

Phase II study of S-1 plus leucovorin in patients with metastatic colorectal cancer

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Background: S-1, a novel oral fluoropyrimidine, is well tolerated in patients with metastatic colorectal cancer (mCRC). The response rate of S-1 for colorectal cancer is high, ranging from 35% to 40%. This study aimed to evaluate the safety and efficacy of S-1 combined with oral leucovorin (LV) to enhance antitumor activity in chemotherapy-naïve patients with mCRC.

Patients and methods: S-1 was given orally twice daily for two consecutive weeks at a daily dose of 80–120 mg, followed by a 2-week rest period, within a 4-week cycle. LV was given orally twice a day at a daily dose of 50 mg, simultaneously with S-1.

Results: Of the 56 patients with previously untreated mCRC, 32 (57%) had partial responses. The median follow-up period was 27.2 months. The median time to progression was 6.7 months (95% confidence interval 5.4–7.9). The median survival time was 24.3 months. There was no treatment-related death or grade 4 toxicity. The most common grade 3 toxic effects were diarrhea (32%), anorexia (21%), stomatitis (20%), and neutropenia (14%).

Conclusion: S-1 combined with LV therapy demonstrated promising efficacy and acceptable safety in chemotherapy-naïve patients with mCRC without the concurrent use of irinotecan, oxaliplatin, or molecular-targeted drugs.

Key words: colorectal cancer, leucovorin, LV, phase II, S-1

introduction

Recently, the development of irinotecan and oxaliplatin in combination with 5-fluorouracil (5-FU)-based regimens has led to significant improvement of survival in patients with metastatic colorectal cancer (mCRC). Various phase III studies of first-line chemotherapy have reported combination therapy with i.v. 5-FU/leucovorin (5-FU/LV) plus oxaliplatin (FOLFOX regimen) or 5-FU/LV plus irinotecan (FOLFIRI regimen) as a standard regimen for mCRC [1–4]. Recent clinical trials have examined whether oral fluoropyrimidines such as uracil–tegafur (UFT)/LV and capecitabine could be a replacement for i.v. 5-FU/LV. A combination of capecitabine and oxaliplatin (XELOX regimen) was found not to be inferior to FOLFOX in terms of progression-free survival (PFS) [5]. The standard treatment of mCRC is consequently shifting from 5-FU/LV-

based regimens, which require central venous access, to more convenient oral-based care.

S-1 is a capsule preparation combining FT, an oral 5-FU derivative, with gimeracil (CDHP) and oteracil potassium (Oxo) at a molar ratio of 1.0 : 0.4 : 1.0. CDHP reversibly inhibits the activity of dihydropyrimidine dehydrogenase (DPD), a metabolizing enzyme of 5-FU. Oxo inhibits the activity of orotate phosphoribosyltransferase and is distributed in high concentrations in the gastrointestinal (GI) tract, where it suppresses GI disorders caused by 5-FU.

In Japan, S-1 was approved for the treatment of gastric cancer in 1999 and was subsequently approved for the treatment of colorectal cancer (CRC), head and neck cancer, non-small-cell lung cancer, inoperable or recurrent breast cancer, pancreatic cancer, and biliary tract cancer. Recently, several phase III studies have established S-1 as a standard treatment of gastric cancer, including postoperative adjuvant chemotherapy [6–8]. Two phase II studies of S-1 were conducted in patients with mCRC. Single-agent S-1 was shown to be very effective, with high response rates (36% and 40%) and good median survival times (MSTs) (12 months) for at

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the time these studies were conducted given the lack of second-line therapies available [9, 10].

LV is known to enhance the efficacy of 5-FU by inhibiting thymidylate synthase. A meta-analysis consisting of >3000 patients' clinical data revealed that LV improves response rates and overall survival (OS) when combined with 5-FU, as compared with 5-FU alone [11]. Oral UFT/LV has been shown to be as effective as i.v. 5-FU/LV (Mayo regimen), with significantly favorable safety profile against metastatic disease [12, 13]. In an adjuvant setting, oral UFT/LV regimen was demonstrated to be as effective as i.v. 5-FU/LV (Roswell Park Memorial Institute regimen) in patients with curatively resected stage II/III colon cancer [14]. On the other hand, addition of oral LV to another fluoropyrimidine, capecitabine, leads to increased GI toxicity or hand-foot skin reaction, with no enhancement of response [15].

