Randomized phase II trial of first-line treatment with tailored irinotecan and S-1 therapy versus S-1 monotherapy for advanced or recurrent gastric carcinoma (JFMC31-0301)

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The pharmacokinetics of irinotecan vary markedly between individuals. This study sought to compare tailored irinotecan and S-1 therapy with S-1 monotherapy for the treatment of patients with advanced/recurrent gastric cancer. Patients with advanced/recurrent gastric cancer were randomized to receive tailored irinotecan and S-1 (arm A) therapy or S-1 therapy alone (arm B). Arm A received S-1 (80–120 mg/m^2/day) for 14 days, with irinotecan on days 1 and 15. The initial irinotecan dose of 75 mg/m^2 (level 0) was adjusted for toxicity during an earlier course. In arm B, S-1 (80–120 mg/day) was administered alone for 28 days, followed by 14 days without therapy. Ninety-five patients were randomized (48 patients to arm A and 47 patients to arm B). The response rate of the primary tumor (Japanese criteria) was 25.0% in arm A (12 of 48 patients) and 14.9% in arm B (seven of 47 patients), whereas the response rates according to Response Evaluation Criteria In Solid Tumors were 27.8% (10 of 36) versus 21.9% (seven of 32). Hematological toxicity, anorexia, and diarrhea were significantly more common in arm A, but both arms had similar grades 3–4 toxicities. These findings suggest the usefulness of tailored irinotecan and S-1 therapy for gastric cancer. *Anti-Cancer Drugs* **22:576–583 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Irinotecan hydrochloride (irinotecan) and 5-fluorouracil (5-FU) derivatives differ in their mechanism of action, and the efficacy of combined therapy with these agents has been shown in animal experiments [1,2]. The combination of irinotecan with S-1 (an oral derivative of 5-FU developed in Japan in the 1990s) and irinotecan/S-1 (IRIS) has also been examined, particularly in recent years [3–5].

In phase I/II studies of advanced gastric cancer, although response rates of 44 [6] and 49% [7] and overall survival rates of 207 and 250 days, respectively, have been shown with S-1 monotherapy, higher response rates have been reported when used in combination with irinotecan [3–5]. Phase I/II clinical trials of IRIS therapy showed that the recommended dose of irinotecan is 80 mg/m^2 for a weekly regimen and 80 or 125 mg/m^2 for a fortnightly regimen, with the response rate being 50, 54, and 50% in patients receiving 80 mg/m^2 weekly, 80 mg/m^2 fortnightly, and 125 mg/m^2 fortnightly, respectively [3–5]. However, severe adverse events occurred even at low irinotecan doses, suggesting that special care needs to be taken during the administration of this drug. In Japan, chemotherapy for gastric cancer (an extremely common tumor in this country) is often given on an outpatient basis; hence a safe regimen is required.

The rationale for tailored chemotherapy, in which the dosage is varied according to each patient's response, is based on individual variations of drug-metabolizing enzyme activity related to genetic polymorphisms that influence pharmacokinetics and also lead to individual differences of toxicity and efficacy. In brief, tailored therapy aims to limit toxicity, improve compliance, and therefore maintain treatment for as long as possible and prolong survival. The efficacy of tailored FEC (5-FU, epirubicin, and cyclophosphamide) therapy as a postoperative adjuvant chemotherapy for breast cancer has been shown [8]. In Japan,

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Takahashi *et al.* [9] administered tailored gemcitabine therapy to patients with pancreatic cancer, and found improvements in both symptoms and quality of life in 75% of the patients.

Importantly, advanced gastric cancer generally has a poor prognosis and a standard chemotherapy treatment, that is better than continuous infusion of 5-FU, has not been established in Japan. We have earlier used an IRIS regimen for ambulatory treatment of patients with advanced gastric cancer, as reported by Komatsu *et al.* [4]. Although the recommended dose of irinotecan was set at 125 mg/m^2 in that study, grade 3 adverse events still occurred at the lowest dose administered (100 mg/m^2). In this randomized, phase II study, therefore, we set the initial dose of irinotecan at 75 mg/m^2 (one dose level below 100 mg/m^2) to investigate the tolerability and survival benefit of tailored IRIS therapy compared with S-1 monotherapy for the ambulatory treatment of gastric cancer. The study was also designed to determine the best candidate for, and feasibility of, conducting a phase III comparative trial with continuous infusion of 5-FU [10,11].

