15.4 months, but no significant difference was observed between the four arms. Response rates were higher in the concurrent arms than in the sequential arms.

Conclusion Our study did not show sufficient prolongation of survival with the concurrent strategy to proceed to a phase-III trial; however, the sequential arms showed survival comparable to that in the concurrent arms, with less toxicity. In patients who are ineligible for cisplatin (CDDP), sequential treatment starting with S-1 and proceeding to PTX would be a good alternative strategy, considering quality of life (QOL) and the cost-benefits of an oral agent as first-line treatment.

Keywords Advanced gastric cancer · Paclitaxel · S-1 · Sequential chemotherapy · Concurrent combination chemotherapy · Randomized phase-II trial

Introduction

Gastric cancer is the second most common cause of cancer-related death worldwide [1]. Most patients (except those from northeast Asian countries) present with advanced, inoperable, or metastatic disease, and the 5-year survival rate is approximately 10–15%. Palliative chemotherapy for advanced disease improves survival as compared with the best supportive care [2–4]. Despite the innumerable efforts of investigators in various countries to test various chemotherapeutic and immunotherapeutic agents and combination regimens, there has been little progress in the therapy for patients with advanced gastric cancer.

Probably because there is less evidence regarding the treatment of gastric cancer compared to that of other malignancies, the standard treatment for gastric cancer differs from country to country, although most of the "standard" regimens do not have sufficient evidence. Moreover, the insurance systems in most western countries approve only first-line treatment, and in these countries, doublet or triplet therapies could be the standard choice, while some countries, including Japan, approve second- and greater-line strategies, where we can choose not only concurrent but also sequential strategies. Reflecting these historical and social circumstances, "standard" treatment for gastric cancer shows wide variety, with some confusion. In Japan, the evidence-based standard regimen involved continuous infusion of 5-fluorouracil (5-FU) only (JCOG9205) before the results of the Japan Clinical Oncology Group (JCOG) 9912 and SPIRITS trials had been obtained [5–7]. After the results of SPIRITS trial were shown, S-1 plus cisplatin (CDDP) has been accepted as the standard first-line treatment for patients with good condition, but S-1 without CDDP was also widely used in general practice. This means we still need an alternative strategy, whose sequence starts from a fluoropyrimidine (infusional 5-FU or oral S-1) with or without other agents.

As for candidates as the fluoropyrimidine partner, some potent agents have been approved for gastric cancer in the past two decades. One of the promising agents was paclitaxel (PTX) [8], which had shown beneficial results in single use or concurrent use with a fluoropyrimidine [9–12]. However, these studies were conducted as single-arm phase I–II trials. Hence, the choice between sequential and concurrent strategies for fluoropyrimidine and PTX remains unclear.

We therefore planned a randomized phase-II trial to compare the following four treatment regimens: A, sequential 5-FU monotherapy followed by PTX monotherapy; B, sequential S-1 monotherapy followed by PTX monotherapy; C, concurrent 5-FU plus PTX [11]; and D, concurrent S-1 plus PTX [12]. The purpose of the study was twofold: (1) to compare S-1 with infusional 5-FU to determine which was the better partner of PTX, and (2) to compare a concurrent strategy with a sequential one, the latter strategy being the one that is widely used in Japanese general practice.

Patients and methods

The detailed study design and protocol treatment of this study has already been described by Morita et al. [13]. Below we outline a summary of the methodological issues in this study with the protocol (informed consent form) that was amended after the SPIRITS trial.

Eligibility criteria

Patients more than 20 years of age with histologically confirmed non-resectable advanced or recurrent gastric cancer were eligible. Patients who had undergone prior anti-tumor therapy (except for surgery and postoperative adjuvant chemotherapy) were excluded. Patients had to have adequate renal, hepatic, hematologic, and cardiac function, with an Eastern Cooperative Oncology Group performance status (PS) of 0–1. Patients had to be able to take food via the oral route to be considered for enrolment in the study.

The protocol was approved by the Institutional Review Board (IRB) of each institution, and written informed consent was obtained before treatment. Participating investigators were instructed to send an eligibility criteria report to the data center operated by the non-profit organization Epidemiological and Clinical Research Information Network (ECRIN). Eligible patients were registered and then randomized to receive either of the four treatment regimens (A, B, C, and D), using a centralized dynamic

randomization method with the following balancing factors: measurable disease according to criteria set by Response Evaluation Criteria in Solid Tumours (yes/no); disease type [inoperable advanced/postoperative recurrent (with postoperative chemotherapy)/postoperative recurrent (with no postoperative chemotherapy)]; PS (0/1); peritoneal metastasis based on diagnosis with images (yes/no); age (<75 years/≥75 years), and institution. Information regarding the necessary follow-up examinations and chemotherapy schedule was then sent from the ECRIN data center. The accrual started in December 2005 and was continued for 3 years.

