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ORIGINAL ARTICLE

Feasibility study of adjuvant chemotherapy with S-1 plus cisplatin for gastric cancer

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Abstract
Purpose To evaluate the feasibility of S-1 plus cisplatin as adjuvant chemotherapy for stage III gastric cancer after curative resection.
Methods Japanese patients with stage III gastric cancer who underwent gastrectomy with D2 lymph node resection were enrolled. Treatment consisted of 3 cycles of S-1 (80 mg/m^2/day, b.i.d.) for 21 days followed by a 14-day rest, and cisplatin (60 mg/m^2 iv) on day 8. After that, S-1 monotherapy was given on days 1–28 every 6 weeks until 1-year postsurgery. After protocol amendment, the first chemotherapy cycle consisted of S-1 monotherapy; cisplatin was added to cycles 2, 3, and 4, followed by S-1 monotherapy up to 1-year postsurgery. The primary endpoint was the completion rate of three cycles of S-1 plus cisplatin.

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Results A total of 63 enrolled patients have been evaluated. Grade 3/4 toxicities included neutropenia (40%), anorexia (28%), and febrile neutropenia (4%) before protocol amendment ($n = 25$), and neutropenia (37%), anorexia (8%), and febrile neutropenia (3%) after amendment implementation ($n = 38$). Excluding ineligible cases, treatment completion rates were 57% (12/21) before and 81% (30/37) after the protocol amendment.

Conclusions The amended S-1 plus cisplatin is more feasible than the original protocol because of early dose reduction of S-1 prior to cisplatin addition and greater recovery time from surgery prior to cisplatin. This treatment should be considered as a feasible experimental arm for the next postoperative adjuvant phase III trial.

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

Introduction

Gastric cancer (GC) remains a major health problem with approximately 8,03,000 deaths worldwide in 2004, although the mortality rate has steadily decreased in recent years [1]. The primary treatment for GC is surgery, which is almost always curative in early GC (stage I) patients, who have a >90% 5-year survival rate. However, locally advanced (stage II–III) GC often recurs, even after curative resection is performed. Therefore, it is very important to develop adjuvant chemotherapy regimens that can improve survival in GC patients with stage II–III disease after surgical resection.

Until recently, several randomized controlled trials of postoperative adjuvant chemotherapy for GC were conducted [2–12]. Although most of them have failed to show clinical benefit in particular multi-agent anthracycline or cisplatin-based regimens, a recent meta analysis showed that postoperative adjuvant chemotherapy was associated with reduced risk of death compared with surgery alone [13].

S-1 (TS-1, Taiho Pharmaceutical Co.) is an orally active combination of tegafur (a prodrug that is converted by cells to fluorouracil), gimeracil (an inhibitor of dihydropyrimidine dehydrogenase, which degrades fluorouracil), and oteracil (inhibits the phosphorylation of fluorouracil in the gastrointestinal tract, thereby reducing the toxic gastrointestinal effects of fluorouracil) [14] approved in Japan, Korea, Singapore, and China for GC. In 2007, the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) trial demonstrated the efficacy of S-1 for stage II–III GC patients who underwent curative resection with D2 lymphadenectomy [15]. S-1 improved the 3-year overall survival (OS) rate from 70.1% for surgery alone to 80.1%, with a low incidence of adverse events and good compliance with treatment for 3 months in 87.4% and for 6 months in 77.9%. However, the 3-year OS rates in stage IIIA and stage IIIB patients receiving S-1 were 77.4 and 63.4%, respectively, which are less satisfactory compared with the rate for stage II (90.7%). Therefore, further investigation into more effective treatments for patients with stage III GC is urgently needed.

Meanwhile, for metastatic or recurrent GC, the phase III trial comparing S-1 alone to S-1 plus cisplatin (S-1 Plus cisplatin vs. S-1 In RCT In the Treatment for Stomach cancer; SPIRITS trial) showed that S-1 plus cisplatin resulted in a significantly higher response rate, longer progression-free survival (PFS), and longer OS [16]. Another phase III trial (the First-Line Advanced Gastric Cancer Study; FLAGS trial) showed that S-1 plus cisplatin was associated with fewer toxic effects and demonstrated noninferiority compared with infusional fluorouracil and cisplatin [17]. Therefore, S-1 plus cisplatin is now considered to be one of the standard regimens for metastatic or recurrent GC, as well as a candidate for an experimental arm in the next adjuvant chemotherapy trial.