Materials and methods

Patients

The protocol for this study has been reported earlier [11], and an update is provided here. The participants enrolled in this phase II study at the Hokkaido University Graduate School of Medicine (Internal Medicine, Gastroenterology and Hematology), Sapporo Medical University School of Medicine (Surgery I), Hokkaido Cancer Center (Gastroenterology) Sapporo Social Insurance General Hospital, Sapporo Memorial Hospital of Surgery, Hokkaido Gastroenterology Hospital, Nikko Memorial Hospital, Asahikawa Kosei Hospital, Kushiro Rosai Hospital (Internal Medicine), Hirosaki University School of Medicine (Surgery II), Iwate Medical University (Surgery I), Senseki Hospital, Chiba Cancer Center (Clinical Oncology), Showa University School of Medicine (Surgery II), Kitasato Institute Hospital (Surgery), Tokyo Medical University St Marianna University School of Medicine (Gastroenterological Surgery), Kanazawa University School of Medicine (Surgical Oncology), Fukui Red Cross Hospital, Gifu Municipal Hospital (Surgery), Ogaki Municipal Hospital (Surgery), Aichi Cancer Center (Gastroenterological Surgery), Nagoya City University Graduate School of Medical Sciences (Gastroenterological Surgery), NTT West Osaka Hospital, Osaka City University Graduate School of Medicine (Surgical Oncology), Saiseikai Senri Hospital, Osaka Medical College (General and Gastroenterological Surgery), Osaka Minami National Hospital, Hyogo Prefectural Nishinomiya Hospital, Kansai Rosai Hospital, Tottori University Faculty of Medicine (Surgical Oncology), Hiroshima University Research Institute for Radiation Biology and Medicine (Surgical Oncology), or Yamaguchi University School of Medicine (Digestive Surgery and Surgical Oncology) fulfilled the following criteria: (i) they had histologically or cytologically proven gastric cancer, (ii) curative resection was impossible or the cancer was recurrent, (iii) measurable or assessable lesions, (iv) no radiation therapy or earlier chemotherapy (adjuvant therapy with a 5-FU derivative and methotrexate, leucovorin, or low-dose cisplatin was allowed, provided that it had been ceased at least 28 days before enrollment in this study), (v) age ranged from 20 to 80 years, (vi) expected survival time 12 weeks or more, (vii) Eastern Cooperative Oncology Group performance status of 0 or 1, (viii) no severe dysfunction of major organs (bone marrow, heart, lungs, liver, and kidneys), and (ix) provided written informed consent. The protocol was approved by the institutional review board at each site at which the study was conducted, and the Japanese Foundation for Multidisciplinary Treatment of Cancer.

Randomization

The patients were allocated to study arm A or B by the minimization method using the following factors for stratification: unresectable gastric cancer versus recurrent gastric cancer with adjuvant chemotherapy versus recurrent gastric cancer without adjuvant chemotherapy; well-differentiated versus poorly differentiated cancer; and institution (Fig. 1).

Treatment schedule

Tailored irinotecan/S-1 therapy (arm A)

Irinotecan was administered at an initial dose of 75 mg/m^2 as an intravenous infusion on days 1 and 15 of a 28-day cycle. S-1 was administered orally, with the initial dose being set at 40–60 mg/m^2. It was administered twice daily for 14 days, followed by a 14-day withdrawal period to complete one cycle.

In subsequent cycles, the doses of these drugs were varied according to the most severe adverse events during the preceding cycle (Tables 1 and 2).

S-1 monotherapy (arm B)

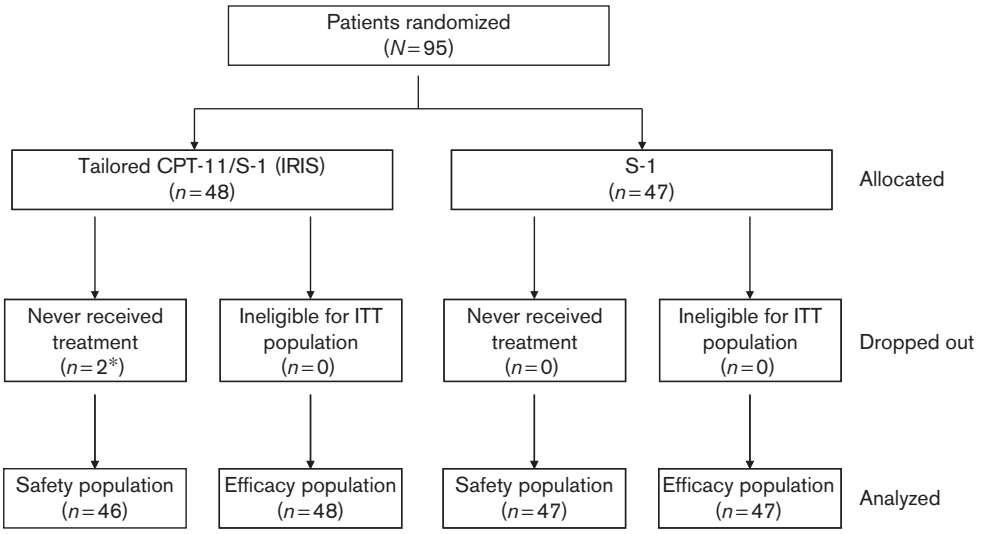
S-1 was administered orally, with the initial dose being set at 40–60 mg/m^2. It was given twice daily for 28 days (days 1 to 28), followed by a 14-day withdrawal period to complete one cycle (42 days in total). In subsequent cycles, the dose was varied according to the most severe adverse events during the preceding cycle by the same dose reduction schedule as that used in arm A (Tables 1 and 2).

