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Phase II Clinical Trial of Postoperative S-1 Monotherapy for Gastric Cancer Patients with Free Intraperitoneal Cancer Cells Detected by Real-Time RT-PCR

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Abstract

Background We have previously reported the molecular detection of peritoneal micrometastases in patients with gastric cancer by quantifying carcinoembryonic antigen (CEA) mRNA in the peritoneal washes. Patients with CEA mRNA exceeding a cutoff value have a significant risk for developing peritoneal carcinomatosis, but optimal treatment for this population remains unknown.

Methods CEA mRNA (+) patients with gastric cancer were treated postoperatively with S-1 monotherapy. Overall survival, the primary endpoint of this phase II trial, was compared with the historical control, which is comprised of CEA mRNA (+) patients who were not given postoperative chemotherapy.

Results A total of 32 patients with CEA mRNA (+) gastric cancer were enrolled. Twelve patients (37.5%) relapsed; ten showed peritoneal relapse. Three-year survival was similar between the study population and the historical control (67.3% vs. 67.1%, respectively).

Conclusions S-1 monotherapy, which significantly reduced risk for recurrence in stage II/III gastric carcinoma in another phase III trial, seems not to be as effective in eradicating free cancer cells in the abdominal cavity.

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Gastric cancer is the second-most common cause of cancer death worldwide, and peritoneal carcinomatosis represents the most common route of tumor dissemination in patients with this disease [1–3]. This pathology is most likely caused by the presence of metastatic free cancer cells exfoliated from serosal surfaces of the primary cancer. We previously reported the detection of peritoneal micrometastases by reverse-transcriptase polymerase chain reaction (RT-PCR) analysis of peritoneal wash samples using carcinoembryonic antigen (CEA) mRNA as a target [3–7]. In these studies, CEA mRNA values correlated with depth of tumor invasion (pT category), and both overall survival and survival free from peritoneal relapse were significantly inferior among the CEA mRNA (+) patients. Several experimental studies have shown that micrometastases are more sensitive to chemotherapy compared with macrometastases [8–10]. Accordingly, micrometastasis detected by CEA RT-PCR could represent an important target of therapy.

Meta-analyses have suggested that adjuvant chemotherapy is effective in treating gastric cancer, but no definitive conclusion had been reached in the early 2000s regarding the efficacy of postoperative adjuvant chemotherapy for gastric-cancer patients treated with D2-lymphadenectomy [11]. S-1 (Taiho Pharmaceutical, Tokyo, Japan) is an orally active combination of tegafur (a prodrug converted by cells into fluorouracil), gimeracil (an inhibitor of dihydropyrimidine dehydrogenase, which degrades fluorouracil), and oteracil (which inhibits phosphorylation of

fluorouracil in the gastrointestinal tract, thereby reducing gastrointestinal toxic effects of fluorouracil) in a molar ratio of 1:0.4:1 [12]. Response rates for S-1 monotherapy exceeded 40% in two late phase II trials, which involved patients with advanced or recurrent gastric cancer [13, 14]. Toxicity profile was moderate, and use in the postoperative adjuvant setting was considered feasible [15]. We therefore initiated a phase II trial of postoperative S-1 therapy for patients with CEA mRNA (+) gastric cancer.

A total of 32 patients with CEA mRNA(+) gastric cancer had been enrolled by the middle of 2006, when postoperative S-1 therapy was shown to improve significantly the prognosis for patients with stage II/III gastric cancer compared with observation alone in a pivotal phase III study [16]. Because most CEA mRNA (+) patients would have been categorized as stage II/III if RT-PCR had not been performed and would thus be treated by S-1 anyway, the trial was closed and survival data were analyzed after all patients had been followed for 12 months or more.

Patients and methods

Eligibility criteria

Patients entered into this study were required to fulfill the following eligibility criteria: (1) previously untreated patients with histologically proven adenocarcinoma; (2) between 20 and 80 years old; (3) Eastern Cooperative Oncology Group performance status (PS) of 2 or less; (4) treated with R0 resection of the primary lesion, and showing no distant or peritoneal metastases on preoperative imaging or at laparotomy; (5) no tumor cells in peritoneal fluid on routine cytological examination through Papanicolaou staining; (6) positive free cancer cells in the abdominal cavity detected through CEA RT-PCR; (7) adequate organ function (leukocyte count 3,000/mm^3; platelet count 100,000/mm^3; hemoglobin 8.0 g/dl; total bilirubin 1.5 mg/dl; aspartate aminotransferase and alanine aminotransferase levels 2.5 times the upper limit of the normal range; and serum creatinine no greater than the upper limit of the normal range); and (8) life expectancy >3 months. Written informed consent was obtained from all patients, and the study protocol was approved by the institutional review board.

Peritoneal washing

Aliquots of 100–200 ml of saline were introduced into the Douglas cavity and left subphrenic space at the beginning of each operation and aspirated shortly after gentle agitation. Half of each wash was sent for routine cytopathology with conventional Papanicolaou staining and the other half was used to measure CEA mRNA levels. Intact cells collected from washes by centrifugation at 1,800 rpm for 5 min were rinsed with phosphate-buffered saline (PBS), dissolved in ISOGEN-LS RNA extraction buffer (Nippon Gene, Tokyo, Japan), and stored at −80°C.

Real-time quantitative RT-PCR

Frozen samples in ISOGEN-LS were thawed and total RNA was extracted using guanidinium isothiocyanate–phenol–chloroform, then cDNA was synthesized from total RNA using SuperScript II RNase H^- reverse transcriptase (Invitrogen, Carlsbad, CA, USA) according to the instructions of the manufacturer. The resultant first-strand cDNA was stored at −80°C until analysis. Single-step real-time RT-PCR for CEA mRNA was performed using CEA-specific oligonucleotide primers and two fluorescent hybridization probes on a LightCycler instrument (Roche Diagnostics, Mannheim, Germany), as described previously [5, 7]. To quantify and confirm the integrity of the isolated RNA, glyceraldehyde-3-phosphate dehydrogenase (GAPDH) also was analyzed by real-time RT-PCR using the appropriate primers and hybridization probes. All primers and probes were synthesized and purified by reverse-phase high-performance liquid chromatography at Nihon Gene Research Laboratories (Sendai, Japan). Six external CEA mRNA standards were prepared by tenfold serial dilution (1–10^5 cells) of cDNA equivalent to 1×10^6 COLM-2 cells (a colon cancer cell line that expresses large amounts of CEA) spiked into 1×10^7 peripheral blood leukocyte. Each run comprised six external standards, a negative control without a template, and patient samples with unknown mRNA concentrations. The amount of mRNA in each sample was then automatically measured by reference to the standard curve constructed each time on the LightCycler software. CEA mRNA was quantified in each patient using the peritoneal washing samples from Douglas cavity and subphrenic space. If at least one CEA mRNA value from the two washes was above the cutoff value (>0.1), the patient was considered as CEA mRNA (+). The cutoff value had been selected by the authors to maximize the sensitivity for detection of peritoneal micrometastasis. This cutoff value was then validated using an independent set of patients in the previous study [4].

Study design and treatment

The primary endpoint of the trial was overall survival, and secondary endpoints were peritoneal recurrence-free survival and the safety profile of S-1. Patients were to receive two oral doses of S-1 at 40 mg/m^2 per day for 4 weeks, followed by 2 weeks of no chemotherapy. This 6-week cycle was to be repeated throughout the first year after

surgery and was to be evaluated as effective if 3-year survival was shown to be higher than that of historical controls. The historical control was comprised of 58 patients who had CEA mRNA >0.1 at Aichi Cancer Center between 1995 and 2000 and were given no postoperative adjuvant chemotherapy. The sample size was calculated as 40 to confirm that the lower limit of the 95% confidence interval (CI) for 3-year survival among the study population exceed 65%, which is the 3-year survival proportion for historical control. The survival curve was estimated using Kaplan–Meier methods. Patients were to be followed up for 3 years postoperatively. Differences between curves were evaluated by log-rank testing. Adverse events were assessed according to the Common Toxicity Criteria of the National Cancer Institute (version 2.0).