Before comparing S-1 monotherapy with S-1 plus cisplatin in a phase III trial, we first evaluated the feasibility of S-1 plus cisplatin as adjuvant chemotherapy for stage III GC after curative resection, to confirm that S-1 plus cisplatin can safely be used.

Patients and methods

Eligibility criteria

The following eligibility criteria were employed: (1) histologically proven adenocarcinoma of the stomach; (2) ≥ D2 lymphadenectomy, with complete resection of the primary tumor (R0 surgery); (3) stage IIIA/IIIB disease (T2, N2; T3, N1–2; or T4, N0–1 [Japanese classification]); (4) ECOG performance status 0–1; (5) age 20–75 years; (6) no prior chemotherapy or radiotherapy; (7) able to be enrolled 4–8 weeks after surgery; (8) sufficient oral food intake; (9) adequate organ function (white blood cells [WBCs] ≥3,000/mm^3 and ≤1,20,000/mm^3, neutrophils ≥1,500/mm^3, hemoglobin ≥8.0 g/dl, platelets ≥1,00,000/mm^3, aspartate aminotransferase [AST] and alanine aminotransferase [ALT] levels ≤100 IU/l, total serum bilirubin ≤2.0 mg/dl, serum creatinine concentration ≤1.2 mg/dl, estimated creatinine clearance ≤60 ml/min, normal electrocardiogram); and (10) written informed consent obtained from the patient. Disease stage was classified according to Japanese Gastric Cancer Association guidelines [18]. The protocol was approved by the institutional review board at each participating center.

Treatment and toxicity assessment

Treatment according to the original protocol was begun 4–8 weeks after surgery with 3 cycles of S-1 plus cisplatin ("S-1+ cisplatin [SP] step") followed by S-1 monotherapy ("S-1 step") up to 1 year after surgery. In the "SP step", each cycle consisted of 40 mg/m^2 of S-1 taken orally twice daily for 21 days plus a 2-hour infusion of 60 mg/m^2 of cisplatin on day 8. Each cycle was administered at 5-week intervals. In the "S-1 step", 40 mg/m^2 of S-1 was taken orally twice daily as monotherapy for 28 days at 6-week intervals. All patients received 5-HT3 antagonists and dexamethasone on administration of cisplatin as antiemetics.

Patients were assessed before registration, on days 1, 8, and 15 during the "SP step", and every 2 weeks during the "S-1 step". The baseline assessment included physical examination and laboratory tests. Patients were monitored for adverse effects throughout the treatment period, in addition to receiving follow-up for treatment-related adverse effects. Toxicity was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.

For adverse effects, the subsequent chemotherapy cycle was delayed until patient recovery, which included the following parameters: WBCs $\geq$3,000/mm^3, neutrophils $\geq$1,500/mm^3, hemoglobin $\geq$8.0 g/dl, platelets >75,000/mm^3, AST or ALT levels $\leq$100 IU/l, total serum bilirubin level $\leq$2.0 mg/dl, and serum creatinine concentration <1.5 mg/dl. Nonhematological toxicities, excluding stomatitis, alopecia, pigmentation changes, nail changes, and watery eyes, were required to be grade 0/1. Cisplatin administration was delayed and administered within 1 day of recovery of the following parameters: WBCs $\geq$3,000/mm^3, neutrophils $\geq$1,500/mm^3, platelets >75,000/mm^3, and serum creatinine <1.5 mg/dl. Both S-1 and cisplatin doses were reduced in the event of grade 4 leukopenia or neutropenia, grade 3/4 thrombocytopenia, serum creatinine $\geq$1.5 mg/dl, or other drug-related nonhematological grade 3/4 toxicities. For level -1 dose reduction, S-1 was reduced from 120 to 100 mg/day, from 100 to 80 mg/day, or from 80 to 50 mg/day, while cisplatin was reduced from 60 to 50 mg/m^2. Dose reduction was permitted twice. When dose-limiting toxicities as described previously occurred again at level -2 (S-1 reduced from 100 to 80 mg/day or from 80 to 50 mg/day [if the -1 level of S-1 was already 50 mg, the patient was withdrawn from the study]; cisplatin administration reduced from 50 to 40 mg/m^2), the patient was withdrawn from the study. A patient was also withdrawn from the study whenever the beginning of the subsequent cycle was delayed by toxicity for more than 3 weeks. When cisplatin administration was delayed beyond day 15, the cisplatin portion of the cycle was skipped.