In a phase I study of oral LV plus S-1 in patients with mCRC, recommended treatment schedule with fixed dose of S-1 and LV was determined. S-1 and LV were administered twice a day at a daily dose of 80–120 mg for S-1, a conventional dose of S-1, and 25 mg for LV. The dose (schedule)-limiting toxic effects (DLTs) were mainly GI symptoms such as grade 3 stomatitis/pharyngitis, nausea, diarrhea or ileus, and exanthema. The response rate was 67% (10 of 15). The recommended treatment schedule was 2 weeks of administration followed by 2 weeks of rest [16]. To evaluate the safety and efficacy of a combination of S-1 and LV (S-1/LV regimen) given in the recommended schedule, we conducted a phase II study in chemotherapy-naïve patients with mCRC.

patients and methods

patient selection

Eligible patients had histologically confirmed CRC; have at least one measurable lesion; adequate oral intake; aged 20–74; no previous treatment of metastatic disease (adjuvant chemotherapy was allowed if finished 180 days before enrollment); an Eastern Cooperative Oncology Group performance status of zero to two; adequate bone marrow, liver, and renal functions as follows: a serum hemoglobin concentration of ≥ 9.0 g/dl, a white blood cell count of 4000–12 000/mm³, a neutrophil count of ≥ 2000 /mm³, a platelet count of ≥ 100 000/mm³, a serum total bilirubin concentration of ≤ 1.5 mg/dl, serum aspartate aminotransferase and alanine aminotransferase concentrations of ≤ 100 IU/l, a serum alkaline phosphatase level of less than twice the upper limit of the normal institutional level (ULN), and a serum creatinine level of less than ULN; and written informed consent. Patients were excluded from this study if they had a contraindication for S-1; a history of serious hypersensitivity to LV; an active infection; serious concomitant diseases or conditions (intestinal obstruction, pulmonary fibrosis, heart failure, renal failure, liver failure, etc.); severe ascites or pleural effusion; extensive bone metastasis; brain metastasis or symptoms of brain metastasis; diarrhea (watery stools); or another synchronous cancer. We also excluded patients participating in other clinical studies; women who were pregnant, nursing infants, possibly pregnant, or planning to become pregnant; and men who were intending to conceive children.

treatment plan

S-1 (capsules containing 20 or 25 mg of FT) and LV (25-mg tablets) were provided by Taiho Pharmaceutical Co., Ltd, Tokyo, Japan. The dose of S-1 was determined according to body surface area as follows: <1.25 m²,

40 mg; 1.25–1.50 m², 50 mg; and ≥ 1.50 m², 60 mg. LV was given at a fixed dose of 25 mg each time. S-1 and LV were given together orally twice a day for two consecutive weeks, followed by 2 weeks rest. This 4-week cycle was repeated until the onset of disease progression or unacceptable adverse events. No pretreatment was allowed. The dose of S-1 could be decreased by one level in the event of the following toxicity: grade 4 leucopenia or thrombocytopenia; grade 4 non-hematologic toxicity; or grade 3 diarrhea, stomatitis, skin conditions, or febrile neutropenia that did not resolve with symptomatic treatment. The dose of LV could not be decreased.

toxicity and response criteria

Laboratory and clinical examinations were carried out within 15 days before enrollment, every 1 week during the first course of treatment and every 2 weeks from the second course onward. Tumors were evaluated on the basis of computed tomographic scans and serum carcinoembryonic antigen levels within 30 days before enrollment and every 4–6 weeks after the start of treatment. In the assessment of the best overall response, a complete response (CR: the disappearance of all lesions and normalization of tumor marker level) or partial response (PR: at least a 30% decrease in the sum of the longest diameter of all measured lesions taking as reference the baseline sum longest diameter) had to continue for at least 4 weeks and to be confirmed. A best overall response of stable disease (SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum longest diameter since the treatment started) required no evidence of progressive disease (PD: at least a 20% increase in the sum of the longest diameter of all measured lesions taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of new lesion) for at least 6 weeks after the start of treatment. Response to S-1/LV treatment was externally reviewed and analyzed. Tumors were assessed according to RECIST criteria. Toxicity was evaluated according to the Common Terminology Criteria for Adverse Events (version 3.0).

statistical analysis

The response rate in previous phase II studies of S-1 alone in patients with CRC was 33% [42 of 129; 95% confidence interval (CI) 25–41]. Therefore, the threshold rate of response to the S-1/LV regimen was set at 30%, and the expected response rate was estimated to be 50%, which was ~20 percentage points higher than the response rate for S-1 alone. Assuming that the response rate follows a binomial distribution, we calculated the number of patients required to obtain the expected response rate (given a threshold response rate of 30%), with a one-sided test, a significance level of 2.5% ($\alpha/2 = 2.5\%$), and a statistical power ($1-\beta$) of 80%. We estimated that a target sample size of 54 patients would be needed to reject the null hypothesis with a power of 80%.