Postoperative surveillance

The follow-up program consisted of interim history, physical examination, hematology, and blood chemistry panels including tests for CEA and CA19-9, performed every 3 months for 2 years. Computed tomography was performed every 6 months. Peritoneal recurrence, evident on the basis of clinical symptoms, digital examination, and physical and radiologic findings of bowel obstruction and ascites, was confirmed by paracentesis, laparotomy, and autopsy performed at the discretion of the surgeon.

Results

Patient demographics

Thirty-two patients with gastric cancer with CEA mRNA (+) status (23 men, 9 women) who underwent R0 surgery were registered between September 2003 and April 2006 at Aichi Cancer Center Hospital. Median duration of follow-up was 31.5 months after surgery (minimum 16.2 months, and maximum 51.4 months). Characteristics of the 32 patients with CEA mRNA (+) gastric cancer are summarized in Table 1. Mean age was 57.8 years (minimum 35 years, and maximum 75 years). Serosal invasion and lymph node metastasis was observed in 24 patients (75%) and 23 patients (71.9%), respectively. T1-stage patients and macroscopic type 0 (gross finding suggestive of early stage cancer) were more frequent among the control group, but other characteristics showed similar distributions.

Table 1 Baseline characteristics of the patients

	S-1 adjuvant ($n = 32$)	Control ($n = 58$)	P value
Age (year)	57.8	58.4	0.83
Gender			
M	23	39	0.81
F	9	19	
Location			
L	11	16	0.07
M	18	24	
U	3	18	
Macroscopic type			
0	1	15	0.01
1	2	0	
2	5	12	
3	19	19	
4	5	12	
Operative procedure			
Total	9	25	0.23
Proximal	0	1	
Distal	23	32	
Lymph node dissection			
≤D1	2	3	NS
≥D2	30	55	
Depth of invasion			
T1	1	15	<0.01
T2	7	13	
T3	23	20	
T4	1	10	
Lymph node metastases			
N0	9	18	0.25
N1	11	11	
N2	12	29	
Histological type			
pap	0	1	0.10
tub1	2	1	
tub2	5	16	
por1	3	5	
por2	20	27	
sig	0	7	
muc	0	1	
Other	2	0	

NS not significant, *pap* papillary adenocarcinoma, *tub1* well differentiated tubular adenocarcinoma, *tub2* moderately differentiated tubular adenocarcinoma, *por1* poorly differentiated adenocarcinoma solid type, *por2* poorly differentiated adenocarcinoma non-solid type, *sig* signet-ring cell carcinoma, *muc* mucinous adenocarcinoma

Overall survival and peritoneal recurrence-free survival

No significant difference in survival curves was identified between the study population and the historical control ($P = 0.46$; Fig. 1). Twelve patients (37.5%) relapsed, including 10 patients with peritoneal relapse (Table 2). Two-year survival proportion was 93.5% in the S-1 adjuvant chemotherapy group as opposed to 77.6% in the

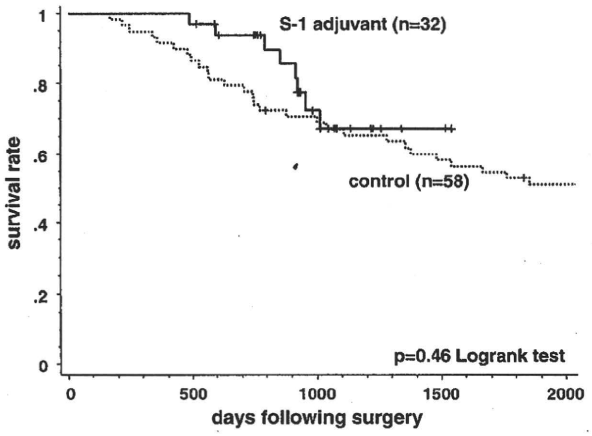

Fig. 1 Overall survival curve of patients with S-1 adjuvant therapy and historical controls. Three-year survival rates were comparable between groups. The difference in survival curves was not significant ($P = 0.46$; log-rank test)

Table 2 Site of first relapse, according to treatment group

Site	S-1 adjuvant ($n = 32$)		Control ($n = 58$)	
No. of relapses	12	(37.5%)	31	(53.4%)
Local	0	(0.0%)	4	(6.9%)
Lymph nodes	2	(6.3%)	14	(24.1%)
Peritoneum	10	(31.3%)	24	(41.4%)
Hematogenous	2	(6.3%)	7	(12.1%)

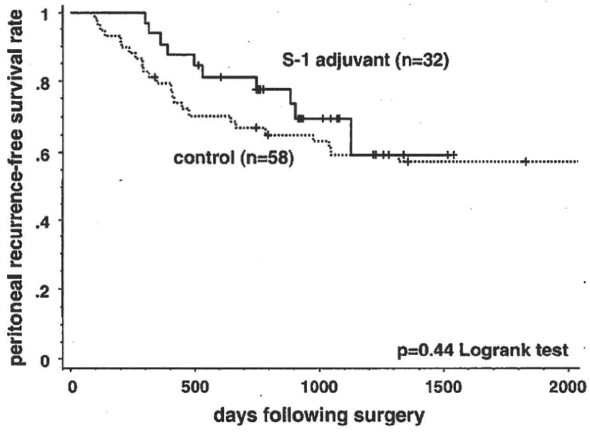

Fig. 2 Peritoneal recurrence-free survival curve of patients with S-1 adjuvant treatment and historical controls. Survival of the S-1 adjuvant group tended to be slightly favorable, but this was not significant ($P = 0.44$; log-rank test)

historical control group, but the difference was nullified by 3 years after surgery (67.3% vs. 67.1%, respectively). The difference in peritoneal recurrence-free survival curves was not significant ($P = 0.44$; Fig. 2).

Discussion

A significant survival benefit of postoperative adjuvant chemotherapy with S-1 was demonstrated for stage II/III gastric cancer in the ACTS-GC study [16]—a pivotal phase III trial comparing surgery followed by 1 year of S-1 monotherapy with surgery alone. In that study, peritoneal relapse was observed in 143 of 1,059 patients enrolled, representing the most frequent site of relapse. Peritoneal dissemination is considered to arise from free cancer cells in the peritoneal cavity exfoliated from the serosal surface of the stomach after penetration by the primary tumor. Patients with free cancer cells detectable through conventional cytological examination (CY1) had not been eligible for that trial. This suggests that conventional cytological examination lacks sensitivity and fails to detect minute quantities of free cancer cells. Our previous study revealed that RT-PCR mediated detection of CEA mRNA in the peritoneal washes offers a more sensitive tool to detect subgroups of patients at high risk for peritoneal relapse [3–5, 7, 17] and could be a powerful tool in selecting patients for postoperative adjuvant therapy.

There are several reports describing the detection of minimal residual disease in gastric cancer using peritoneal washes and other body fluids, using both RT-PCR based and other techniques [18]. Of these, studies using peritoneal washes had been the most successful. CEA had been the commonest target, but false-positive cases have often been an issue, given that the expression of CEA is not confined to cancer cells. Use of multiple markers combining highly specific molecules and use of microarray tips would eventually minimize this problem [19]. Analysis of other samples, such as peripheral blood and bone marrow aspirates, have led to inconsistent results and had been less convincing as prognostic markers for gastric cancer [20, 21]. We have shown again in the current study that a CEA mRNA (+) population who are negative for conventional cytology (CY0) exists and has a risk for peritoneal carcinomatosis. Survival of our 32 patients was shown not to be dismal compared with CY1 patients [22] or those with stage IV disease in general, however. The notion that CEA RT-PCR may be useful to identify patients who are not indicated for surgery [23] could be challenged by the opinion that the CY0/CEA mRNA(+) population may benefit from adequate multimodal treatments.

Needless to say, a one-arm phase II study comparing survival data with a historical control is seriously flawed. Because the study involved CEA RT-PCR, which is not commercially available, a single institutional study was the only feasible option. Given the low incidence of CY0/CEA mRNA (+) patients, a more sophisticated study design had been considered unrealistic. Of note is that S-1, irinotecan, and taxanes were available by the time patients in the

historical control group relapsed. Thus, most patients in the control group were treated by essentially the same anticancer drugs in the same sequence, and the major difference between the current phase II patients and the historical control was whether chemotherapy had been started immediately after surgery or after relapse. Whereas the current trial was ongoing, CEA mRNA in the peritoneal washes also had been quantified in several patients outside of the trial as referent data. Some of CEA mRNA (+) patients were not treated with S-1 because they were allocated to the surgery alone group in another trial or did not wish to be registered to the present study. The 3-year survival proportion of these 11 cases was 63.6%, equivalent to the historical control of our study.

