that S-1 yielded no efficacy in the third-line setting for colorectal cancer either. It is considered that the ability of S-1 to produce tumor shrinkage in the second-line setting might not be as strong as that of other antitumor agents, such as CPT-11 or taxanes. The disease control rate, which was defined as the rate of partial response plus the rate of stable disease, was 47.6% and PFS was 91 days in this study. This means that more than half of the patients receiving second-line chemotherapy showed progressive disease at the first evaluation.

The MST in this study seemed to be longer than that reported from other trials (3,7). The MST is influenced by the patients' medical condition, such as the performance status and tumor burden, especially in the second-line setting. The subjects of this study could take S-1 orally and more than half of them could also receive third-line

chemotherapy, which means that the medical condition of the subjects in this analysis was relatively good. It is considered that the good survival time in this study may have been related to the patient selection.

In this study, Grade 3 or 4 anemia was observed in 38%, neutropenia in 10%, thrombocytopenia in 10%, diarrhea in 10%, nausea in 5% and vomiting in 5% of the patients. There were no unexpected or life-threatening toxicities. The incidences of Grade 3 or 4 leukopenia and neutropenia have been reported to be 75% and 81%, respectively, for CPT-11 + CDDP, 8% and 21%, respectively, for CPT-11 + MMC and 29% and 32%, respectively, for weekly paclitaxel. Although S-1 seemed to be less toxic when compared with other agents in the second-line setting, it produced substantial toxicity in the absence of tumor shrinkage

In conclusion, monotherapy with S-1 cannot be recommended for the treatment of unresectable or recurrent gastric cancer in the second-line setting.

Conflict of interest statement

None declared.

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Retrospective Analysis of S-1 Monotherapy in Patients with Metastatic Colorectal Cancer After Failure to Fluoropyrimidine and Irinotecan or to Fluoropyrimidine, Irinotecan and Oxaliplatin

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Objective: Chemotherapy with irinotecan (CPT-11) or oxaliplatin (l-OHP) in combination with infusional 5-fluorouracil (5-FU) and their cross-over as second-line therapies are standard treatments for metastatic colorectal cancer (MCRC). Molecular target agents, which are used as third-line therapies in Western countries after failure of these three drugs, have not been available in Japan. Monotherapy with S-1 [Tegafur, Oteracil potassium and 5-chloro-2,4-dihydroxypyrimidine (CDHP)] showed activity against colorectal cancer with a response rate of 35% as a first-line therapy. It is not clear whether inhibition of dihydropyrimidine dehydrogenase by CDHP can modulate the activity of 5-FU even after patients initially fail with 5-FU. This retrospective study evaluated the efficacy and safety of monotherapy with S-1 for MCRC after the failure of standard chemotherapy.
Methods: The subjects of this study comprised two cohorts; the first was 27 patients with MCRC who had failed with 5-FU and CPT-11 before approval of l-OHP in Japan (cohort 1), and the second was 23 patients who had failed with 5-FU, CPT-11 and l-OHP (cohort 2). S-1 was given orally twice daily (80 mg m^2/day) for 28 days followed by a 14-day rest.
Results: In cohorts 1 and 2, the response rates were 7% and 0%, and the median progression-free survivals were 2.8 and 2.7 months, and overall survivals after initiation of S-1 were 10.5 and 4.7 months, respectively. The common grade 3 and 4 adverse events in cohorts 1 and 2 were diarrhea 15% and 13%, anorexia 11% and 17% and anemia 26% and 30%, respectively.
Conclusions: S-1 monotherapy did not show promising activity against MCRC after the failures with 5-FU, CPT-11 and l-OHP.

INTRODUCTION

In Japan, colorectal cancer is the fourth most common malignancy and its incidence has been rising in recent years. Approximately 30–40% of patients with colorectal cancer have metastatic disease at the time of diagnosis. For patients with metastatic colorectal cancer (MCRC), treatment is generally palliative and mainly consists of systemic chemotherapy. Although palliative chemotherapy can relieve symptoms and prolong survival, the long-term prognosis remains poor (1,2).