In patients from either arm, treatment was continued until progression occurred. Patients were also withdrawn from the study if their adverse events met the specified criteria or if they refused further treatment.

Outcome measures

The primary endpoint was the antitumor activity of each regimen, which was evaluated according to the Japanese Rules for Assessment of Gastric Carcinoma (13th version)

Fig. 1



CONSORT diagram for the study. CPT-11, irinotecan hydrochloride; IRIS, irinotecan/S-1; ITT, intent-to-treat. *One patient switched to another hospital and the condition of the other patient deteriorated because of stenosis.

Table 1 Dose modification of irinotecan and S-1

	Escalation		No change		Reduction	
	Irinotecan	S-1	Irinotecan	S-1	Irinotecan	S-1
Hematological toxicity[a]	Gr. 0 – 1	–	Gr. 2	Gr. 0 – 2	Gr. 3 – 4	
Symptoms/signs[a] (excluding nausea and vomiting)	Gr. 0 – 1	–	Gr. 2	Gr. 0 – 2	Gr. 3	
Diarrhea[a]	Gr. 0	–	Gr. 1	–	Gr. 2	–
Serum creatinine	–	–	–	≤ ULN	–	≤ ULN × 1.1 – 1.5
Others	–	–	–	–	Skip the second dose	–

Gr, grade; ULN, upper limit of normal.
[a]Graded according to the National Cancer Institute Common Toxicity Criteria (version 2) [12].

Table 2 Dose levels of irinotecan and S-1

		S-1		
		Body surface area		
Irinotecan		$< 1.25\ m^2$	$\geq 1.25^2$– $< 1.5\ m^2$	$\geq 1.5\ m^2$
125 mg/m^2	↑	–	–	–
125 mg/m^2	Level + 2	–	–	–
100 mg/m^2	Level + 1	–	–	–
75 mg/m^2	Starting dosage	40 mg × 2	50 mg × 2	60 mg × 2
50 mg/m^2	Level – 1	25 mg × 2	40 mg × 2	50 mg × 2
25 mg/m^2	Level – 2	Discontinue	25 mg × 2	40 mg × 2
Discontinue	Level – 3	–	Discontinue	25 mg × 2
–	Level – 4	–	–	Discontinue

[12] and the internationally recognized Response Evaluation Criteria In Solid Tumors (RECIST) from the Guidelines for Evaluation of the Response to Treatment in Solid Tumors [13]. The response rate was determined as the percentage of patients with either a complete response (CR) or a partial response.

Secondary endpoints were adverse events, time to treatment failure (TTF), time to progression (TTP), and overall survival. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria (version 2) [14].

Statistical analysis

The target number of patients was determined by the method used in the randomized phase II clinical trials conducted by Simon *et al.* [10], that is, the number of patients per group required to select the best treatment with a probability $\geq 90\%$ based on an assumed difference of the response rate between the baseline and best treatments. Assuming that the response rate was 40% for S-1 monotherapy [7] and 55% for IRIS therapy [5], 37 patients per group would be required. Considering the possible enrollment of ineligible patients, the number per group was set at 45.

For patient background data, percentages were calculated and intergroup differences were assessed by Fisher's exact

test or the χ^2 test for continuous variables and by Wilcoxon's rank-sum test for discrete variables. Adverse events were graded according to severity and intergroup comparison was made by Wilcoxon's rank-sum test. Intergroup comparison of the response rate was made by Fisher's exact test. For the TTF, TTP, and overall survival, probability curves were drawn by the Kaplan–Meier method and comparison between the two arms was made by the log-rank test. Cessation of therapy, tumor progression, and death were used to determine the TTF, whereas tumor progression and death were used to define the TTP.

The level of significance was $P = 0.15$ for the analysis of background factors and $P = 0.05$ for other analyses. Statistical analysis was carried out with SAS version 9.1 software (Kachidoki, Tokyo, Japan).