In the recent phase III trial, postoperative S-1 led to significant improvements in overall and relapse-free survival over observation alone at the first interim analysis and became a standard of care for stage II/III gastric cancer in Japan. Because the CY0/CEA mRNA(+) population, the target of the current study, mostly fall into the same stage II/III category, exploring the efficacy of identical treatment in this particular population seemed to have lost meaning, and we decided to close the trial. However, it remains unclear whether the improved survival of the interventional group as observed in the interim analysis eventually leads to cure of the corresponding number of patients or just a delay in relapse. In the present study, although more patients were alive at an earlier phase of follow-up compared with historical controls, the fates of patients at 3 years after surgery were basically identical. This suggests that gastric cancer relapse, at least in a high-risk population identified through CEA RT-PCR, is only delayed by S-1 monotherapy; not cured.

The specificity of CEA RT-PCR in detecting peritoneal relapse was 81.6% and occasional false-positive results were deemed unavoidable [24]. In the current analysis, 15 pathologically T1-stage cancers were included in the control group and 1 T1 cancer was identified in the treatment group. This difference is due to characteristics of patients between the control and treatment groups. We rarely examined lavage cytology nor CEA mRNA test in surgically T1 patients after the time of treatment group, because our previous analysis showed uselessness of CEA mRNA detection in pT1 patients. After analyzing only surgical T3 patients, no significant difference in survival curves was identified between the study population and the historical control ($P = 0.18$; Fig. 3). The difference in peritoneal recurrence-free survival curves was not significant ($P = 0.27$; Fig. 4). Considering that the rate of risk reduction was lower among stage IIIB than among stage II in the ACTS-GC trial, there is a potential need for more powerful chemotherapy than S-1 for high-risk populations among those who are eligible for postoperative adjuvant

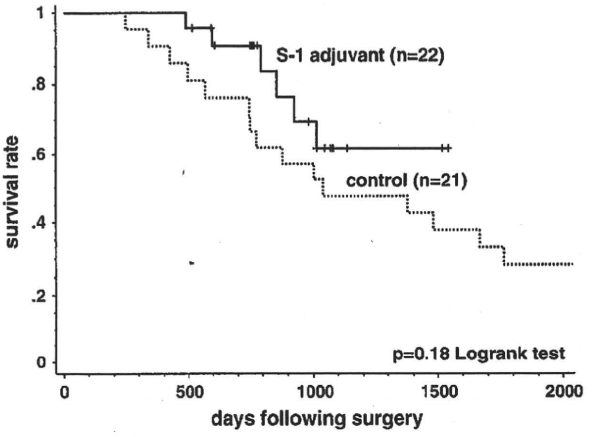

Fig. 3 Overall survival curve of surgical T3 patients with S-1 adjuvant treatment and historical controls. Survival of the S-1 adjuvant group tended to be slightly favorable, but this was not significant ($P = 0.18$; log-rank test)

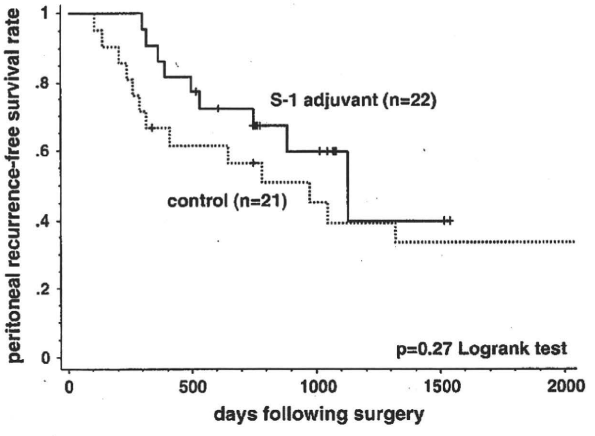

Fig. 4 Peritoneal recurrence-free survival curve for surgical T3 patients with S-1 adjuvant therapy and historical controls. Survival of the S-1 adjuvant group tended to be slightly favorable, but was not significant ($P = 0.27$; log-rank test)

therapy. Results of the current study reinforce the notion that S-1 monotherapy may be insufficient for some high-risk patients.

To combat peritoneal micrometastasis, sequential use of paclitaxel and S-1 or UFT (tegafur and uracil) is currently being explored in another pivotal phase III trial using a 2 × 2 factorial design with S-1 or UFT monotherapy as active controls [25]. Furthermore, the feasibility of S-1 combined with cisplatin or taxotere has been tested in the postoperative adjuvant setting. However, addition of cytotoxic agents to S-1 may lead to increased frequencies of adverse events, leading to poor compliance. Conversely, intraperitoneal administration of anticancer drugs has the theoretical advantage of exposing higher levels of

anticancer agents with lower systemic doses [26]. Indeed, a recent study [27] showed that adjuvant chemotherapy containing intraperitoneal cisplatin significantly improved RFS and OS in patients with grossly serosa-positive advanced gastric cancer. The pharmacokinetic and therapeutic advantages of paclitaxel when administered intraperitoneally have been well documented for gastric cancer as well [28, 29]. Studies to improve the cure rate among high-risk subsets of stage II/III patients using a combination of S-1 with other drugs or modalities are warranted.

Conclusions

Adjuvant chemotherapy with S-1 may delay cancer relapse but does not always eradicate micrometastases in the abdominal cavity. More effective treatments, possibly directed toward peritoneal micrometastasis, could be proposed to treat high-risk subsets of curatively resected gastric cancer, and CEA RT-PCR might be used to identify these high-risk patients.

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Conflict of interest There are no conflicts of interest to report.

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ORIGINAL ARTICLE

Randomized phase III study comparing the efficacy and safety of irinotecan plus S-1 with S-1 alone as first-line treatment for advanced gastric cancer (study GC0301/TOP-002)

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Abstract
Background Irinotecan hydrochloride and S-1, an oral fluoropyrimidine, have shown antitumor activity against advanced gastric cancer as single agents in phase I/II studies. The combination of irinotecan and S-1 (IRI-S) is also active against advanced gastric cancer. This study was conducted to compare the efficacy and safety of IRI-S versus S-1 monotherapy in patients with advanced or recurrent gastric cancer.
Methods Patients were randomly assigned to oral S-1 (80 mg/m^2 daily for 28 days every 6 weeks) or oral S-1 (80 mg/m^2 daily for 21 days every 5 weeks) plus irinotecan (80 mg/m^2 by intravenous infusion on days 1 and 15 every 5 weeks) (IRI-S). The primary endpoint was overall survival. Secondary endpoints included the time to treatment failure, 1- and 2-year survival rates, response rate, and safety.
Results The median survival time with IRI-S versus S-1 monotherapy was 12.8 versus 10.5 months ($P = 0.233$), time to treatment failure was 4.5 versus 3.6 months ($P = 0.157$), and the 1-year survival rate was 52.0 versus 44.9%, respectively. The response rate was significantly higher for IRI-S than for S-1 monotherapy (41.5 vs. 26.9%, $P = 0.035$). Neutropenia and diarrhea occurred more frequently with IRI-S, but were manageable. Patients treated with IRI-S received more courses of therapy at a relative dose intensity similar to that of S-1 monotherapy.
Conclusions Although IRI-S achieved longer median survival than S-1 monotherapy and was well tolerated, it did not show significant superiority in this study.

Keywords Irinotecan S-1 · Gastric cancer · Phase III · Randomized controlled trial

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Introduction

Gastric cancer is the second leading cause of cancer-related deaths after lung cancer in Japan, and it was responsible for approximately 50,000 deaths in 2005 [1]. While surgery and appropriate adjuvant chemotherapy have resulted in superior stage-by-stage survival when compared with that in other parts of the world [2], the prognosis of unresectable or recurrent gastric cancer remains dismal. The development of more effective chemotherapeutic regimens is therefore warranted.