In 2004, the results of a randomized trial (V308) comparing oxaliplatin (FOLFOX6) and irinotecan (FOLFIRI) in combination with short-term infusional 5-fluorouracil (5-FU) and leucovorin in 226 previously untreated patients were reported (3). Cross-over between FOLFOX6 and FOLFIRI was allowed as a second line of treatment after failure of the first drug due to progression or toxicities. The V308 trial demonstrated similar efficacies in response rates, progression-free survival (PFS) and median overall survival for FOLFOX6 and FOLFIRI. Therefore, either FOLFOX or FOLFIRI as the first-line therapy and subsequent cross-over to the other regime as the second-line therapy has been recognized as the standard treatment for MCRC all over the world. At present, the number of patients with MCRC who have failed to respond to 5-FU, irinotecan and oxaliplatin has been increasing remarkably. However, little is known about third-line treatments after the failure of these three drugs.

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In Japan, neither infusional 5-FU regimens nor oxaliplatin was approved for MCRC until early 2005, so the regimen of irinotecan plus a bolus injection of 5-FU/LV (IFL) was the recognized standard treatment for MCRC instead of FOLFOX or FOLFIRI. Before early 2005, when oxaliplatin was approved in Japan, oxaliplatin had not been available for the subsequent treatment of patients after the failure with both 5-FU and irinotecan.

S-1 is an oral fluorinated pyrimidine developed by Taiho Pharmaceutical Co. Ltd (Tokyo, Japan). The agent contains tegafur (a masked 5-FU compound), 5-chloro-2, 4-dihydroxypyrimidine (CDHP) and potassium oxonate in a molar ratio of 1:0.4:1, the last two components being biochemical modulators (4). S-1 showed promising activity against colorectal cancer in phase II studies (5,6), resulting in response rates of 35% and median overall survival of 12 months. These results suggest that S-1 may be more active than UFT (7) and 5-FU alone, and it is speculated that this difference may be brought about by inhibition of dihydropyrimidine dehydrogenase by CDHP. S-1 showed a response rate of 12% for advanced gastric cancer after failure of various first-line chemotherapies, including 5-FU (8).

For these reasons, before the approval of oxaliplatin, monotherapy with S-1 was one of the treatment options in clinical practice for patients with colorectal cancer who had failed with 5-FU and irinotecan. S-1 was also used in patients who had not responded to a combination of 5-FU, irinotecan and oxaliplatin after approval of oxaliplatin. Recently, it was reported that a phase II study of monotherapy with S-1 for colorectal cancer after the failure to respond to chemotherapy regimens containing 5-FU, irinotecan and oxaliplatin demonstrated a response rate of 14.3%, and a median time to progression of 91 days (9). However, its efficacy and safety profile, especially in clinical practice, remain controversial because of the small number of patients and the selection bias inherent in this phase II study.

In this retrospective study, the efficacy and safety of monotherapy with S-1 for MCRC after failure with both 5-FU and irinotecan, or failure of 5-FU, irinotecan and oxaliplatin, was assessed.

PATIENTS AND METHODS

Patients

In total, 57 patients with MCRC at the Shizuoka Cancer Center Hospital were treated by monotherapy with S-1 between December 2003 and October 2006, comprising 29 patients after the failure of both 5-FU and irinotecan and 28 patients after failing to respond to the three drugs, 5-FU, irinotecan and oxaliplatin. The subjects of this study were selected from these 57 patients according to the following criteria: (i) age 75 years or younger, (ii) Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2, (iii) unresectable or recurrent colorectal cancer, (iv) histologically confirmed tubular adenocarcinoma, (v) the clinical course from initiation of S-1 was fully monitored in our hospital, (vi) absence of any other active malignant disease, and (vii) the absence of any central nervous system involvement.