Results

Enrollment and follow-up

Patients were enrolled from August 2003 to March 2005. The follow-up period was set at 2 years, commencing from the completion of patient enrollment, and a final follow-up was conducted in April 2007.

Patient profile

All of the 95 patients enrolled were eligible. Two patients in arm A did not receive any treatment because of refusal to start therapy (the patient switched to another hospital) and deterioration of the general condition in one case each. All 95 eligible patients were included in the analyses, except that the two untreated patients who were excluded from safety evaluation (Fig. 1). When background factors were assessed, age showed a bias between the two arms ($P = 0.022$, Wilcoxon's rank-sum test). Patients aged from 71 to 80 years accounted for 45.8% of arm A, and this treatment arm was older than arm B. However, the two arms were well matched with respect to the other background factors (Table 3).

Table 3 Patient characteristics

	Arm A	Arm B	Total	*P* value
Total	48 (100%)	47 (100%)	95 (100%)	
Diagnosis				
Unresectable	33 (68.8%)	33 (70.2%)	66 (69.5%)	0.85 (C)
Recurrence (with Adj.)	9 (18.8%)	7 (14.9%)	16 (16.8%)	
Recurrence (without Adj.)	6 (12.5%)	7 (14.9%)	13 (13.7%)	
Histology				
Well differentiated	22 (45.8%)	20 (42.6%)	42 (44.2%)	0.81 (C)
Poorly differentiated	25 (52.1%)	25 (53.2%)	50 (52.6%)	
Others	1 (2.1%)	2 (4.3%)	3 (3.2%)	
BSA (daily dose of S-1)				
$<1.25\,m^2$ (80 mg)	3 (6.3%)	1 (2.1%)	4 (4.2%)	0.58 (C)
$\geq 1.25-<1.5\,m^2$ (100 mg)	19 (39.6%)	18 (38.3%)	37 (38.9%)	0.48 (W)
$\geq 1.5\,m^2$ (120 mg)	26 (54.2%)	28 (59.6%)	54 (56.8%)	
Sex				
Male	34 (70.8%)	37 (78.7%)	71 (74.7%)	0.48 (F)
Female	14 (29.2%)	10 (21.3%)	24 (25.3%)	
Age (years)				
20–50	4 (8.3%)	9 (19.1%)	13 (13.7%)	0.005 (C)
51–60	10 (20.8%)	9 (19.1%)	19 (20.0%)	0.02 (W)
61–70	12 (25.0%)	22 (46.8%)	34 (35.8%)	
71–80	22 (45.8%)	7 (14.9%)	29 (30.5%)	
Range	47–78	24–76	24–78	
Median	70	63	66	
ECOG PS				
0	38 (79.2%)	35 (74.5%)	73 (76.8%)	0.63 (F)
1	10 (20.8%)	12 (25.5%)	22 (23.2%)	
Before treatment				
Surgery	2 (4.2%)	4 (8.5%)	6 (6.3%)	
Others	1 (2.1%)	0 (0.0%)	1 (1.1%)	

Adj, adjuvant therapy; BSA, body surface area; C, χ^2 test; ECOG, Eastern Cooperative Oncology Group; F, Fisher's exact test; PS, performance status; W, Wilcoxon test.