Protocol amendment

During enrollment, some toxicity was reported during the first cycle of SP, especially neutropenia and anorexia. To minimize patient risk, the Data and Safety Monitoring Committee recommended that patient enrollment be halted and that an interim analysis be conducted using the first 25 registered cases (see "Results"). After the analysis, we decided to amend the protocol.

Treatment according to the amended protocol was begun 4–6 weeks after surgery as in the ACTS-GC trial, and consisted of the following: (1) The first cycle of chemotherapy consisted of S-1 monotherapy, and cisplatin was added to cycles 2, 3, and 4. After that, S-1 monotherapy was administered up to 1 year after surgery; (2) The dose of S-1 in the first SP cycle was reduced in case of severe toxicity during the first cycle of S-1 monotherapy; (3) The criterion for delaying cisplatin administration was changed from a neutrophil count of <1,500/mm^3 to <1,200/mm^3; (4) Dexamethasone was recommended for treatment-induced nausea with 20 mg on day 8 (the day of cisplatin administration) and 16 mg on days 9 and 10.

Statistical analysis

The primary endpoint was the rate of completion of 3 cycles of S-1 plus cisplatin; secondary endpoints were the rate of completion of 2 cycles of S-1 plus cisplatin, the proportion of patients receiving treatment according to protocol, and adverse events. Treatment completion was defined as administration of S-1 for more than 14 days in each cycle plus administration of cisplatin. Completion rate of S-1 plus cisplatin was evaluated in all eligible patients. Toxicity was evaluated among patients who received more than one cycle of S-1 plus cisplatin.

In the present trial, the rate of treatment completion was expected to be lower than compliance in the ACTS-GC trial because of the addition of cisplatin. Moreover, if the rate of treatment completion using 3 cycles of S-1 plus cisplatin were lower than 50%, this regimen would be considered inappropriate for adjuvant therapy and would not be evaluated in a phase III trial. Assuming a null hypothesis of 50% for the rate of completion of 3 cycles and an alternative hypothesis of 70%, and using a 1-sided alpha of 0.1 and a statistical power of 0.1, it is necessary to enroll a minimum of 44 patients. Therefore, the target enrollment was 50 patients, in order to make accommodations for ineligible patients.

After protocol amendment, a minimum of 33 patients is needed for a 1-sided alpha of 0.1 and a statistical power of 0.2. Therefore, 38 more patients were added to allow for ineligible patients. Statistical analysis was performed independently for patients enrolled before and after amendment.

Table 1 Patient characteristics

Characteristic	Original ($n = 25$)	Amended ($n = 38$)
Median age, years (range)	60 (47–72)	62 (40–74)
Gender		
Male	16	25
Female	9	13
PS (ECOG)		
0	17	26
1	8	12
Pathological type		
Intestinal	14	5
Diffuse	11	33
Type of gastrectomy		
Total	8	13
Distal	16	25
Proximal	1	0
T stage		
pT1	2	0
pT2	8	9
pT3	14	28
pT4	1	1
N stage[a]		
pN0	1	0
pN1	10	8
pN2	14	30
Cancer stage[a]		
IB	1[b]	0
II	2[b]	0
IIIA	17	16
IIIB	5	21
IV	0	1[b]

Original before protocol amendment, *Amended* after protocol amendment, *PS* performance status, *ECOG* Eastern Cooperative Oncology Group

[a] Japanese classification; [b] excluded after enrollment

Results

Patient characteristics

From August 2007 to July 2009, 63 patients (25 patients in the original protocol/38 patients in the amended protocol) were accrued from 5 Japanese hospitals. To date, all 63 patients have finished the "SP step" and have been evaluated. Clinical characteristics are summarized in Table 1. The median age was 60/62 (original/amended protocol) years (range, 47–72/40–74 years), and the following types of resection were performed: total gastrectomy ($n = 8/13$), distal gastrectomy ($n = 16/25$), and proximal gastrectomy ($n = 1/0$). In the original protocol, 17 patients had stage IIIA disease and 5 had stage IIIB disease; whereas 16 had stage IIIA and 21 had stage IIIB disease in the amended protocol. After enrollment, 4 patients were deemed ineligible during the original protocol because of confirmed stage II disease ($n = 2$), stage IB disease ($n = 1$), and cancer other than GC ($n = 1$), and 1 patient was considered ineligible during the amended protocol because of pathological stage IV ($n = 1$) disease.