Projected treatments

Based on previous trials, we adapted four promising regimens for this selection design trial [13]. Patients in arm A received sequential therapy with intravenous (i.v.) 800 mg/m^2 5-FU daily for 5 days every 4 weeks until progression, followed by PTX 80 mg/m^2 on days 1, 8, and 15 every 4 weeks. Patients in arm B received sequential therapy with 80 mg/m^2 of oral S-1 daily for 4 weeks and 2-week rest after the administration (total of 6 weeks per single course) until progression. This was followed by PTX, utilizing the same administration dose and schedule as that in arm A's second-line PTX. Patients in arm C received a combination therapy with 600 mg/m^2 5-FU (i.v.) daily for 5 days from day 1 and infusion of 80 mg/m^2 PTX on days 8, 15, and 22 every 4 weeks. Patients in arm D received a combination therapy with 80 mg/m^2 oral S-1 for 14 days from day 1 and infusion of 50 mg/m^2 PTX on days 1 and 8 every 3 weeks. In the sequential treatment arms A and B, the administration of 5-FU or S-1 monotherapy was discontinued if the following were observed: (1) disease progression or occurrence of new disease; (2) grade-4 nonhematological toxicities evaluated according to the Common Terminology Criteria for Adverse Events version 3.0; (3) adverse events causing patients to refuse treatment or causing a clinician to discontinue treatment; (4) increase in the tumor markers carcinoembryonic antigen (CEA) and/or cancer antigen (CA) 19-9 in two or more consecutive measurements or symptomatic progression (e.g., cancer pain and dysphagia). An irinotecan-containing regimen was recommended for use in case further lines of treatment were to be given.

Follow-up

Disease progression and occurrence of new disease were examined using radiographs, computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen, and thoracic CT and measurements of the tumor markers CEA and CA19-9. These examinations were performed at baseline and at least every 4–5 weeks during treatment. Blood tests and symptom checks were performed before treatment and at least every 2 weeks during treatment. In cases where therapy was discontinued owing to toxicity, clinicians followed up patients until they recovered from the effects of toxicity.

Study design and statistical methods

The primary aim of this study was to compare treatment regimens A–D in terms of the primary endpoint of the 10-month overall survival (OS) rate. In addition, OS and treatment failure curves were constructed as time-to-event plots using the Kaplan–Meier method [14]. Time-to-event curves were compared using log-rank tests and the hazard ratio (HR) estimated by Cox regression models [15]. The prevalence of grade-3 or grade-4 adverse events was compared between the treatment arms. Calculation of the sample size required 40 patients in each arm to assure 80% probability in order to select the best treatment arm [16] as long as the true expected 10-month OS rate exceeded that of any other arm by at least 15%. The total number of patients to be accrued was set at 160.

Protocol amendment after SPIRITS trial

After the results of the SPIRITS trial were publicized, standard first-line therapy in Japan shifted from monotherapies with 5-FU or S-1 to an S-1/CDDP combination. The protocol committee of the present trial discussed this issue and decided not to change the protocol treatments, because none of the treatment arms has actually been shown to be inferior to the S-1/CDDP combination. Instead, all patients who became candidates for accrual in the trial after the results of the SPIRITS trial were publicized were to be informed of the novel standard treatment in Japan, using a newly compiled explanatory note, and they were to be offered the alternative of receiving the combination therapy instead of participating in the trial. Each participating institution agreed on the use of the newly compiled explanatory note without correction in the study protocol itself, and case recruitment was re-started after the IRB approval of the amendment was obtained.

Results

A total of 161 patients were enrolled in the trial from December 2005 to November 2008. The numbers of patients in arms A, B, C, and D were 40, 40, 41, and 40, respectively. Two patients in arm A and two in arm C declined therapies before the start of the assigned treatment. Therefore, 38, 40, 39, and 40 patients in arms A, B,

C, and D, respectively, were considered to be eligible for evaluation (Fig. 1). Initial patient characteristics in the four arms were well matched (Table 1). The median age was 67 years (range 40–90 years).