In Western countries where a combination of 5-fluorouracil (5-FU) and cisplatin (CDDP) [3] has served as a reference arm in several phase III studies [4–6], triplets employing epirubicin [7] or docetaxel [5] in addition to this combination are the current standards, with modifications such as the replacement of CDDP with oxaliplatin and the replacement of infusional 5-FU with oral agents such as capecitabine [8]. Failure with the first-line treatment usually denotes the termination of chemotherapy, and second-line treatments are rarely considered outside of clinical trials. In Japan, where a phase III study (JCOG9205) failed to show superiority of a 5-FU/CDDP combination over 5-FU alone [9], the 5-FU monotherapy remained a standard of care, and other cytotoxic agents were usually delivered sequentially as second-line and third-line therapies rather than concurrently as combination therapy. With this strategy, the median survival time (MST) of patients with advanced gastric cancer whose treatment started with infusional 5-FU alone actually reached 10.8 months [9].

In the 1990s, S-1 (TS-1; Taiho Pharmaceutical, Tokyo, Japan), an oral derivative of 5-FU, was developed for the treatment of gastric cancer [10–12]. With an exceptionally high response rate of 46% as a single agent, this drug rapidly established itself as a community standard in Japan and was used widely in clinical practice. Phase III trials eventually proved the non-inferiority of S-1 when compared with infusional 5-FU in the advanced/metastatic setting [13], along with the superiority of S-1 monotherapy over observation alone in the postoperative adjuvant setting [14]. In addition, S-1 was found to be a unique cytotoxic drug, in that Japanese patients tolerated higher doses than Western patients, due to differences in the gene polymorphism of relevant enzymes [15]. Thus, the development of novel chemotherapeutic regimens in Japan during the 2000s has inevitably centered around this drug.

The establishment of doublets to enhance response rates and improve on survival was the next important step, and several phase I/II studies were performed to explore combinations of S-1 with other cytotoxic drugs such as CDDP [16], docetaxel [17], paclitaxel [18], and irinotecan (Yakult Honsha, Tokyo, Japan; Daiichi Sankyo, Tokyo, Japan) [19]. All these combinations were found to be promising, with response rates of around 50% and relatively favorable safety profiles. A series of phase III trials comparing these doublets with S-1 monotherapy were subsequently planned and conducted to seek optimal first-line treatments. Of these, a phase III trial to explore S-1/CDDP was the first to complete accrual, and a significant improvement in MST of this combination over S-1 monotherapy was proven [20]. The present study, entitled GC0301/TOP-002, represents another of these attempts, exploring the efficacy of a combination of S-1 and irinotecan (IRI-S). The dose and schedule for this combination had been established by a phase I trial [21], and treatment at the recommended dose has shown a response rate of 47.8% [95% confidence interval (CI) 27.4–68.2%] with an MST of 394 days in a phase II study [19]. Given these earlier results and the synergistic effect of irinotecan and 5-FU observed in preclinical studies, the results of this present trial have been eagerly awaited.

Patients and methods

Eligibility

The eligibility criteria were histologically and cytologically confirmed unresectable or recurrent gastric adenocarcinoma; oral food intake possible; age between 20 and 75 years; no prior radiotherapy or chemotherapy; expected survival for $\geq$12 weeks; Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; and adequate major organ function before chemotherapy (leukocyte count of 4,000–12,000/mm^3, hemoglobin $\geq$ 8.0 g/dl, platelet count $\geq$ 100,000/mm^3, total bilirubin $\leq$ 1.5 mg/dl, aspartate aminotransferase $\leq$ 100 IU/l, alanine aminotransferase $\leq$ 100 IU/l, creatinine $\leq$ 1.2 mg/dl). The main exclusion criteria were massive ascites, active concomitant malignancy, uncontrolled diabetes mellitus, and pregnancy or breast-feeding. Written informed consent was obtained from each patient. Institutional review board approval was obtained at each participating institution. An independent data monitoring committee evaluated safety throughout this study. The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. This trial was registered with the Japan Pharmaceutical Information Center (JapicCTI-050083).

Treatment schedule

In the S-1 monotherapy group, patients received oral S-1 twice daily for 28 days every 6 weeks. In the IRI-S group, S-1 (80 mg/m^2) was given orally for 21 days and irinotecan (80 mg/m^2) was infused intravenously on days 1 and 15 every 5 weeks. In both groups, the dose of S-1 was

based on body surface area: 40 mg if the area was <1.25 m^2; 50 mg for 1.25–1.5 m^2, and 60 mg for ≥1.5 m^2. Dose modification criteria were defined in the protocol. Treatment was discontinued if there was documented disease progression, unacceptable toxicity, or withdrawal of consent.

Assessment of response and toxicity

All patients who had at least one measurable lesion were evaluated for tumor response according to the Response Evaluation Criteria in Solid Tumors (RECIST) [22]. All radiologic assessments were confirmed by extramural review. Toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria (version 2.0).

Statistical analysis

Eligible patients were registered with the data center and randomized by centralized dynamic allocation with stratification for advanced/recurrent disease (with or without adjuvant chemotherapy), performance status (0/1/2), and institution. The full analysis set was defined as all patients who received treatment at least once and met all inclusion criteria. The per-protocol set was defined as all patients who received treatment at least once and had no major protocol violations.

The primary endpoint was overall survival, which was compared between groups using the stratified log-rank test. Secondary endpoints were the time to treatment failure (TTF), the 1- and 2-year survival rates, the response rate, and safety. Overall survival time was defined as the interval from the date of registration to the date of death (patients who remained alive at the final follow-up were censored at that time). Survival curves were estimated by the Kaplan–Meier method, and differences were analyzed with the stratified log-rank test. Hazard ratios (HRs) for various prognostic factors were calculated using a stratified Cox proportional hazards model. TTF was defined as the time from the date of registration to the date of detection of progressive disease, death, or treatment discontinuation.

In addition, subset analyses were conducted, using the Cox proportional hazards model, to identify factors that influenced overall survival in each group. As well as the predetermined variables such as gender, age, performance status, and disease status (whether the disease was unresectable or recurrent), subset analyses were conducted for 6 additional variables; the presence or absence of a measurable lesion by the RECIST, hepatic metastasis, peritoneal metastasis, existent of primary focus, metastasis the number of metastatic foci, and tumor histology. All analyses were performed using SAS system version 8.2 (SAS Institute, Cary, NC, USA).

This study was designed to detect a 40% improvement in MST at a two-tailed significance level of $P \leq 0.05$ with 80% power. The MST for S-1 monotherapy was assumed to be 8.5 months, based on the results of previous phase I/II studies [12, 23]. A total of 142 patients per group were required according to calculations made with nQuery Advisor version 4.0 (Statistical Solutions, Boston, MA, USA), and the sample size was set as 300 (150 patients per group).

We initially planned to continue follow-up for ≥1.5 years after the registration of all patients, with a cut-off date of April 2007. However, an unexpectedly high survival rate of 22% (68 of 315 patients) at the cut-off date prompted the Coordinating Committee, the medical expert, and the biostatistician to advise the sponsor to continue follow-up for a further year before performing the final analysis. Thus, the MST was also calculated using 2.5-year follow-up data.

Results

Patient characteristics

Between June 2004 and November 2005, a total of 326 patients (S-1 monotherapy, $n = 162$; IRI-S, $n = 164$) were enrolled from 54 institutions and randomized (Fig. 1). Seven patients were subsequently found to be ineligible or withdrew before receiving any treatment. Another 4 patients were found to be ineligible after starting treatment and were not included in the analysis. Therefore, 315 patients (S-1 monotherapy, $n = 160$; IRI-S, $n = 155$) were evaluable and were included in the full analysis set to assess overall survival and TTF. In addition, 187 patients were evaluable for tumor response. Baseline patient characteristics are shown in Table 1.