Table 2 Toxicities

Toxicities	Original ($n = 25$)				Amended ($n = 38$)			
	All		Grade 3/4		All		Grade 3/4	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)
(A) Hematological toxicities								
Leucopenia	19	(76)	1	(4)	26	(68)	2	(5)
Neutropenia	20	(80)	10	(40)	30	(79)	14	(37)
Anemia	23	(92)	5	(20)	35	(92)	3	(8)
Thrombocytopenia	10	(40)	1	(4)	17	(45)	1	(3)
Febrile Neutropenia	1	(4)	1	(4)	1	(3)	1	(3)
(B) Nonhematological toxicities								
Anorexia	23	(92)	7	(28)	34	(89)	3	(8)
Nausea	17	(68)	2	(8)	31	(82)	1	(3)
Vomitting	7	(28)	0	(0)	8	(21)	0	(0)
Diarrhea	13	(52)	0	(0)	24	(63)	1	(3)
Fatigue	17	(68)	0	(0)	34	(89)	2	(5)
Stomatitis	2	(8)	0	(0)	8	(21)	0	(0)
AST	5	(20)	0	(0)	10	(40)	0	(0)
ALT	5	(20)	0	(0)	8	(36)	0	(0)
Total bilirubin	6	(30)	0	(0)	22	(22)	0	(0)
Creatinine	5	(20)	0	(0)	11	(10)	0	(0)

Original before protocol amendment, *Amended* after protocol amendment, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase

Toxicity

A total of 202 cycles from the 63 cases were assessable for toxicity (Table 2). Under the original protocol ($n = 25$), neutropenia was the most common hematological toxicity, with grade 3/4 neutropenia observed in 10 patients (40%). Additional grade 3/4 hematological toxicities included anemia in 5 patients (20%), and leucopenia, thrombocytopenia, and febrile neutropenia in 1 patient (4%) each. Grade 3/4 anorexia was the most frequent nonhematological toxicity ($n = 7$ [28%]), followed by nausea ($n = 2$ [8%]). There was no grade 3/4 creatinine elevation seen.

Under the amended protocol ($n = 38$), the frequency of grade 3/4 neutropenia was similar to the original; it was seen in 14 patients (37%). Grade 3/4 anemia decreased to 3 patients (8%), and the frequencies of grade 3/4 leukopenia ($n = 2$

[5%]), thrombocytopenia ($n = 1$ [3%]), and febrile neutropenia ($n = 1$ [3%]) were also similar to the original. Among nonhematological toxicities, grade 3/4 anorexia was remarkably reduced to 3 patients (8%) and nausea also decreased to 1 patient (3%). The incidences of grade 3/4 fatigue and diarrhea slightly increased to 2 (5%) and 1 (3%) patients, respectively. There was no grade 3/4 creatinine elevation seen. There were no treatment-related deaths occurring within 30 days after completion of "SP step" treatment.

Compliance

As mentioned previously, 4 and 1 patients were determined to be ineligible after enrollment in the original and amended protocols, respectively, and therefore 21 and 37 patients were analyzed for compliance, respectively. Under the original protocol, 57% (12/21; 95% CI 34–78%) achieved treatment completion with 3 cycles of S-1 plus cisplatin, and 76% (16/21; 95% CI 53–92%) achieved treatment completion with 2 cycles. The proportion of patients receiving treatment according to protocol was 57% (12/21; 95% CI 34–78%). Of note, 6/21 (29%) patients did not complete the first cycle of the "SP step". Reasons for not completing the first cycle included neutropenia on the day of cisplatin administration (day 8) in 3 patients, anorexia in 2 patients, and infection in 1. Dose reductions of S-1 and cisplatin were required once in 9 (43%) and 8 (38%) patients, respectively, and twice in 1 (5%) and 1 (5%) patients, respectively. There were 6 patients (29%) withdrawn from treatment as follows: 3 because of toxicity (neutropenia), 2 because of patient refusal of additional treatment because of toxicity, and 1 because of refusal of additional treatment for other reasons.