The Kaplan–Meier method was used to estimate time to progression (TTP), time to treatment failure (TTF), and OS. All data obtained until the completion of the study period were included in the safety analyses. Clinical cut-off date for this study was 25 June 2008.

The study was approved by the institutional review board at each participating center. For the duration of the study, an independent data-monitoring committee monitored safety. The study was undertaken in accordance with the Helsinki Declaration and Japanese Good Clinical Practice Guidelines.

results

patient characteristics

From October 2005 through June 2006, a total of 56 patients were enrolled from 12 hospitals: all were eligible. Patient characteristics are described in Table 1. A total of 406 courses of

Table 1. Patient characteristics

Characteristics	N = 56	
	n	%
Gender		
Male	30	54
Female	26	46
Age, years		
Median	62	
Range	32–72	
ECOG performance status		
0	53	95
1	3	5
2	0	0
Primary site		
Colon	32	57
Rectum	24	43
Histologic grading		
Well differentiated	20	36
Moderately differentiated	29	52
Poorly differentiated	5	9
Mucinous	2	4
Site of metastases		
Liver	39	70
Lung	26	46
Lymph nodes	24	43
Peritoneum	3	5
Other	7	13
No. of sites evaluated		
1	24	43
2	20	36
3	8	14
4	2	4
≥5	2	4
Prior adjuvant therapy		
Yes	10	18
No	46	82
Hemoglobin (g/dl)		
Median	12.50	
Range	9.0–16.8	
Alkaline phosphatase (IU/l)		
Median	280.0	
Range	137–1408	

ECOG, Eastern Cooperative Oncology Group.

the study treatment cycles were delivered to patients. The median number of treatment courses was 6 (range 1–26). The median treatment period was 5.1 months (range 0.3–29.4). The median relative dose intensity was 81% (range 43–109) for S-1 and 93% (range 49–113) for LV.

response to therapy

The response rate, which was the primary end point of this study, was evaluated in all 56 patients. No patient had a complete response, but 32 had PRs, 16 had stable disease, and 8 had progressive disease. The response rate was 57% (95% CI 43–70) (Table 2). The median time to response was 1.9 months (range 0.9–5.3).

Table 2. Tumor response

	N = 56	
	n	%
Complete response	0	0
Partial response	32	57
Stable disease	16	29
Progressive disease	8	14
Not evaluable	0	0
Overall response rate (%)	32	57
95% CI	43.2–70.3	
Time to progression, months		
Median	6.7	
95% CI	5.4–7.9	

Tumor response was externally assessed according to the RECIST criteria. CI, confidence interval.

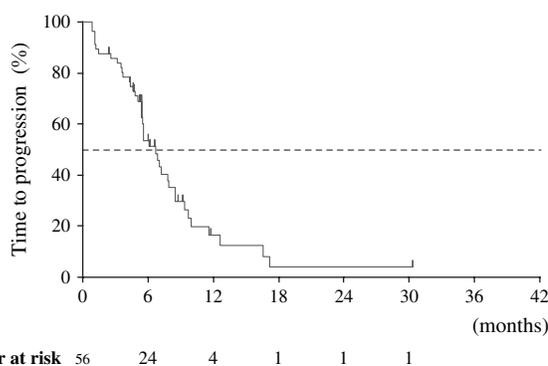


Figure 1. Kaplan–Meier curve of time to progression.

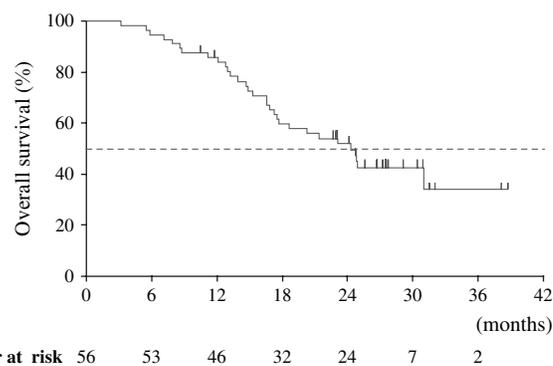


Figure 2. Kaplan–Meier curve of overall survival.