Treatments given

The median number of treatment courses was three (range 1–19) for S-1 monotherapy whose duration was 6 weeks, and four (range 1–25) for IRI-S whose duration was 5 weeks. The main reasons for treatment discontinuation were disease progression [S-1 monotherapy vs. IRI-S, 116/160 (72.5%) vs. 89/155 (57.4%)], adverse events [12/160 (7.5%) vs. 23/155 (14.8%)], attending physician's decision [18/160 (11.3%) vs. 18/155 (11.6%)], and consent withdrawal [11/160 (6.9%) vs. 17/155 (11.0%)]. The median TTF was 3.6 months (95% CI 2.9–4.1) and 4.5 months (95% CI 3.7–5.3), respectively ($P = 0.157$). The relative dose intensity was 88.9% for S-1 monotherapy, versus 90.0% for S-1 and 86.2% for irinotecan

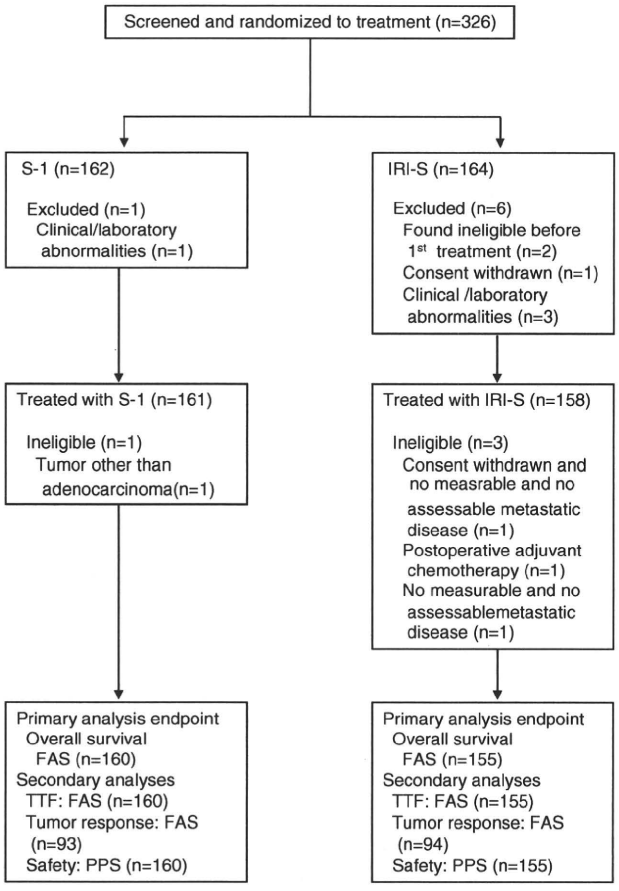

Fig. 1 Patient disposition. *FAS* Full analysis set, *IRI-S* S-1 plus irinotecan, *PPS* per-protocol set, *TTF* time to treatment failure

among those treated with IRI-S. Most patients in both groups received the scheduled dose of chemotherapy.

Second-line chemotherapy was administered to 240 patients (76%; S-1 monotherapy, $n = 112$; IRI-S, $n = 128$) (Table 2). The most common second-line therapy in both groups was a taxane alone (S-1 monotherapy, 26.9%; IRI-S, 40.6%). Among patients initially treated with S-1, 13 received crossover treatment with IRI-S, while 31 patients originally treated with IRI-S received second-line S-1 monotherapy.

Response and survival

The overall response rate was determined in 187 patients evaluable by the RECIST, and was significantly higher with IRI-S than with S-1 monotherapy (39/94, 41.5% vs. 25/93, 26.9%; $P = 0.035$) (Table 3).

The MST at the predetermined cut-off date was 12.8 months with IRI-S compared with 10.5 months with S-1 monotherapy (HR 0.856, $P = 0.233$) (Fig. 2), but the difference was not statistically significant. The 1-year survival rates were 44.9% [95% CI 37.2–52.6%] with S-1 monotherapy and 52.0% (95% CI 44.1–59.9%) with IRI-S, while the 2-year survival rates were 19.5% (95% CI 12.6–26.4%) and 18.0% (95% CI 11.2–24.8%), respectively.

MST was additionally calculated as an exploratory analysis after 2.5 years of follow-up, but the result was identical to the initial analysis at 12.8 months for IRI-S and at 10.5 months for S-1 monotherapy (HR 0.927; log-rank test $P = 0.536$). Again, the difference was not statistically significant.

Table 1 Baseline characteristics and prior therapy

Characteristic	Treatment					
	S-1		IRI-S		Total	
	n	%	*n*	%	*n*	%
Patients randomized	162		164		326	
Patients receiving at least one dose of study medication (full analysis set)	160		155		315	
Sex						
Male	127	79	110	71	237	75
Female	33	21	45	29	78	25
Age (years)						
Median	63		63		63	
Range	27–75		33–75		27–75	
ECOG performance status						
0	109	68	102	66	211	67
1	46	29	48	31	94	30
2	5	3	5	3	10	3
Tumor histology						
Intestinal	71	44	61	39	132	42
Diffuse	88	55	93	60	181	57
Other	1	1	1	1	2	1
Resection of primary tumor						
+	93	58	93	60	186	59
−	67	42	62	40	129	41
Advanced	133	83	129	83	262	83
Recurrent						
Adjuvant chemotherapy (+)	5	3	5	3	10	3
Adjuvant chemotherapy (−)	22	14	21	14	43	14

IRI-S S-1 plus irinotecan, *ECOG* Eastern Cooperative Oncology Group

Prognostic factors of all patients and factors that favored treatment with IRI-S

Baseline risk factors with a significant influence on the overall survival of all patients accrued ($P < 0.05$) were performance status (HR 1.348, 95% CI 1.079–1.686, Wald test $P = 0.009$), tumor histology (HR 1.720, 95% CI

Table 2 Second-line chemotherapy

Regimen	S-1 ($n = 160$)		IRI-S ($n = 155$)	
	n	%	*n*	%
IRI-S	13	8.1	–	–
Irinotecan-based regimen[a]	27	16.9	4	2.6
S-1 alone	–	–	31	20.0
S-1-based regimen[b]	9	5.6	11	7.1
Taxane alone	43	26.9	63	40.6
Others	20	12.5	19	12.3
None	48	30.0	27	17.4

IRI-S S-1 plus irinotecan

[a] Irinotecan/cisplatin, irinotecan/taxane

[b] S-1/cisplatin, S-1/taxane

Table 3 Response to treatment

	S-1 ($n = 93$)		IRI-S ($n = 94$)	
	n	%	*n*	%
Complete response	0	0	0	0
Partial response	25	27	39	41
Stable disease	35	38	40	43
Progressive disease	30	32	12	13
Not assessable	3	3	3	3
Overall response rate	26.9		41.5*	
95% CI	18.2–37.1		31.4–52.1	

CI confidence interval

* $P = 0.035$ (χ^2 test)

1.161–2.548, $P = 0.007$), target lesion (HR 1.525, 95% CI 1.164–1.999, $P = 0.002$), and surgery for the primary tumor (HR 0.698, 95% CI 0.538–0.906, $P = 0.007$).

Stratified analysis according to baseline patient characteristics (Fig. 3) showed that IRI-S was significantly more effective than S-1 monotherapy for patients with diffuse-type histology (HR 0.632, 95% CI 0.454–0.880) and for those with an ECOG performance status of 1 or 2 (HR 0.614, 95% CI 0.401–0.940). No differences were observed for the other factors assessed.

Safety

Adverse events that occurred in each group are listed in Table 4. The incidence of major hematological toxicities was higher with IRI-S than with S-1 monotherapy. Grade 3 or 4 neutropenia was observed in 10.6% of patients treated with S-1 monotherapy versus 27.1% of patients treated with IRI-S, while the corresponding incidences of infection/febrile neutropenia were 3.8 versus 1.9%. The most common grade 3 or 4 non-hematological toxicities were diarrhea (S-1 monotherapy vs. IRI-S, 5.6 vs. 16.1%),