From 29 patients in cohort 1, two patients were excluded because of the coexistence of hepatocellular carcinoma in one patient and incomplete information on the clinical course till progression in the other. From the 28 patients in cohort 2, five patients were excluded because of ages exceeding 75 years in three patients, central nervous system involvement in one and the coexistences of pancreas cancer in one. Thus, 27 patients (cohort 1) and 23 patients (cohort 2) were the subjects of this retrospective analysis.

Treatment Schedule

S-1 was orally administered twice daily after a meal at the following doses on the basis of body surface area: $<1.25\ m^2$, 40 mg; $<1.50\ m^2$, 50 mg; and $>1.50\ m^2$, 60 mg, for 28 days followed by a 2-week rest. This schedule was repeated every 6 weeks until disease progression, unacceptable toxicities or patient's refusal.

Evaluation of Antitumor Effects and Adverse Events

All clinical data were obtained from the medical records retrospectively. Pretreatment evaluations included medical history, physical examination, laboratory tests and computed tomography (CT). Laboratory tests and toxicity were assessed at least biweekly during treatment cycle. The tumor was assessed every two cycles or when there were clinical signs suggesting tumor progression. Response was evaluated by CT or MRI according to the Response Evaluation Criteria in Solid Tumors (RECIST). Adverse events were evaluated according to the National Cancer Institute Common Toxicity Criteria (NCICTC version 2.0).

Statistical Analysis

PFS was calculated from the date of the first administration of S-1 to the earliest date when the treatment was discontinued for any reason including tumor progression or when the patient died from any cause. The overall survival time was calculated from the date of the first administration of S-1 to the date of death from any cause, or to the last date of confirmed survival. Survivals were analyzed by the Kaplan–Meier method.

RESULTS

Patient Characteristics

Patient characteristics for the 27 patients in cohort 1 and the 23 patients in cohort 2 are summarized in Table 1. Good performance status 1 or 0 was preserved in >90% of the patients in both cohorts. Major organs involved were liver, lung and lymph nodes in both cohorts, and the median numbers of organs involved were 2 (1–3) in cohort 1 and 1 (1–4) in cohort 2. The prior therapy is summarized in

Table 1. Baseline characteristics

	Cohort 1		Cohort 2	
	No. of patients	%	No. of patients	%
No. of patients	27		23	
Baseline characteristics				
Age, years, median (range)	57 (35–71)		57 (40–74)	
Sex, female	11	41	12	52
Performance status				
0	16	59	9	39
1	10	37	12	52
2	1	4	2	9
Primary disease site				
Colon/rectum	2	7	—	—
Colon	13	48	17	74
Rectum	12	45	6	26
Primary disease resection	22	81	20	87
Pathologic histology				
Well	7	26	9	39
Moderate	12	44	8	35
Others (por, muc)	1	4	1	4
Data missing	7	26	5	22
Organs involved[a]				
Any lung involvement	15	56	12	52
Any liver involvement	14	52	8	35
Any lymph node involvement	11	41	7	30

[a]No. of patients were overlapped.

Table 2. Priory therapy

	Cohort 1		Cohort 2	
	No. of patients	%	No. of patients	%
No. of priory regimens				
1	9	33	—	—
2	8	30	6	26
3	8	30	9	39
≥4	2	7	8	35
Priory therapy[a]				
IFL	14	52	10	43
CPT-11 (±MMC)	13	48	7	30
UFT (±LV)	7	26	2	9
5-FU+ LV	7	26	9	39
5-Fuci	6	22	0	0
New drugs	3	11	5	22
5-FUai (WHF)	3	11	5	22
FOLFIRI	1	4	7	30
FOLFOX	—	—	17	74
FLOX	—	—	7	30
Type of previous 5-FU regimen				
Infusion	3	11	0	0
Bolus	21	78	6	26
Bolus and infusion	3	11	17	74

IFL, irinotecan plus a bolus injection of 5-fluorouracil/leucovorin; CPT-11, irinotecan; MMC, mitomycin C; UFT, uracil and tegafur; LV, leucovorin; 5-FU, 5-fluorouracil; WHF, weekly high-dose 5-fluorouracil (weekly hepatic arterial infusion therapy)
[a]No. of patients were overlapped.