Treatment

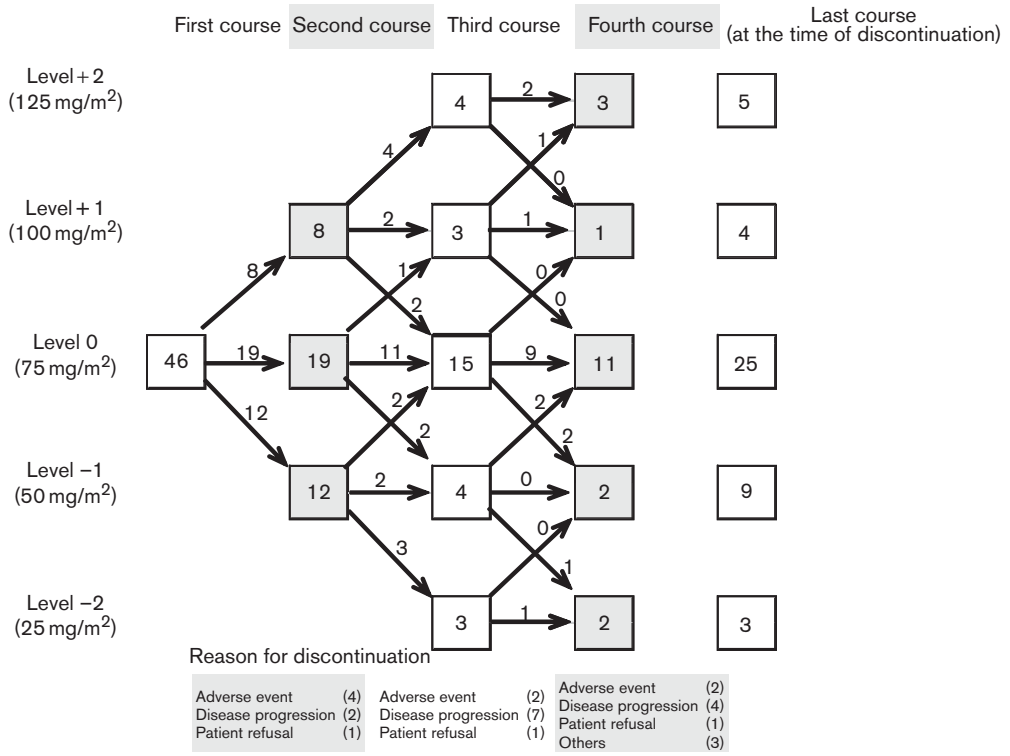
The median number of cycles of chemotherapy was 3 (range, 0–15) in arm A and 2 (range, 1–12) in arm B. The median duration of treatment was 84.5 days (95% confidence interval, CI: 65–99 days) in arm A and 92 days (95% CI: 64–126 days) in arm B, showing no difference. The reasons for ceasing therapy in arm A included tumor progression in 47.9%, adverse events in 27.1%, and other reasons in 25.0% of patients, whereas the corresponding values for arm B were 66.0, 23.4, and 10.6%. The percentage of patients who ceased treatment due to adverse events was similar in both arms. In arm A, only two patients stopped therapy due to grade 3 or 4 diarrhea. The frequency of S-1 dose reduction did not differ between the two arms. Reduction of the irinotecan dose was done in 39.1% of patients in arm A, whereas the dose was increased in 30.4% of patients. Dose reduction of irinotecan was undertaken for hematological toxicity in 21.7%, diarrhea in 10.9%, and other symptoms in 15.2% of patients.

In arm A, eight of the 46 patients started irinotecan at dose level 0 and then received a higher dosage (dose level +1) in the second cycle, whereas 19 patients stayed at dose level 0 and 12 patients had a reduction of one level (dose level −1). By the third cycle, the 46 patients were distributed from dose level −2 to dose level +2 (Fig. 2). In contrast, no patient in arm B needed reduction of the dose to level −2.

Antitumor effect

Overall evaluation was made according to the Japanese rules for gastric carcinoma (Japanese Gastric Cancer Association, 1998), including evaluation of the primary tumor and RECIST for the evaluation of measurable metastases [12]. According to the Japanese criteria, 12 patients from arm A (including two with CR) showed a response (CR or partial response) and the response rate was 25.0%, whereas seven patients from arm B (including one with CR) showed a response and the response rate was 14.9%. According to RECIST, the response rate was 27.8% in arm A and 21.9% in arm B. Among the eligible patients, seven from arm A and three from arm B withdrew during the first cycle owing to adverse events, complications, or patient request. Two patients each in arms A and B had incomplete data for

Fig. 2



Pattern of changes in the dose level of irinotecan (first–fourth courses) and final dose level in arm A.

other reasons. All these patients were classified as unevaluable. When they were excluded, the response rate was 30.8% in arm A and 16.7% in arm B according to the Japanese criteria, whereas the corresponding RECIST rates were 33.3% and 24.1% (Table 4).

To assess whether dose modification of irinotecan (tailored therapy) influenced the antitumor effect of therapy in arm A, the response rate over three cycles was determined for each dose level in patients receiving at least three cycles of treatment. As a result, no influence of the different irinotecan dosages was noted (Table 5).

Adverse events

Common grade 3 or 4 adverse events were a decreased neutrophil count (23.9%), anorexia (17.4%), decreased hemoglobin (10.9%), and fatigue/malaise (10.9%) in arm A, whereas decreased neutrophil count (12.8%) and anorexia (10.6%) were common adverse events in arm B. The only grade 4 adverse events were anorexia in one patient from arm A, and a decreased white blood cell count/neutrophil count and vomiting in one patient each from arm B (Table 6).

Outcome

The median TTF was 82 days in arm A (95% CI: 60–105 days) and 73 days in arm B (95% CI: 59–113 days), whereas the median TTP was 148 days (95% CI: 97–210 days) and 115 days (95% CI: 59–168 days), respectively. Both endpoints showed no significant difference between the two arms ($P = 0.855$ and 0.214). The median survival time (MST) was 276 days in arm A (95% CI: 210–393 days) and 373 days in arm B (95% CI: 305–523 days), and there was also no significant difference in overall survival ($P = 0.203$). As the number of patients aged 71 years or more showed a bias between the arms, MST was calculated separately for patients aged 70 years or less; it was 280 days in arm A (95% CI: 192–424 days) and 321 days in arm B (95% CI: 270–451 days), showing no significant difference ($P = 0.874$).