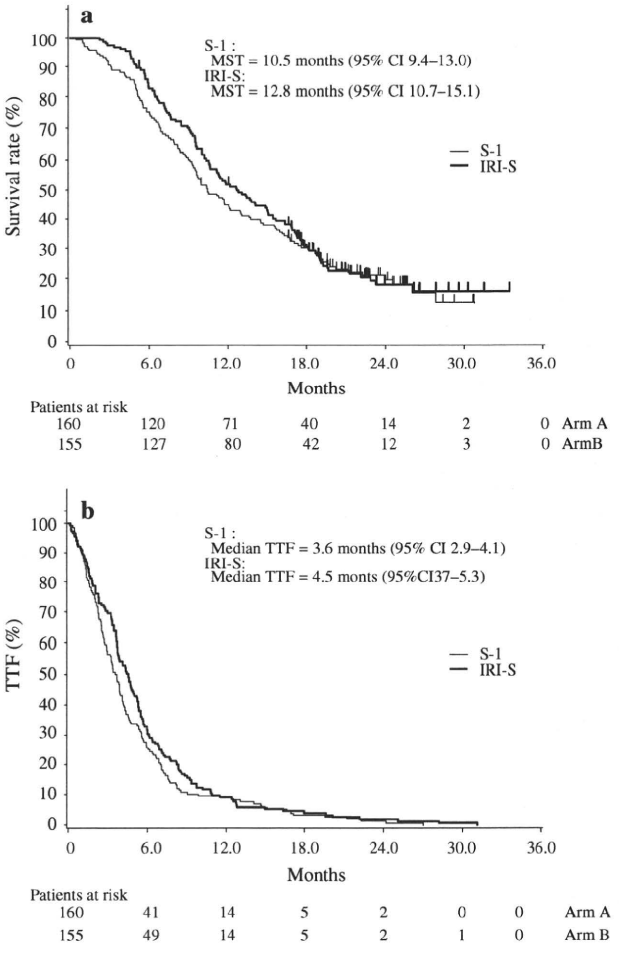

Fig. 2 Kaplan–Meier estimates of overall survival (**a**) and time to treatment failure (**b**) for 315 evaluable patients treated with S-1 monotherapy or S-1 plus irinotecan (IRI-S). *MST* Median survival time, *TTF* time to treatment failure, *CI* confidence interval

anorexia (18.8 vs. 17.4%), nausea (5.6 vs. 7.1%), and vomiting (1.9 vs. 3.2%). Hand-foot skin reaction, a characteristic adverse event associated with some oral fluoropyrimidines, was confined to grade 2 or less and was observed in only 4.4 and 5.2% of patients treated with S-1 monotherapy and IRI-S, respectively. There were no treatment-related deaths among patients treated with S-1 monotherapy, whereas two patients in the IRI-S died of potentially treatment-related conditions (severe bone marrow dysfunction, multiple organ failure that was probably associated with multiple duodenal ulcers).

Discussion

This study was conducted to determine whether IRI-S could prolong MST compared with S-1 monotherapy. Basic studies have indicated that irinotecan has a multifactorial synergistic effect with the anti-tumor activity

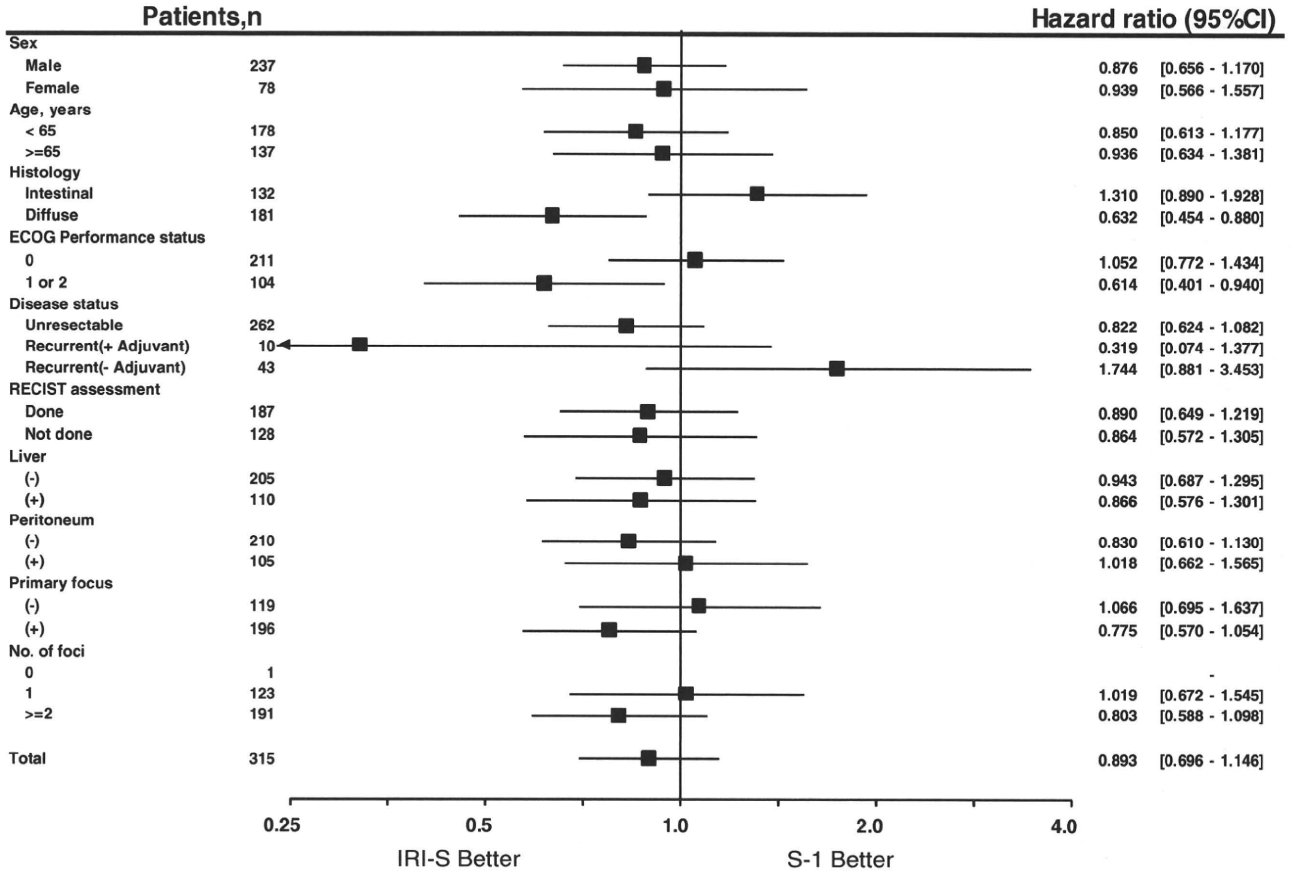

Fig. 3 Subset analysis of overall survival stratified by baseline patient characteristics. *CI* Confidence interval, *ECOG* Eastern Cooperative Oncology Group, *RECIST* Response Evaluation Criteria in Solid Tumors

of 5-FU [24, 25]. In addition, several trials exploring combinations of S-1 and irinotecan have reported promising response rates [19, 23, 26, 27]; the dose and schedule in the present study was selected based on the lower incidence of grade 3 neutropenia and gastrointestinal toxicity evidenced from phase II studies among these trials.

Although the combination therapy in the present study achieved a significantly higher response rate, the initial expectation that the addition of irinotecan would improve the MST by 40% was not met. Thus, the combination of S-1 and CDDP remains the first-line chemotherapy that can be recommended for Japanese patients, while patients who are frail or those who wish to refrain from the short stay in the hospital required for hydration could turn to S-1 monotherapy. Another standard treatment could be available pending the results of a phase III trial comparing S-1 with an S-1/docetaxel combination [17]. A combination of CDDP with 5-FU or its derivative capecitabine has been used as a platform for molecularly targeting agents in recent international trials [28]; however, the place of platinum agents in the first-line treatment of gastric cancer would seem indispensible at present.

Irinotecan has often been delivered in combination with CDDP for gastric cancer in the West [29]. This combination was also explored in Japan in a phase II trial [30] and subsequently in a phase III trial [13], but failed to show statistically significant superiority over infusional 5-FU alone. Irinotecan was more recently found to be similarly effective to CDDP when delivered with 5-FU [31], with benefit in terms of a more favorable toxicity profile. The combination then went on to be compared with a 5-FU/CDDP combination [4], but, again, failed to show a survival advantage. With similar results obtained from the present study, irinotecan-based chemotherapy would no longer be expected to surpass 5-FU or its derivatives with or without CDDP in the first-line setting.