Table 2. In cohort 1, more than half of the patients had received the IFL regimen and 5-FU had been administered in a bolus injection in 21 patients (78%). Prior therapies in cohort 2 were mainly FOLFOX; 17 patients (74%) had received this treatment regimen, which contained both bolus and infusional injection of 5-FU.

Adverse Events and Feasibility

The grade 3 and 4 toxicities in both cohorts are summarized in Table 3. The most frequent grade 3 or 4 non-hematological toxicities were diarrhea (15% and 13% in cohort 1 and 2, respectively) and anorexia (11% and 17% in cohort 1 and 2, respectively). Grade 3 or 4 nausea was more frequent in cohort 2 (22%) than in cohort 1 (7%). As for hematological toxicities, grade 3 or 4 anemia (hemoglobin) was observed in 26% (cohort 1) and 30% (cohort 2). S-1 treatment discontinuation due to toxicity occurred in one patient in cohort 1 and in four patients in cohort 2 during the first treatment course. The reason for discontinuation in cohort 1 was diarrhea, whereas in cohort 2, the reasons were nausea in three patients and anemia in one. In neither cohort, was there early death within 60 days of the initiation of S-1 treatment or treatment-related death.

Response

The responses to monotherapy with S-1 are summarized in Table 4. Partial response was obtained in two patients (7%) in cohort 1, but there was no partial response in cohort 2. Stable disease was observed in 14 patients (52%) in cohort 1 and in 4 (17%) of cohort 2. The prior chemotherapy in the two patients with a partial response was based on the bolus injection of 5-FU. When categorized according to the type of 5-FU administration in the prior chemotherapy, 13 of 21 patients (62%) in cohort 1 who had received only a bolus injection of 5-FU and 3 of 6 patients (50%) who received infusional 5-FU showed partial response or stable disease. In cohort 2, 1 of 6 patients (17%) receiving a bolus injection of 5-FU and 3 of 17 patients (18%) receiving infusional 5-FU showed stable disease.

Subsequent Therapy

The subsequent therapies in each cohort were summarized in Table 5. In cohort 1, 16 of 27 patients (60%) received

Table 3. Grade 3/4 toxicities

	Cohort 1						Cohort 1					
	Grade 3		Grade 4		Grade ≥3		Grade 3		Grade 4		Grade ≥3	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Nausea	2	7	—	—	2	7	5	22	—	—	5	22
Vomiting	1	4	—	—	1	4	1	4	0	0	1	4
Diarrhea	4	15	0	0	4	15	3	13	0	0	3	13
Mucositis	0	0	0	0	0	0	1	4	0	0	1	4
Anorexia	3	11	0	0	3	11	4	17	0	0	4	17
Hand-foot skin reaction	0	0	0	0	0	0	0	0	0	0	0	0
Febrile neutropenia	0	0	1	4	1	4	0	0	0	0	0	0
Leukocytopenia	0	0	1	4	1	4	1	4	0	0	1	4
Neutropenia	0	0	1	4	1	4	1	4	0	0	1	4
Hemoglobin	4	15	3	11	7	26	5	22	2	9	7	30
Thrombocytopenia	1	4	0	0	1	4	0	0	0	0	0	0

Table 4. Response, survival and disease progression

	Cohort 1		Cohort 2	
	No. of patients	%	No. of patients	%
Complete response (CR)	0	0	0	0
Partial response (PR)	2	7	0	0
CR + PR	2	7	0	0
Stable disease	14	52	4	17
Progressive disease	10	37	15	65
Not evaluable	1	—	4	—
Time to disease progression: median, months	2.8 (0.4–9.7)		2.7 (0.4–12.6)	
Overall survival: median, months	10.5 (1.7–25.3)		4.7 (1.0–28.9)	
Follow-up duration: median, months	—		6.5 (1.1–10.5+)	

subsequent therapy, which mainly comprised FOLFIRI and FOLFOX after infusional 5-FU combined with leucovorin and oxaliplatin was approved in Japan. In cohort 2, only 3 of 23 patients (13%) received any chemotherapy after failure to respond to S-1.