With a median follow-up time of 27.2 months, the median TTP was 6.7 months (95% CI 5.4–7.9) (Figure 1). The median TTF was 6.0 months (95% CI 5.4–7.8). The MST was 24.3 months (95% CI 17.5–XXX; upper bound of 95% CI was not estimable) (Figure 2) with the survival rate of 86% at 1 year and 52% at 2 years. Second-line treatment, including curative or palliative surgery, was given to 52 (93%) of the 56 patients, among whom 36% received oxaliplatin-based chemotherapy and 41% received irinotecan-based chemotherapy (Table 3).

Table 3. Further treatment after study chemotherapy

	N = 56	
	n	%
Oxaliplatin based	20	36
Irinotecan based	23	41
Surgery		
Curative	3	5
Palliative	2	4
None	4	7
Other	4	7

Table 4. Hematological and non-hematological adverse events

	N = 56		
	All grade (%)	Grade 3 (%)	Grade 4 (%)
Leucopaenia	31 (55)	0	0
Neutropaenia	36 (64)	8 (14)	0
Anemia	35 (63)	2 (4)	0
Thrombocytopaenia	14 (25)	1 (2)	0
AST	17 (30)	0	0
ALT	20 (36)	1 (2)	0
Bilirubinaemia	25 (45)	1 (2)	0
Nausea	42 (75)	1 (2)	0
Vomiting	20 (36)	1 (2)	0
Stomatitis	49 (88)	11 (20)	0
Abdominal pain	18 (32)	0	0
Diarrhea	46 (82)	18 (32)	0
Fatigue	48 (86)	0	0
Anorexia	48 (86)	12 (21)	0
Weight loss	21 (38)	1 (2)	0
Rash	33 (59)	1 (2)	0
Skin exfoliation	21 (38)	0	0
Hand-foot syndrome	4 (7)	0	0
Pigmentation disorder	50 (89)	0	0
Lacrimation increased	18 (32)	1 (2)	0
Dysgeusia	31 (55)	0	0

Numbers are patients who reported events. Severity was graded according to the CTCAE, version 3.0.

AST, aspartate aminotransferase; ALT, alanine aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events.

safety assessment

The most frequent common adverse events are shown in Table 2. Grade 3 toxicity occurred in 35 patients (55%). There was no grade 4 toxicity. Grade 3 toxic effects with an incidence of $\geq 10\%$ were given to diarrhea (32%), anorexia (21%), stomatitis (20%), and neutropaenia (14%) (Table 4).

The dose had to be decreased at least once in 33 patients (59%). The median number of treatment courses until the dose of S-1 was initially decreased was 2 (range 1–4). The main reasons for dose reductions were diarrhea, stomatitis, and rash. Rest periods were prolonged in 53.6% of the patients, mainly because of diarrhea, stomatitis, and rash, similar to the reasons for dose reductions.

The median times to the onset of diarrhea, stomatitis, and rash were 15 days (range 1–169), 12 days (range 3–201), and 8 days (range 3–148), respectively. The median times to the worst grade of these toxic effects were 20 days (range 1–769), 14 days (range 5–237), and 10 days (range 3–148), respectively. The median times from the worst grade to the resolution of these toxic effects were 7 days (range 1–29), 10 days (range 2–79), and 10 days (range 1–70), respectively.

The reasons for the withdrawal of treatment were mainly disease progression (86%). Withdrawal due to toxic effects was rare (4%) and there were no treatment-related deaths.

discussion

This phase II trial was conducted to evaluate the response rate of the S-1/LV regimen in patients with previously untreated mCRC. All 56 enrolled patients were eligible. S-1/LV regimen yielded promising results, without combination with oxaliplatin, irinotecan, or molecular-target agent as first-line treatment. The response rate, the primary end point of this trial, was 57%. With a median follow-up time of 27.2 months, the median TTP was 6.7 months, the MST was 24.3 months, and survival rates were 86% at 1 year and 52% at 2 years. In previous phase II studies of single-agent S-1, the response rate was 35%–40%, the median TTP was 5.3 months, and the MST was 12 months. In these studies, S-1 was given for 4 weeks, followed by 2 weeks of rest [9, 10]. In our study, the S-1 combined with LV was clearly more effective than S-1 alone, despite a shorter treatment period (2 versus 4 weeks). The antitumor activity of 5-FU is thought to involve the following mechanism: 5-fluoro-2'-deoxyuridine-5'-monophosphate, a metabolite of 5-FU, forms a ternary complex with thymidylate synthase and 5,10-methylenetetrahydrofolate, a metabolite of LV. This complex inhibits thymidylate synthase, thereby blocking DNA synthesis [17]. In our study, enhancement of the antitumor activity of S-1 by oral LV is ascribed to this mechanism.