Survival

The ten-month OS rates predetermined as the primary endpoint were 63, 65, 61, and 73% in arms A, B, C, and D, respectively. Although concurrent therapy with S-1 plus PTX demonstrated the best survival benefit among the four arms, the difference in OS rates between the arms with highest (D) and lowest (C) rates was less than the predetermined criterion (i.e., 15%). Kaplan–Meier survival curves did not show a significant difference between the four arms (Fig. 2). The survival rates in the sequential (A, B) and concurrent (C, D) arms were almost identical ($p = 0.93$) (Fig. 3a). In addition, no difference in survival was observed between the 5-FU-containing regimens (arms A and C) and the S-1-containing regimens (arms B and D) ($p = 0.83$) (Fig. 3b).

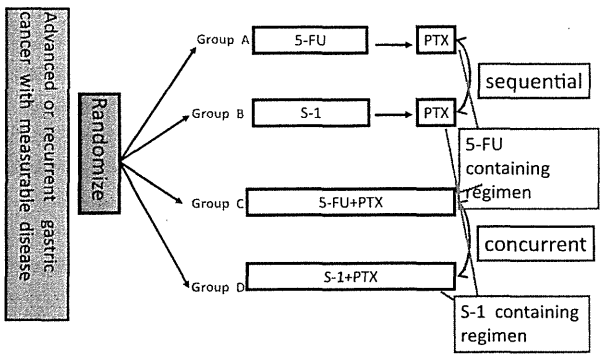

Fig. 1 CONSORT diagram that accounts for all patients. *5-FU* 5-fluorouracil, *PTX* paclitaxel

Time to treatment failure (TTF)

In arms A and B, TTF was calculated by the addition of the prior 5-FU or S-1 treatment period and the sequential PTX period. Median TTF values were 213, 222, 177, and 189 days in arms A, B, C, and D, respectively. No difference was observed between the four arms. However, Kaplan–Meier TTF curves for sequential and concurrent regimens showed better TTF in favor of sequential treatment compared with concurrent treatment (HR 0.71, 95%

Table 1 Patient characteristics

Treatment arm	Arm A 5-FU→PTX $n = 38$	Arm B S-1→PTX $n = 40$	Arm C 5-FU+PTX $n = 39$	Arm D S-1+PTX $n = 40$
Gender				
Male	25 (65.8%)	28 (70.0%)	28 (71.8%)	32 (80.0%)
Female	13 (34.2%)	12 (30.0%)	11 (28.2%)	8 (20.0%)
Age (years)				
Median	67.0	68.0	67.3	66.6
Range	48–79	51–81	40–82	47–90
74≤	31 (81.6%)	33 (82.5%)	31 (79.5%)	31 (77.5%)
≤75	7 (18.4%)	7 (17.5%)	8 (20.5%)	9 (22.5%)
Performance status				
0	29 (76.3%)	27 (67.5%)	25 (64.1%)	28 (70.0%)
1	9 (23.7%)	13 (32.5%)	14 (35.9%)	12 (30.0%)
Stage				
Non-resectable, no previous chemotherapy	31 (81.6%)	33 (82.5%)	32 (82.1%)	32 (80.0%)
Recurrent after curative surgery, adjuvant chemotherapy (+)	2 (5.3%)	1 (2.5%)	3 (7.7%)	3 (7.5%)
Recurrent after curative surgery, adjuvant chemotherapy (–)	5 (13.2%)	6 (15.0%)	4 (10.3%)	5 (12.5%)
Peritoneal metastasis				
Yes	9 (23.7%)	13 (32.5%)	5 (12.8%)	10 (25.0%)
No	29 (76.3%)	27 (67.5%)	34 (87.2%)	30 (75.0%)
Measurable disease				
Yes	19 (50.0%)	23 (57.5%)	17 (43.6%)	20 (50.0%)
No	19 (50.0%)	17 (42.5%)	22 (56.4%)	20 (50.0%)

5-FU 5-fluorouracil, *PTX* paclitaxel

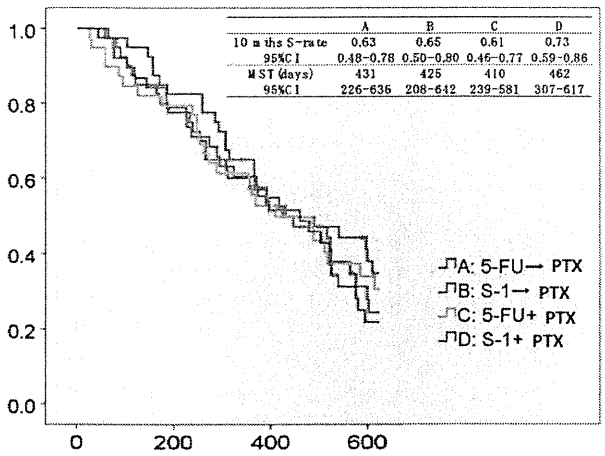

Fig. 2 Kaplan–Meier plot of overall survival in the four treatment arms. *S-rate* survival rate, *CI* confidence interval, *MST* median survival time