Our stratified analysis revealed that IRI-S had a significant effect on overall survival in patients with diffuse-type histology and an ECOG performance status of 1 or 2 (Fig. 3). IRI-S was more effective in symptomatic patients. This finding may be related to its higher response rate,

Table 4 Summary of adverse events

	S-1 (n = 160)				IRI-S (n = 155)			
	All events		Grade 3/4		All events		Grade 3/4	
	n	%	n	%	n	%	n	%
Anemia	83	51.9	19	11.5	113	72.9	24	15.5
Leukopenia	83	51.9	5	3.1	115	74.2	18	11.6
Neutropenia	86	53.8	17	10.6	113	72.9	42	27.1
Infection/febrile neutropenia	28	17.5	6	3.8	40	25.8	3	1.9
Thrombocytopenia	18	11.3	6	3.8	17	11.0	2	1.3
Increased AST	75	46.9	8	5.0	69	44.5	5	3.2
Increased ALT	58	36.3	3	1.9	69	44.5	3	1.9
Increased bilirubin	74	46.3	9	5.6	56	36.1	5	3.2
Increased creatinine	17	10.6	2	1.3	19	12.3	3	1.9
Fatigue	101	63.1	12	7.5	123	79.4	10	6.5
Alopecia	13	8.1	0	0.0	87	56.1	0	0.0
Anorexia	104	65.0	30	18.8	125	80.6	27	17.4
Diarrhea	63	39.4	9	5.6	103	66.5	25	16.1
Nausea	84	52.5	9	5.6	115	74.2	11	7.1
Vomiting	60	37.5	3	1.9	68	43.9	5	3.2
Stomatitis/pharyngitis	27	16.9	2	1.3	34	21.9	4	2.6
Hand-foot skin reaction	7	4.4	0	0.0	8	5.2	0	0.0
Pigmentation changes	74	46.3	0	0.0	77	49.7	0	0.0

Adverse events were graded according to National Cancer Institute Common Toxicity Criteria, version 2.0

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *IRI-S* S-1 plus irinotecan

resulting from tumor shrinkage, with subsequent attenuation of clinical symptoms, possibly leading to enhanced survival time. The effect of IRI-S in cancer with diffuse-type histology was in line with the finding of the subset analysis of another phase III study that an irinotecan/CDDP combination improved the survival of patients with undifferentiated gastric cancer [13]. However, these data are contradictory to data from a phase II study of the combination of S-1 and irinotecan [19], where a higher response rate was observed for intestinal-type histology. It would not seem feasible at this time, therefore, to attempt to identify patients who may benefit from the IRI-S, using clinicopathologic factors that are easily accessible.

As mentioned previously, cytotoxic drugs tend to be used sequentially as second-line and third-line therapies in some countries, including Japan. Recently, Thuss-Patience et al. [32] reported on second-line treatment for metastatic gastric cancer, and stated that irinotecan monotherapy significantly extended survival compared with best supportive care. A retrospective study exploring a combination of irinotecan and CDDP for patients who failed first-line therapy with S-1 has shown a promising response rate of 28.6% and a MST of 9.4 months from the first day of the second-line treatment [33]. Another retrospective study, also in the second-line setting, has shown promising MSTs, ranging from 9.5 to 10.1 months [34]. These studies suggest a role for irinotecan after the failure of a 5-FU-based first-line treatment, provided that the patients retain sufficient performance status to tolerate this drug. Because definite evidence remains unavailable, further prospective studies in the second-line and third-line settings are warranted to confirm the place of irinotecan in the treatment of gastric cancer. IRI-S uses up one of promising drug combination for the second line treatment without sufficient prolongation of TTF when compared with S-1 monotherapy. It could partially explain why the combination failed to attain significant gain in MST in the present study.

IRI-S was generally well tolerated in the present study. The dose intensity of S-1 in patients treated with IRI-S was equivalent to that in patients receiving S-1 monotherapy, demonstrating the good tolerability of the IRI-S. The most common grade 3 or 4 adverse events associated with this regimen included neutropenia (27.1%) and diarrhea (16.1%), both of these being more frequent than in patients receiving S-1 monotherapy. IRI-S appears to be better tolerated than either the S-1/CDDP or irinotecan/CDDP regimens explored in other phase III studies [13, 20]. Grade 3 or 4 neutropenia was less common with IRI-S than with the S-1/CDDP and irinotecan/CDDP regimens (27 vs. 40% and 65%, respectively), as was anorexia (17 vs. 30% and 33%) and nausea (7 vs. 12% and 21%). Only diarrhea was more common with IRI-S than with the S-1/CDDP and irinotecan/CDDP regimens (16 vs. 4% and 9%, respectively) [13, 20]. However, it is of note that, in the present study, two patients who received IRI-S died of potentially treatment-related conditions. The evaluation of uridine 5′-diphospho-glucuronosyl-transferase gene polymorphism, which had not been approved at the time the trial was conducted, could now identify a small number of patients who may suffer from overt adverse reactions to IRI-S [35].

Although manageable in most cases, the IRI-S was found to be more toxic than S-1 monotherapy. To conclude, the improvement in the response rate observed with the IRI-S did not translate into the predicted prolongation of MST.

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Conflict of interest Chikuma Hamada has received advisory fees from Yakult Honsha Co., Ltd. (Tokyo, Japan) and Daiichi Sankyo

Co., Ltd. (Tokyo, Japan). Yuh Sakata has received advisory fees and honoraria from Yakult Honsha Co., Ltd. (Tokyo, Japan), Daiichi Sankyo Co., Ltd. (Tokyo, Japan), and Taiho Pharmaceutical Co., Ltd. (Tokyo, Japan). The other authors have no conflicts of interest to declare.

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ORIGINAL ARTICLE

Survival and prognosticators of gastric cancer that recurs after adjuvant chemotherapy with S-1

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Abstract
Background Some patients experience a recurrence of cancer even after curative D2 gastrectomy followed by adjuvant S-1 chemotherapy. The objective of this retrospective study was to clarify the survival and prognosticators in these patients.
Methods The study selected patients who underwent curative D2 surgery, were diagnosed with stage II, IIIA, or IIIB cancer, received adjuvant S-1 for more than 4 weeks, and experienced recurrence confirmed by an imaging study.
Results A total of 34 patients were evaluated. The median overall survival (OS) was significantly longer in the 26 patients who received palliative chemotherapy than that in the 8 who did not (8.5 vs. 2.5 months, $P = 0.002$). Only 1 patient received S-1, 21 received taxane-containing regimens, and 4 received irinotecan plus cisplatin as the first-line chemotherapy. Univariate and multivariate analyses showed that the histological type was only independent significant prognosticator.
Conclusions These results suggested that the survival did not reach the level expected for first-line chemotherapy. The histological type was a significant prognosticator in patients who experienced recurrence after adjuvant S-1 therapy and thereafter received palliative chemotherapy.

Keywords Gastric cancer · Adjuvant chemotherapy · Recurrence · S-1

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Introduction

5-Fluorouracil (5-FU)-based chemotherapy is widely used for unresectable advanced or recurrent gastric cancer and has a survival benefit in comparison to the best supportive care [1]. Two phase III studies to evaluate chemotherapy regimens for gastric cancer were recently reported from Japan [2, 3]. The JCOG9912 trial compared 5-FU to S-1 alone or cisplatin (CDDP) plus irinotecan (CPT-11), and found S-1 alone to be comparable to 5-FU alone, but CDDP plus CPT-11 therapy failed to demonstrate superiority to 5-FU alone in overall survival (OS; 11.4 vs. 12.3 vs. 10.8 months). The SPIRITS trial compared the efficacy of S-1 plus CDDP to that of S-1 alone, and found that S-1 plus CDDP showed a significantly longer overall survival (OS; 13 vs. 11 months; $P = 0.037$). These trials included patients with recurrent gastric cancer who did not receive adjuvant chemotherapy or those who received an oral fluoropyrimidine other than S-1. However, prior to these studies, no drugs had been confirmed to be effective as adjuvant chemotherapy after curative surgery.

The ACTS-GC trial first demonstrated that S-1 was effective as adjuvant chemotherapy for Japanese patients who underwent curative gastrectomy for locally advanced gastric cancer and were diagnosed as pathological stage II or III [4]. Therefore, adjuvant S-1 chemotherapy has been established as the standard therapy for stage II or III gastric cancer in Japan. However, about 30% of the patients still develop recurrence after a curative resection followed by adjuvant S-1. The survival of patients who experience recurrence after adjuvant S-1 has not been fully clarified. It is unclear whether these patients should be treated as candidates for first-line chemotherapy.