Under the amended protocol, 81% (30/37; 95% CI 65–92%; $P < 0.001$ under the null hypothesis) achieved treatment completion with 3 cycles of S-1 plus cisplatin, and 95% (35/37; 95% CI 82–99%) achieved treatment completion with 2 cycles. The proportion of patients receiving treatment according to protocol was 78% (29/37; 95% CI 62–90%). The number of patients not completing the first cycle of the "SP step" was remarkably decreased to only 1 (3%) patient. There were 10 (27%) patients requiring S-1 dose reduction after the first chemotherapy cycle of S-1 monotherapy. Dose reductions of S-1 and cisplatin were required once in 12 (32%) and 8 (22%) patients, respectively, and twice in 7 (19%) and 6 (16%) patients, respectively. Withdrawal of treatment occurred in 2 (5%) patients as follows: one because creatinine elevation did not recover and the other because of patient refusal of additional treatment because of toxicity.

The relative dose intensities (RDIs) of S-1 were 0.67 in the original and 0.78 in the amended protocol, and for cisplatin were 0.65 and 0.81, respectively.

Discussion

To the best of our knowledge, this is the first report on a safety analysis of S-1 plus cisplatin treatment for stage III GC patients who have undergone curative resection with D2 lymphadenectomy. The overall frequencies of major toxicities under the original protocol were almost similar to those of the SPIRITS trial [16] (neutropenia 40 vs. 40%; anemia 20 vs. 26%; and anorexia 28 vs. 30% in this study and the SPIRITS trial, respectively). However, the completion rate of 3 cycles of S-1 plus cisplatin as a primary endpoint (57%) and RDI of S-1 or cisplatin were unexpectedly low in this study. Among the 9 patients who could not complete the 3 cycles of S-1 plus cisplatin, 6 patients could not complete treatment even during the first cycle, mainly because of neutropenia on day 8 and anorexia. We found that toxicity of chemotherapy was more likely to occur during the first cycle.

Therefore, to improve the completion rate of the treatment, we decided to amend the protocol by establishing S-1 monotherapy as the first cycle of chemotherapy, followed by 3 cycles of S-1 plus cisplatin. Although it might be possible that efficacy is decreased by changing the first cycle to S-1 monotherapy, we prioritized complying with postoperative adjuvant chemotherapy, which might also be important in improving survival [19, 20].

In our amended protocol, not only was cisplatin administration omitted in the first cycle, but also the dose of S-1 in subsequent combination cycles was reduced if there were severe toxicities during the "first-cycle" administration of S-1 monotherapy. In addition, the neutropenia count for delaying cisplatin administration was also changed, from $<1{,}500/mm^3$ to $<1{,}200/mm^3$. As a result, 81% of patients achieved treatment completion with 3 cycles of S-1 plus cisplatin with improved RDIs of both S-1 (0.78 from 0.65) and cisplatin (0.81 from 0.65). The frequency of grade 3/4 anorexia and nausea also decreased, from 28 to 8% and 8 to 3%, respectively, although we do not use Substance P inhibitor in both protocol because it was not approved in Japan at that time.

The actual cause of the poor compliance during the early post-gastrectomy course in this study was not discovered. There are several reports about the effect of gastrectomy on S-1 pharmacokinetics [21–23], although this issue remains controversial. Kim et al. reported that total gastrectomy significantly increased the maximum concentration and the areas under the curves of plasma fluorouracil and 5-chloro-2,4-dihydroxypyridine (CDHP) after S-1 administration, which may be one explanation for the toxicity seen in this study [23]. Additionally, there may be a hidden cause, such as relatively poor nutritional status due to gastrectomy, although this study included patients with sufficient oral intake and adequate organ function.

Although this was not a randomized study, in comparison with the original protocol, the amended protocol was more feasible, with a higher completion rate and higher RDIs. Relapse-free survival and overall survival were not reached in this study; therefore, it is difficult to speculate that the addition of 3 cycles of cisplatin might improve the prognosis compared with S-1 alone. Now in Japan, another feasibility study of S-1 plus docetaxel as postoperative adjuvant chemotherapy is ongoing [24]. The addition of any other agent to S-1 as an adjuvant chemotherapy needs to be validated in a randomized phase III trial with S-1 as the control arm.

In conclusion, the postoperative adjuvant S-1 plus cisplatin regimen of the amended protocol is more feasible than the original protocol, because of (1) early dose reduction of S-1 prior to cisplatin addition (2) greater recovery time from surgery prior to cisplatin. It should be regarded as a feasible experimental arm for the next adjuvant phase III trial comparing this S-1 plus cisplatin regimen and S-1 alone as adjuvant chemotherapy for stage III GC patients who have undergone curative resection with D2 lymphadenectomy.

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