UFT is a derivative of 5-FU which is the same as S-1 and is a compounding oral agent of FT and uracil. *In vitro*, CDHP has been shown to inhibit DPD activity 180-fold higher than uracil [18]. In the previous pharmacokinetic (PK) studies, there was difference in PK profile about 5-FU between S-1 and UFT. Compared with UFT, S-1 showed longer maximum plasma concentration time (T_{max}) (3.5 versus 1.1 h), lower maximum plasma concentration (C_{max}) (128.5 versus 265 ng/ml) and longer half-time ($T_{1/2}$) (1.9 versus 0.34 h). The area under the curve (AUC) of 5-FU were 723.9 ng-h/ml for S-1 ($AUC_{0-14 h}$) and 338 ng-h/ml for UFT ($AUC_{0-8 h}$) [19, 20]. In this study, S-1/LV regimen demonstrated higher response rate and longer TTP compared with previously reported UFT/LV [12, 13]. Although these comparisons are limited in value, it was considered that these differences were due to the difference in the inhibitory effect of DPD.

In phase III studies of 5-FU/LV reported in the past decade or so, response rates were 10%–30%, with a PFS/TTP of 4.5–6.0 months. Response rates with FOLFOX or FOLFIRI range from 30% to 55%, with a PFS/TTP of 7.0–8.5 months [21, 22]. XELOX regimen showed response rates of 48% and a PFS of 7.1 months [23]. Although there is limitation to

compare due to the differences in study population between this study (Asians) and referred studies (Western countries), the S-1/LV regimen has one of the highest response rates, despite the absence of oxaliplatin and irinotecan, among currently available regimens not including molecular-targeted drugs such as bevacizumab. The efficacy profiles of S-1 seemed to be generally better in Asian studies than that of others; however, it remained still unclear whether this difference was due to ethnic difference or good selected study population.

Recent clinical trials in patients with mCRC have not only compared treatment regimens but also examined strategies for subsequent treatment. The capecitabine, irinotecan, and oxaliplatin (CAIRO) trial compared sequential chemotherapy (first-line capecitabine, second-line irinotecan, and third-line capecitabine plus oxaliplatin) with combination chemotherapy (first-line capecitabine plus irinotecan and second-line capecitabine plus oxaliplatin). OS did not differ significantly between sequential chemotherapy and combination chemotherapy [hazard ratio (HR) = 0.92; 95% CI 0.79–1.08; $P = 0.33$ by the log-rank test]. Sequential therapy was thus considered a valid treatment option for mCRC [24]. The 5-FU, oxaliplatin, and irinotecan: use and sequencing (FOCUS) trial, compared three different strategies of sequential and combination chemotherapy in patients with unresectable mCRC: single-agent 5-FU (given with levofofolinate), followed by single-agent irinotecan (strategy A, control group); 5-FU, followed by combination chemotherapy (strategy B); and combination chemotherapy from the outset (strategy C). Compared with strategy A, strategy B did not significantly prolong survival (HR = 0.94; 95% CI 0.84–1.05; $P = 0.24$ by the log-rank test), whereas strategy C did (HR = 0.88; 95% CI 0.79–0.98, $P = 0.02$ by the log-rank test). There was no significant difference in survival between strategy B and strategy C (HR = 1.06; 90% CI 0.97–1.17). The FOCUS trial concluded that maximum tolerable treatment should be used as first line in the noncurative setting, and the staged approach of initial single-agent treatment upgraded to combination was not inferior to first-line combination therapy. This was an alternative option for discussion with patients [25]. At present, sequential therapy is recognized as a useful alternative for combined therapy.