Survival

At the time of analysis, all 27 patients in cohort 1 had died but 7 patients in cohort 2 were alive at our last contact, with a median follow-up time of 6.5 months (range: 1.1–10.5+). The PFS curves are shown in Fig. 1 with events confirmed in all patients. The median progression-free times were 2.8 months (range: 0.4–9.7) in cohort 1 and 2.7 months (range: 0.4–12.6) in cohort 2. Overall survival curves are shown in Fig. 2, and the median survival times were 10.5 months (range: 1.7–25.3) in cohort 1 and 4.7 months (range: 1.0–28.9) in cohort 2. One-year survival rates in cohorts 1 and 2 were 44% and 9%, respectively.

DISCUSSION

After oxaliplatin (l-OHP) appeared, two large trials of the patients pre-treated with 5-FU and irinotecan in the USA were reported by Rothenberg et al. (10) and by Kemeny et al. (11). Rothenberg's trial was a phase III trial comparing three arms of FOLFOX4, l-OHP alone, infusional 5-FU and leucovorin (LV5FU2) in patients with colorectal cancer refractory to IFL therapy. Kemeny's trial was a randomized phase II trial with LV5FU2 or FOLFOX4 and cross-over LV5FU2 to FOLFOX4 after failure to respond to 5-FU and irinotecan. The response rates, time to progression and

overall survival of LV5FU2 were 0%, 2.7 and 8.7 months in the first group, and 2%, 2.4 and 11.4 months in the second group, whereas those of the patients in cohort 1 in the present study were 7%, 2.8 and 10.5 months. As for adverse events, the incidence of grade 3 or 4 diarrhea in monotherapy with S-1 was 15%, which was higher than that for LV5FU2 (3–6%), and the incidence of grade 3 or 4 neutropenia in monotherapy with S-1 was 4%, lower than that for LV5FU2 (5–13%). Overall, it was considered that the clinical outcomes of monotherapy with S-1 may be similar to those of LV5FU2 and, before approval of oxaliplatin in Japan, S-1 was an option after failure to respond to 5-FU and irinotecan.

However, the FOLFOX4 therapy in these two trials showed response rates of 10–13% and time to progression of 4.6–4.8 months, and these results were significantly better than those for LV5FU2. Monotherapy with S-1 seems to be inferior to FOLFOX4 in the second-line setting after 5-FU and irinotecan. Since oxaliplatin is a very potent drug and FOLFOX therapy is now available in Japan, FOLFOX therapy is now recommended instead of S-1 for MCRC after failure with irinotecan and 5-FU.

A phase II study of monotherapy with S-1 for MCRC after failure of chemotherapy regimens containing 5-FU, irinotecan and oxaliplatin demonstrated a response rate of 14.3%, and a median time to progression of 91 days. However, the response rate and PFS after monotherapy with S-1 were 0% and 2.7 months in our cohort 2. The incidence of grade 3 or 4 anemia was 29% associated with total grade 3 or 4 toxicities of 43%. The common S-1 monotherapy treatment schedule in Japan is 40 mg/m^2 administered twice daily for 28 days followed by a 2-week rest. But, in this phase II study, the treatment schedule was 35 mg/m^2 administered twice daily for 14 days followed by a week's rest. Our patients in 74% patients of cohort 2 were pretreated with the above three regimens (25% patients of this phase II study). Capecitabine, which is another oral fluoropyrimidine with

Table 5. Subsequent therapies

	Cohort 1 ($n = 27$)		Cohort 2 ($n = 23$)	
	No. of patients	%	No. of patients	%
No. of after regimens				
0 (best supportive care)	11	40	20	87
1	8	30	2	9
2	7	26	1	4
3	1	4	—	—
Regimens after S-1[a]				
FOLFOX	11	40	—	—
FOLFIRI	7	26	—	—
5-Fu/LV	5	19	1	4
UFT (±LV)	2	7	—	—
5-FUai (WHF)	1	4	1	4
MMC	—	—	2	9

[a]No. of patients were overlapped.