Discussion

Development of a 'patient-friendly treatment' is one of the main goals of the Japanese Foundation for Multidisciplinary Treatment of Cancer. Accordingly, this study investigated tailored therapy with irinotecan, which shows marked interindividual variability in the response to treatment at each dose causing adverse effects, and showed manageable toxicity and improved clinical response with tailored IRIS compared with S-1 monotherapy, suggesting that tailored IRIS therapy is more promising for a phase III trial.

It is noteworthy that tailored therapy did not cause any grade 4 hematological toxicity, whereas grade 4 nonhematological toxicity was limited to anorexia in one

Table 4 Response

	Arm A (%)	Arm B (%)	Total (%)	*P* value
JCGC				
CR	2 (4.2)	1 (2.1)	3 (3.2)	
PR	10 (20.8)	6 (12.8)	16 (16.8)	0.11 (W)
NC	17 (35.4)	19 (40.4)	36 (37.9)	(Excludes NE cases)
PD	10 (20.8)	16 (34.0)	26 (27.4)	
NE	9 (18.8)	5 (10.6)	14 (14.7)	
Total	48 (100.0)	47 (100.0)	95 (100.0)	
R (CR + PR)	12/48 (25.0)	7/47 (14.9)	19/95 (20.0)	0.30 (F)
(Excludes NE cases)	12/39 (30.8)	7/42 (16.7)	19/81 (23.5)	0.19 (F)
RECIST				
CR	1 (2.8)	1 (3.1)	2 (2.9)	
PR	9 (25.0)	6 (18.8)	15 (22.1)	0.13 (W)
SD	14 (38.9)	10 (31.3)	24 (35.3)	(Excludes NE cases)
PD	6 (16.7)	12 (37.5)	18 (26.5)	
NE	6 (16.7)	3 (9.4)	9 (13.2)	
Total	36 (100)	32 (100)	68 (100)	
R (CR + PR)	10/36 (27.8)	7/32 (21.9)	17/68 (25.0)	0.78 (F)
(Excludes NE cases)	10/30 (33.3)	7/29 (24.1)	17/59 (28.8)	0.56 (F)

CR, complete response; F, Fisher's exact test; JCGC, Japanese Classification of Gastric Carcinoma; NC, no change; NE, not evaluable; PD, progressive disease; PR, partial response; R, response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, standard deviation; W, Wilcoxon test.

Table 5 Tumor response in Arm A stratified by the dose level of irinotecan[a]

Dose level	Response	
Level +2	1/4 (25%)	9/22 (40.9%)
Level +1	3/3 (100%)	
Level 0	5/15 (33.3%)	
Level −1	1/4 (25%)	3/7 (42.9%)
Level −2	2/3 (66.7%)	
Total	12/29 (41.4%)	

[a]Patients who received more than three courses were evaluated.

Table 6 Grade 3 or 4 toxicities

	Arm A		Arm B		
	Gr. 3 (%)	Gr. 4 (%)	Gr. 3 (%)	Gr. 4 (%)	*P* value[a]
Anemia	10.9	0	4.3	0	0.26
Leucopenia	8.7	0	2.1	2.1	0.43
Neutropenia	23.9	0	10.6	2.1	0.18
Thrombocytopenia	0.0	0	4.3	0	0.49
Albumin ↓	4.3	–	0	–	0.24
Aspartate aminotransferase ↑	2.2	0	0	0	0.49
Alkaline phosphatase ↑	2.2	0	2.1	0	1.0
Na ↓	6.5	0	0	0	0.11
K ↓	4.3	0	2.1	0	0.61
Stomatitis	2.2	0	0	0	0.49
Anorexia	15.2	2.2	10.6	0	0.38
Nausea	6.5	–	6.4	–	1.0
Vomiting	2.2	0	2.1	2.1	1.0
Diarrhea	4.3	0	2.1	0	0.61
Fatigue	10.9	0	6.4	0	0.61

[a]Fisher's exact test.

patient. As grade 3 or 4 toxicities accounted for more than 35% of all toxicities even at an initial irinotecan dose of 75 mg/m^2, many patients would presumably have suffered from grade 4 toxicity if the starting dose had been 125 mg/m^2, which was the recommended dose according to phase I/II trials. Therefore, tailored IRIS therapy achieved a considerable reduction of risk. When the relationship between the irinotecan dosage and tumor response was assessed in the third cycle, no difference in the response rate was found between the dose levels (although there were small numbers in each dose group). These findings indicate that tailored therapy not only reduces risk, but also sets the appropriate dose for each individual patient. These results are in agreement with the report of a pilot study of tailored gemcitabine therapy for pancreatic cancer conducted by Takahashi *et al.* [15].