After the study treatment, 93% of the patients in our study were given subsequent therapy. Of the 56 patients, 36% received oxaliplatin-based chemotherapy, 41% received irinotecan-based chemotherapy, and 5% underwent curative surgery. At the time of starting this trial, neither the FOLFOX nor the FOLFIRI regimen and no bevacizumab was approved in Japan. Grothey et al. [26] found that 5-FU, oxaliplatin, and irinotecan contributed to prolonged survival. In fact, Tournigand et al. [21] reported that survival exceeded 20 months in patients with mCRC who were enrolled in a crossover study of FOLFOX and FOLFIRI. The good survival in our study seems to be attributed to three reasons. First, the relatively recent approval of the FOLFOX and FOLFIRI regimens for use in Japan increased options for subsequent treatment. Secondly, the S-1/LV regimen, an intensive treatment that does not include oxaliplatin or irinotecan, was given as first-line therapy. Thirdly, the S-1/LV regimen was associated with a low rate of treatment withdrawal due to

toxicity and a high rate of subsequent therapy; consequently, a high proportion of patients were able to receive sequential chemotherapy.

As for safety, there was no grade 4 toxicity or treatment-related mortality in our study. Common non-hematologic toxic effects included pigmentation, stomatitis, anorexia, fatigue, diarrhea, nausea, rash, and taste disorders. The incidences of grade 3 diarrhea, anorexia, and stomatitis were 32%, 21%, and 20%, respectively. Although these rates are higher than those reported for single-agent S-1 or standard chemotherapy, these toxic effects did not raise treatment discontinuation. The median number of courses until the first decrease in the dose of S-1 was 2 (range 1–4). The dose was decreased in 33 patients (59%). The main reasons for decreases in dose were stomatitis (11 patients), diarrhea (11 patients), and rash (nine patients). Mucositis characterized by stomatitis and diarrhea was considered the DLT of the S-1/LV regimen. Observed DLT was shifted from hematological toxicity to GI toxicity when S-1 was administered with LV. The median time to the onset of the worst grade of diarrhea and stomatitis was 14–20 days after the start of treatment. These toxic effects resolved after 7–10 days. Our experience indicates that toxicity associated with the S-1/LV regimen is manageable by appropriately reducing the dose of S-1 or by extending the rest period between treatment courses. So the S-1/LV regimen was generally well tolerated, with an acceptable toxicity profile.

Both S-1 and LV are administered orally, so this regimen does not require a central venous port. Patients therefore have to spend less time on follow-up visits, and the convenience of oral administration makes the S-1/LV regimen extremely useful clinically. Another advantage is the low incidence of hand-foot syndrome, the most common toxicity of capecitabine, another oral fluoropyrimidine.

In phase I/II studies of S-1 combined with oxaliplatin (SOX regimen), S-1 was given for 2 weeks at the conventional dose in Japan, similar to our S-1/LV regimen, followed by 1 week of rest. Oxaliplatin (130 mg/m^2) was given on day 1, within a 3-week cycle. The SOX regimen was very effective, with a response rate of 50% and a median PFS of 6.4 months. The most common toxicity of grade 3 or higher was thrombocytopenia, typically associated with oxaliplatin [27]. Since the DLT of S-1/LV regimen was mucositis such as diarrhea and stomatitis, the combination with oxaliplatin, the toxicity profile of which does not overlap with that of S-1/LV, may be more appropriate than irinotecan for the treatment of metastatic disease requiring intensive chemotherapy. The preliminary results of a phase I study evaluating the S-1/LV regimen plus oxaliplatin have been reported. S-1/LV was given for 1 week followed by 1 week of rest, and oxaliplatin was given every 2 weeks (SOL regimen). The S-1/LV regimen was administered at the standard dose in Japan; the recommended dose of oxaliplatin was determined to be 85 mg/m^2 . In that phase I study, five (83%) of the six patients who received the recommended dose of S-1, LV, and oxaliplatin had PRs. DLTs (grade 3 diarrhea and grade 3 hypertension) occurred in one of the six patients [28]. As for combinations of S-1 and irinotecan, a phase III study is going on to compare survival between the FOLFIRI regimen and S-1 plus irinotecan (IRIS

regimen), given as second-line treatment. The results are scheduled to be available in the near future.

Our results indicate that the S-1/LV regimen is a promising treatment of mCRC. On the basis of these preliminary data, further clinical trials of S-1/LV-based chemotherapy are going on. After the completion of these trials, phase III studies are promptly required to validate the clinical usefulness of S-1/LV-based chemotherapy.

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