The present study investigated the survival, and the factors that could predict the survival, in gastric cancer

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patients who experienced recurrence after adjuvant chemotherapy with S-1 and thereafter received palliative chemotherapy.

Patients and methods

Patients

Patients were selected from the database of the Kanagawa Cancer Center, Department of Gastrointestinal Surgery, Yokohama, Japan, according to the following criteria: (1) histologically proven gastric adenocarcinoma, (2) patients who underwent a curative surgical resection for gastric cancer as a primary treatment between June 2002 and December 2009, (3) stage II, IIIA, or IIIB determined pathologically according to the guidelines of the Japanese Gastric Cancer Association[5], (4) patients who received adjuvant S-1 chemotherapy after surgery for more than 4 weeks at a starting dose of 80 mg/m^2, (5) recurrence was confirmed by computed tomography (CT), magnetic resonance imaging (MRI), barium enema, laparoscopy, or bone scintigraphy.

Evaluation and statistical analyses

The overall survival (OS) was calculated from the date of the imaging study that confirmed the recurrence to the date of any cause of death or last follow-up. Unpaired Student's *t*-test or the χ^2 method was used to compare two groups. Survival curves were calculated using the Kaplan–Meier method and compared by the log-rank test. Cox's proportional hazard model was used to perform univariate and stepwise multivariate survival analyses. A P value of <0.05 was defined to be statistically significant, and the data were expressed as medians ± ranges.

An SPSS software package (v11.0 J Win; SPSS, Chicago, IL, USA) was used for all statistical analyses.

Results

A total of 233 patients underwent surgical resection and were pathologically diagnosed as stage II, IIIa, or IIIb. Among them, 92 patients received adjuvant chemotherapy with S-1. Thirty-four patients were eligible for the present study. The median follow-up was 21.5 months (range from 4.3 to 57.2 months). The median OS was 7.3 months (95% confidence interval [CI], 5–9.6 months). Twenty-six patients received palliative chemotherapy after recurrence, while 8 did not, due to renal dysfunction in 2, liver dysfunction in 1, mechanical intestinal obstruction in 1, and patient's refusal in 4. The median OS was 8.5 months (95% CI, 4.4–12.5 months) in the patients who received chemotherapy and 2.5 months (95% CI, 0.7–4.3 months) in those who did not, and the difference was statistically significant ($P = 0.0022$; Fig. 1).

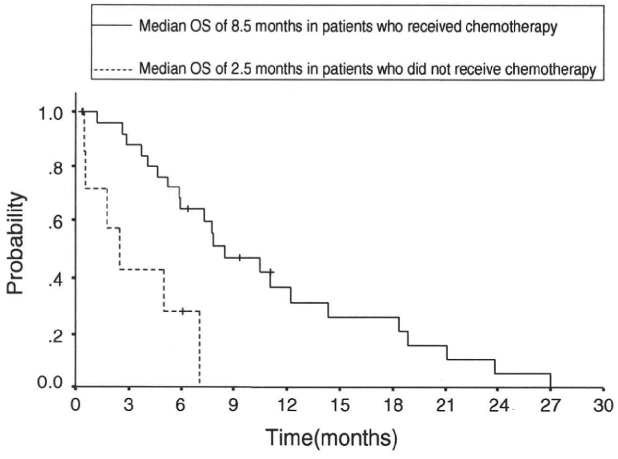

Fig. 1 Kaplan–Meier curves for overall survival (*OS*) showed a significant difference between patients who received chemotherapy (*solid line*) and those who did not receive chemotherapy (*broken line*; $P = 0.0022$)

The backgrounds of the 26 patients who received chemotherapy are shown in Table 1. None of the 26 patients received any other therapies, such as a surgical resection or radiological treatment, in addition to chemotherapy during the clinical course.

Prognosticators in these patients were analyzed by univariate and multivariate analyses. The median duration of adjuvant S-1 administration was 6.2 months, with a range from 1 to 19.9 months. Six patients stop S-1 for ≦3 months due to toxicity. The treatment was withdrawn in 8 of the remaining patients before 6 months, due to recurrence in 5, toxicity in 2, and for other reasons in 1. The treatment was withdrawn in 6 of the remaining patients before 9 months, due to recurrence in 3 and for other reasons in 3. As a result, 8 patients discontinued S1 due to recurrence and 12 patients discontinued S1 due to toxicity or other reasons. The chemotherapy regimens after recurrence were individually selected by the patient's physician. One patient received S-1, 21 received taxane-containing regimens [taxane group (i.e., paclitaxel and docetaxel)], and 4 received irinotecan plus cisplatin (CPT-11 group).

A univariate analysis of factors affecting OS demonstrated that histological type was the only significant factor (Table 2). The OS of the differentiated type was significantly better than that of the undifferentiated type ($P = 0.009$; Fig. 2). The multivariate analysis revealed that histological type remained the only independent significant prognosticator (Table 3). However, the duration of

Table 1 Background of patients who received chemotherapy

Age (years)	58.6 ± 11.6
Gender	
Male	16
Female	10
PS (ECOG) at recurrence	
0	18
1	8
Histological type	
Differentiated	9
Undifferentiated	17
Pathological stage	
Stage II	4
Stage III A	9
Stage III B	13
Site of recurrence	
Peritoneum	14
Liver	5
Lymph node	5
Other	2
Disease-free interval, months median (range)	13.1 (3.9–38.9)
Duration of adjuvant S-1	
<3 Months	6
≧3 Months	20
Treatment-free interval (since last S-1)	
<6 Months	13
≧6 Months	13
Disease-free interval (since surgery)	
<12 Months	12
≧12 Months	14
First-line chemotherapy after recurrence	
Taxane group	21
CPT-11 group	4
S-1	1
Second-line chemotherapy after recurrence	
Taxane group	5
CPT-11 group	6

PS performance status, *ECOG* Eastern Cooperative Oncology Group, *CPT* irinotecan

Table 2 Univariate Cox proportional hazards analysis of clinicopathologic factors

Factor (category)	No. of patients	OR	95% CI	*P* value
Age				0.164
<65 Years	17	1.000		
≧65 Years	9	2.204	0.724–6.716	
PS (ECOG)				0.136
0	18	1.000		
1	8	2.315	0.768–6.975	
Histological type				0.009
Differentiated	9	1.000		
Undifferentiated	17	4.117	1.420–11.931	
Duration of adjuvant S-1				0.173
<3 Months	6	1.000		
≧3 Months	20	0.477	0.164–1.384	
Treatment-free interval (since last S-1)				0.161
<6 Months	13	1.000		
≧6 Months	13	2.026	0.755–5.433	
Recurrence-free interval (since surgery)				0.242
<12 Months	12	1.000		
≧12 Months	14	1.737	0.689–4.383	
Site of recurrence				0.412
Peritoneum	14	1.000		
Other	12	0.688	0.282–1.682	
First-line chemotherapy after recurrence				0.483
S-1	1	1.000		
CPT-11 group	4	0.590	0.076–4.545	
Taxane group	21	0.427	0.097–1.886	

OR odds ratio, *CI* confidence interval, *PS* performance status, *ECOG* Eastern Cooperative Oncology Group

chemotherapy tended to be significant according to the univariate analysis, but not based on the multivariate analysis.

Figure 3 shows details of the regimens of the first- and second-line chemotherapy in 9 patients with the differentiated type and 17 with the undifferentiated type. Most patients received taxane-containing regimens as the first-line chemotherapy. The proportion of patients who received both taxanes and irinotecan was higher in those with the differentiated type (6 of 9 patients, 66.7%) than in those with the undifferentiated type (3 of 17 patients, 17.6%), and the difference was statistically significant ($P = 0.012$).

Discussion

Only Shitara et al. [6] retrospectively examined the efficacy and survival of the treatment in patients who developed recurrence after adjuvant S-1 chemotherapy. The response rate to S-1-containing chemotherapy was 0%. They recommended other chemotherapeutic regimens in this setting. Most patients in the present study received taxane-containing regimens. Only 1 patient received palliative S-1 after recurrence. Despite the use of taxanes in most patients, the median OS of the 26 patients who received chemotherapy after recurrence was only 8.5 months, which did not reach the level expected for