In this study, the respective response rates with tailored IRIS therapy were greater than with S-1 monotherapy, 25.0 and 14.9% according to Japanese criteria, and 27.8 and 21.9% according to RECIST. However, these response rates were lower compared with the results of similar clinical studies (about 50%) and only survival was longer in the S-1 monotherapy arm. Nevertheless, it is difficult to make a direct comparison of response rates between this trial and other studies. The low response rates in this study may have reflected the enrollment of patients who were not highly selected. In addition, survival may have been influenced by the age bias between the arms, as patients aged 71 years or older accounted for 45.8% ($n = 22$) of arm A versus 14.9% ($n = 7$) of arm B, even though this was a randomized trial. In fact, when analysis was conducted after excluding patients aged 71 years or older, the survival time was similar for both arms.

The results of a phase III trial of IRIS versus S-1 monotherapy (study GC0301/TOP-002), which used a different IRIS regimen from that used in this trial (the irinotecan dose being much lower in this study), were reported at the 2008 Gastrointestinal Cancer Symposium [16]. In that study, despite the lack of a statistically significant difference in overall survival between IRIS and S-1 alone, the MST of 12.8 months achieved with IRIS was longer than the 10.5 months achieved with S-1, and was comparable

with the 13 months achieved by standard therapy of cisplatin and S-1 in Japan (SPIRITS trial) [17].

In both studies GC0301/TOP-002 and in this study, S-1 monotherapy was used as the control and no significant difference in survival time was observed between the IRIS and control arms, suggesting that low doses of irinotecan may have led to the lack of a significant difference from the control group in both studies. The starting doses of irinotecan in study GC0301/TOP-002 and in this study, were only 160 mg/m^2 over 5 weeks and 150 mg/m^2 over 4 weeks, respectively, which means weekly doses of only 32 and 37.5 mg/m^2. These are approximately half the weekly dose (62.5 mg/m^2) delivered by the original IRIS regimen used as the model for this study.

There are three major problems with tailored chemotherapy: (i) selection of the starting dose, (ii) selection of the dose modification method, and (iii) the risk of undertreatment with the key drug. The starting dose of irinotecan for this trial was set at 75 mg/m^2 based on the results of a phase I/II study conducted by Komatsu *et al.* [4], who reported grade 4 myelosuppression at 125 mg/m^2 (the recommended dose) and also at 100 mg/m^2. Despite this low starting dose in this study, 16 of the 46 patients (35%) withdrew from treatment or needed a dose reduction in the increase after grade 0 or 1 toxicity was only possible in eight patients (17%). In contrast, the final dose showed a normal distribution centering around dose level 0 in the 25 patients (54%) who could be assessed. Furthermore, among the eight patients receiving at least eight cycles of treatment, three achieved an increase over the starting dose, two had a decrease, and three had no change, that is, the final dose showed a wide dispersion. The criterion for dose reduction was grade 2 toxicity. Of the 46 patients in arm A, 19 had grade 2 toxicity and the same dose of 75 mg/m^2 was administered in the next cycle. None of these 19 patients achieved a dose increase during the cycle after that. Instead, five of them needed a dose reduction or withdrew from treatment. These results suggest that the use of dose-limiting toxicity to set the starting dose and for dose increase/reduction is open to question.

With the use of gemcitabine or taxanes, most severe toxicities are hematological, whereas the dose-limiting toxicities for irinotecan are generally diarrhea, vomiting, and other nonhematological events (e.g. anorexia and malaise). Hematological events are easy to monitor objectively, but many nonhematological events cannot be assessed objectively, and this can lead to problems when modifying the dosage based on toxicities (as was done in this study).

Third, when the doses of anticancer agents are set at levels that will only induce mild adverse reactions, the response to treatment may be reduced. Most clinical trials of chemotherapy agents attempt to maximize efficacy by using the maximum-tolerated dose determined in a phase I trial. Therefore, the low response rate and the short survival time obtained in this study of a low-dose regimen need to be compared with data from other clinical trials, while bearing in mind the dosage differences.

In conclusion, the results of this randomized phase II trial showed manageable tolerability and improved efficacy with tailored IRIS therapy compared with S-1 monotherapy suggesting that IRIS is more promising for a phase III trial. However, if a phase III trial has to be designed to achieve maximum clinical efficacy, it would be difficult to conduct a controlled trial with an arm for tailored IRIS therapy. It might be possible to conduct a tailored-dose trial after the best standard therapy has been determined by an ordinary phase III trial.