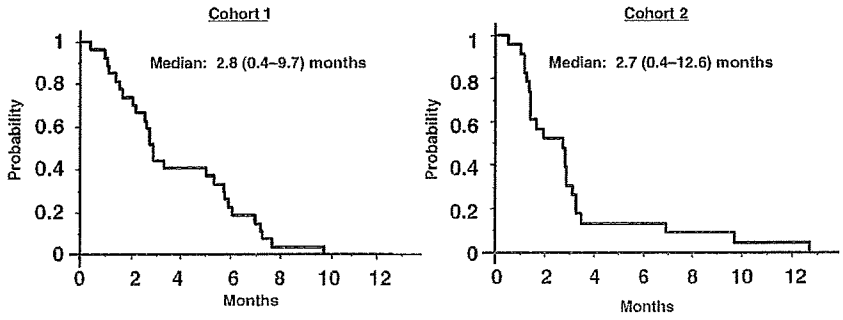

Figure 1. Time to disease progression.

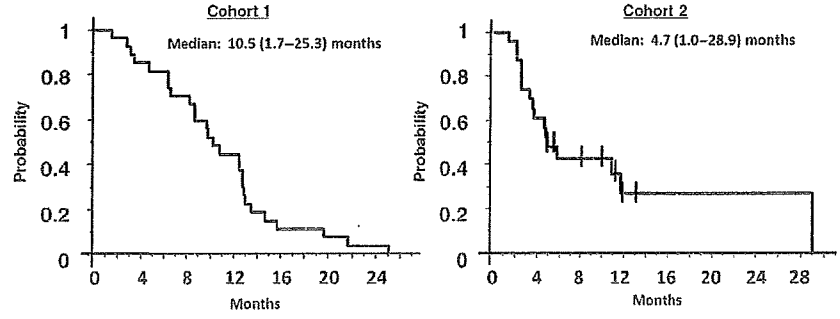

Figure 2. Overall survival.

biological modulation, has recently been tried in patients after failure to respond to the three drugs. It showed no objective response in 5-FU-resistant cancer in a phase II trial (12). Its combination with MMC resulted in a response rate of 15% for irinotecan-resistant cancer, but the response rate fell to 5% for cancer resistant to both irinotecan and oxaliplatin. Its combinations with other drugs such as trimetrexate or irinotecan did not show any additional benefit either (13–15). From these results, treatment with oral fluoropyrimidines with biological modulation, such as S-1 and capecitabine, does not appear to provide a satisfactory outcome.

Recently, several studies with molecular targeted agents have been conducted for colorectal cancer refractory to the three drugs. Lenz et al. (16) reported that monotherapy with cetuximab in colorectal cancer patients refractory to irinotecan, oxaliplatin and 5-FU resulted in a response rate of 12% and PFS of 1.4 months. And Jonker et al. (17) reported that in comparison with best supportive care alone, cetuximab treatment in patients refractory to the three antitumor agents was associated with a significant improvement in overall survival and in PFS. Chen et al. (18) reported that treatment with bevacizumab in addition to 5-FU and leucovorin brought a response rate of 4% and PFS of 3.5 months in patients with colorectal cancers refractory to both irinotecan and oxaliplatin. Malik et al. (19) reported the efficacy of panitumumab in patients who failed to respond to the three drugs (response rate 8%, PFS 4.2 months) and the phase III trial of panitumumab showed a survival benefit compared to best supportive care (20). The PFS time in phase III trial was 8.5 weeks (2.2 months) for best supportive care. There is no difference between best supportive care and S-1 monotherapy in cohort 1 and 2. Recently, cetuximab therapy has now become available in Japan.

In conclusion, S-1 monotherapy cannot be recommended and new treatments based on molecular target agents should be developed and introduced for use after failure with the three anti-tumor agents.

Conflict of interest statement

None declared.

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