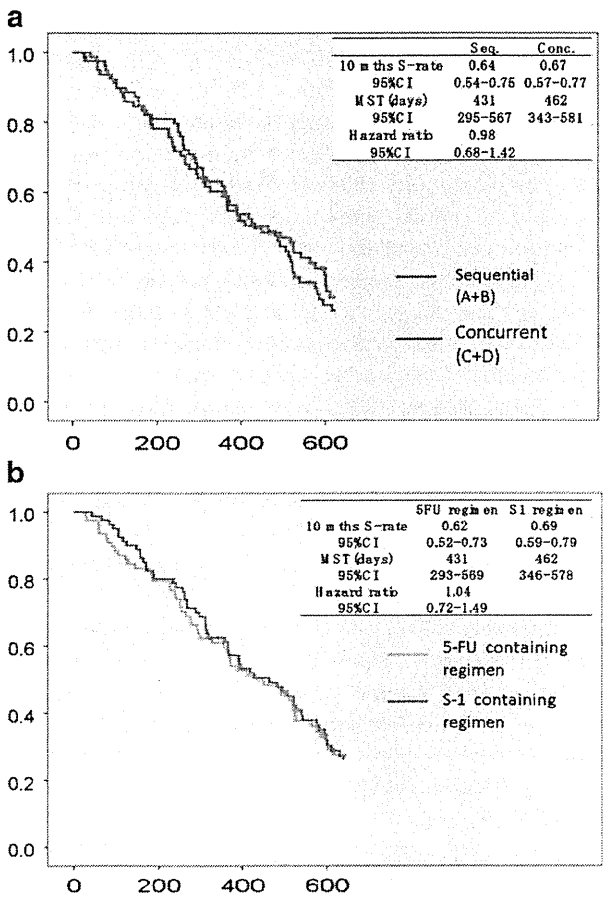

Fig. 3 Kaplan–Meier plot of overall survival by **a** sequential regimens (arms *A* and *B*) and concurrent regimens (arms *C* and *D*), **b** 5-FU-containing regimens (arms *A* and *C*) and S-1-containing regimens (arms *B* and *D*). *seq.* sequential, *conc.* concurrent

Table 2 Tumor response rates

Treatment arm/agent	*n* (With measurable lesion)	CR	PR	SD	PD	Response rate (%)
A						
5-FU	17	0	5	8	4	29.4
PTX	17	0	2	10	5	11.8
B						
S-1	20	1	4	10	5	25.0
PTX	14	1	1	10	2	14.3
C						
5-FU + PTX	13	0	9	2	2	69.2
D						
S-1 + PTX	19	1	7	11	0	42.1

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

confidence interval [CI] 0.50–1.02, $p = 0.06$). A difference in TTF was not observed between the 5-FU-containing and S-1-containing regimens.

Response rates

The overall response rates in patients who had measurable disease are summarized in Table 2. Response rates were higher in the concurrent arms than in the sequential arms. The 5-FU and PTX combination regimen showed the best response rate among the four arms.

Toxicities

All patients could be assessed for hematological and non-hematological toxicities (Table 3). Ten of 78 patients (12.8%) who received sequential therapy and 26 of 79 patients (33.0%) who received concurrent therapy showed grade-3 or grade-4 neutropenia. With respect to hemoglobin decrease, 21 patients (26.2%) with the S-1-containing regimens showed grade-3 or grade-4 adverse events, whereas only 8 patients (10.4%) with the other regimens showed adverse events. No difference was observed in non-hematological toxicity.

Compliance

Compliance with S-1 treatment was inferior to that with 5-FU treatment. The median numbers of courses accomplished in the first- and second-line treatment of the