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References

1 Aiba K, Funakoshi S, Mizunuma N, Dobashi N, Hirano A, Sano M, *et al.* Antitumor effect of SN-38, active form of CPT-11, on human colorectal cancer cell line. *Gan To Kagaku Ryoho* 1994; **21**:1601–1606.
2 Fukushima M, Fujioka A, Uchida J, Nakagawa F, Takechi T. Thymidylate synthase (TS) and ribonucleotide reductase (RNR) may be involved in acquired resistance to 5-fluorouracil (5-FU) in human cancer xenografts in vivo. *Eur J Cancer* 2001; **37**:1681–1687.
3 Narahara H, Takiuchi H, Tsujinaka T, Furukawa H, Tsukuma H, Taguchi H. Phase I study of CPT-11 plus S-1 in patients with metastatic gastric cancer. *Proc Am Soc Clin Oncol* 2002; **21**:170. abstr 677.
4 Komatsu y, Takeda H, Takei M, Kato T, Tateyama M, Miyagishima T. Phase I and PK study of S-1 and irinotecan (CPT-11) in patients with advanced gastric cancer (AGC). *Proc Am Soc Clin Oncol* 2002; **21**:171. abstr 683.
5 Inokuchi M, Yamashita T, Yamada H, Kojima K, Ichikawa W, Nihei Z, *et al.* Phase I/II study of S-1 combined with irinotecan for metastatic advanced gastric cancer. *Br J Cancer* 2006; **94**:1130–1135.
6 Koizumi W, Kurihara M, Nakano S, Hasegawa K. Phase II study of S-1, a novel oral derivative of 5-fluorouracil, in advanced gastric cancer. For the S-1 Cooperative Gastric Cancer Study Group. *Oncology* 2000; **58**:191–197.
7 Sakata Y, Ohtsu A, Horikoshi N, Sugimachi K, Mitachi Y, Taguchi T. Late phase II study of novel oral fluoropyrimidine anticancer drug S-1 (1 mol/l tegafur-0.4 mol/l gimestat-1 mol/l otastat potassium) in advanced gastric cancer patients. *Eur J Cancer* 1998; **34**:1715–1720.
8 Bergh J, Wiklund T, Erikstein B, Lidbrink E, Lindman H, Malmstrom P, *et al.* Tailored fluorouracil, epirubicin, and cyclophosphamide compared with marrow-supported high-dose chemotherapy as adjuvant treatment for high-risk breast cancer: a randomised trial. Scandinavian Breast Group 9401 study. *Lancet* 2000; **356**:1384–1391.
9 Takahashi Y, Mai M, Sawabu N, Nishioka K. A pilot study of individualized maximum repeatable dose (iMRD), a new dose finding system, of weekly gemcitabine for patients with metastatic pancreas cancer. *Pancreas* 2005; **30**:206–210.
10 Simon R, Wittes RE, Ellenberg SS. Randomized phase II clinical trials. *Cancer Treat Rep* 1985; **69**:1375–1381.
11 Takahashi Y, Sakamoto J, Takeuchi T, Mai M, Kubota T, Kitajima M, *et al.* A randomized phase II clinical trial of tailored CPT-11 + S-1 versus S-1 in patients with advanced or recurrent gastric carcinoma as the first line chemotherapy. *Jpn J Clin Oncol* 2004; **34**:342–345.
12 Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma-2nd English edition. *Gastric Cancer* 1998; **1**:10–24.

13 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, *et al.* New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; **92**:205–216.
14 Trotti A, Byhardt R, Stetz J, Gwede C, Corn B, Fu K, *et al.* Common toxicity criteria: version 2.0. An improved reference for grading the acute effects of cancer treatment: impact on radiotherapy. *Int J Radiat Oncol Biol Phys* 2000; **47**:13–47.
15 Takahashi Y, Yamashita K, Kitakata H, Mai M. A new dose finding system in chemotherapy for solid tumors–individualized maximum repeatable dose (iMRD) of weekly gemcitabine for metastatic pancreas cancer. *Proc Am Soc Clin Oncol* 2003; **22**:303. abstr 1217.
16 Imamura H, Ilishi H, Tsuburaya A, Hatake K, Imamoto H, Esaki T, et al. Randomized phase III study of irinotecan plus S-1 (IRIS) versus S-1 alone as first-line treatment for advanced gastric cancer (GC0301/TOP-002). Presented at the 2008 Gastrointestinal Cancers Symposium, Orlando, FL, January 15-17, 2008; 2008. p. abstr 5.
17 Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, *et al.* S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. *Lancet Oncol* 2008; **9**:215–221.