Table 3 Toxicities

	A: 5-FU→PTX (n = 38)	B: S-1→PTX (n = 40)	C: 5-FU+PTX (n = 39)	D: S-1+PTX (n = 40)
Hematological toxicities				
CTC Grade	>=3	>=3	>=3	>=3
Leucopenia (%)	7.9	7.5	10.3	7.5
Neutropenia (%)	13.2	12.5	25.6	22.5
Thrombocyte (%)	0.0	2.5	0.0	2.5
Hemoglobin (%)	10.5	32.5	10.3	20.0
Total Bil (%)	2.6	2.5	0.0	5.0
Hepatic Tox (%)	7.9	5.0	2.6	7.5
Non-hematological toxicities				
CTC Grade	>=3	>=3	>=3	>=3
Weight loss (%)	2.6	0.0	2.6	0.0
Fatigue (%)	0.0	0.0	0.0	0.0
Lassitude (%)	7.9	12.5	5.1	10.0
Anorexia (%)	10.5	12.5	7.7	10.0
Nausea (%)	2.6	5.0	5.1	2.5
Vomiting (%)	0.0	0.0	2.6	0.0
Stomatitis (%)	5.3	0.0	2.6	2.5
Diarrhea (%)	2.6	2.5	5.1	2.5
Neuropathy (%)	0.0	2.5	5.1	5.0

CTC Common Toxicity Criteria

sequential regimens were 4 (range 1–26) and 3 (range 1–8) in arm A and 6 (range 1–24) and 4 (range 1–30) in arm B, respectively. For the concurrent regimens, these numbers were 6 (range 1–24) and 7.5 (range 1–30) in arms C and D, respectively.

Discussion

The strategy for the chemotherapy of gastric cancer differs from country to country. In Japan, according to community standards, fluoropyrimidine monotherapy has been widely used as the first-line of a sequential strategy, whereas most western countries use doublet or triplet concurrent regimens without second-line treatment. In fact, little is known about whether concurrent regimens or a sequential strategy with satisfactory second- and greater-line treatments would be better. Although one trial has shown the superiority of doublet (S-1 with CDDP) treatment compared with S-1 alone even in Japan [7], other pivotal trials have failed to show the superiority of concurrent regimens [17, 18]. This suggests that sequential strategies may not be so bad if we can use adequate second- (and more)-line therapies in sequence. Thus, when we decided to evaluate PTX in a clinical trial, we created the study plan so as to evaluate whether PTX should be used in second-line (sequential) or in first-line (concurrent) treatment.

In accordance with the general rule in a randomized phase-II trial, in the present study we assumed that we should choose the best regimen in the aspect of 10-month overall survival (OS). However, as shown in the results, all four arms showed good survival times with very small differences. This finding suggests that the difference between concurrent and sequential strategies may be very small if we take enough care with the timing of regimen changes and are meticulous in surveying for clinical disease progression. Similar trends have been observed with some other malignancies; breast cancer is one of the examples. Several studies have been conducted to show the survival superiority of concurrent regimens, but superiority was seen only in TTF and the response rate (RR) [19, 20]. As a result, the sequential strategy is still used. Recently, the result of the GEST trial in pancreatic cancer showed a superior RR and a superior TTF in the combination arm. Despite this superiority, this concurrent strategy also failed to improve OS [21]. Our phase-II trial with its small sample size nevertheless suggests that the sequential strategy could be considered for the treatment of gastric cancer, along with other types of cancer, and that the sequential use of S-1 followed by paclitaxel (PTX) remains as an alternative for patients who are for some reason not indicated for the S-1/CDDP combination.

One more issue to be evaluated in our trial was the difference between infusional 5-FU and oral S-1. The results of a worldwide advanced gastric cancer trial (FLAGS trial) comparing S-1 plus CDDP (SF) versus 5-FU plus CDDP (CF) failed to show a superior effect of SF over CF [22]. The JCOG9912 trial has already shown no

inferiority of S-1 compared to infusional 5-FU in the first-line setting [6]. However, that trial did not limit the post-treatment, so the setting of PTX use in first- or second line mandatorily might show different results. The present study had started before the results of these two trials were disclosed. Consequently, it is important to check whether our results are in line with the data obtained in the JCOG9912 and the FLAGS trials. In our study, the OS, PFS, and RR for the 5-FU-containing and S-1-containing regimens were almost the same, without any significant differences, suggesting both oral and infusional fluorinated pyrimidine regimens have similar potency, a finding which would be confirmatory of the previous trials. In general, treatment with an oral agent would be more preferable both for the patients and for medical staff than a treatment requiring continuous intravenous infusion, with its risks of infection and thrombotic events.

In conclusion, our study did not show sufficient prolongation of survival with a concurrent strategy to proceed to a phase-III trial; however, the sequential arms showed survival comparable to that in the concurrent arms, with a lower incidence of neutropenia. In patients who are ineligible for CDDP, sequential treatment starting from S-1 and proceeding to PTX would be a good alternative strategy, considering the quality of life (QOL) and cost-benefits of an oral agent as first-line treatment.

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