Safety and feasibility of S-1 adjuvant chemotherapy for gastric cancer in elderly patients

Toru Aoyama · Takaki Yoshikawa ·
Takafumi Watanabe · Tsutomu Hayashi ·
Takashi Ogata · Haruhiko Cho · Akira Tsuburaya

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Abstract

Background The safety and feasibility of administering S-1 adjuvant chemotherapy for gastric cancer has not been fully evaluated in elderly patients.

Methods This retrospective study selected patients who underwent curative D2 surgery for gastric cancer, were diagnosed with stage II or III disease, and received adjuvant S-1 at our institution. Patients were categorized into two groups; non-elderly patients (age <70 years: group A) and elderly patients (age ≥70 years: group B). The toxicity and S-1 continuation rates in the two groups were compared.

Results A total of 75 patients were evaluated in the study. There were no grade 4 toxicities. The incidences of grade 3 hematological and non-hematological toxicities were <5% in both groups, and the differences were not significant. The continuation rate at 6 months was 69% in group A and 70% in group B, and this difference was also not significant.

Conclusions These results suggest that S-1 adjuvant chemotherapy for gastric cancer is safe and feasible, regardless of the age of the patient; especially for elderly patients who could be candidates for clinical trials.

Keywords Gastric cancer · Adjuvant chemotherapy · S-1 · Elderly patient

Introduction

Every year, there are more than 800,000 new cases of gastric cancer worldwide, and this cancer is the second most common cause of cancer-related death [1, 2]. Generally, more than 60% of the cancer diagnoses and 70% of cancer mortalities occur in elderly patients (aged 65 years or older) [3].

In 2007, the adjuvant chemotherapy trial of TS-1 for gastric cancer (ACTS-GC) demonstrated that S-1 was effective as adjuvant chemotherapy for Japanese patients who had undergone curative D2 gastrectomy for gastric cancer and were diagnosed with pathological disease stage II or III [4]. Based on this trial, curative D2 resection and adjuvant chemotherapy with S-1 are now the standard therapy for such patients in Japan. In the ACTS-GC trial, more than 20% of the patients were more than 70 years old.

The aim of adjuvant chemotherapy is to eradicate micrometastatic tumor cells; therefore, it is essential to continue chemotherapy for a minimal length of time to ensure that these cells are eradicated. Six months of treatment has been shown to be the necessary duration for breast and colon cancer, while 12 months was the duration shown to be necessary for gastric cancer in the ACTS-GC trial. Although the optimal duration of adjuvant chemotherapy for gastric cancer is still unclear, considering the results of studies of other solid malignancies, it seems that S-1 adjuvant treatment should be continued for at least 6 months. It has been shown that incomplete treatment with adjuvant chemotherapy results in a markedly inferior disease-free survival in patients with breast cancer [5]. In the ACTS-GC trial, of the 517 patients who received S-1, the treatment was continued for at least 3 months in 452 patients (87.4%) and for at least 6 months in 403 patients

T. Aoyama · T. Yoshikawa (✉) · T. Watanabe · T. Hayashi ·
T. Ogata · H. Cho · A. Tsuburaya
Department of Gastrointestinal Surgery, Kanagawa Cancer
Center, 1-1-2 Nakao, Asahi-ku, Yokohama 241-0815, Japan
e-mail: yoshikawat@kcch.jp

(77.9%). The most common cause of withdrawal was the occurrence of adverse events.

Elderly cancer patients often have comorbidities and age-related physiological problems that can lead to greater drug toxicity than that occurring in non elderly patients. In their study of patients with advanced gastric cancer, Tsushima et al. showed that S-1 monotherapy exhibited moderate efficacy in elderly patients (≥ 76 years of age) and that these patients were at a higher risk of severe toxicities than the younger patients (age ≤ 75 years). They recommended careful monitoring of toxicities in the elderly patients [6]. However, the safety and feasibility of adjuvant chemotherapy with S-1 in elderly patients has not been clarified. In addition, the use of D2 gastrectomy may or may not affect the toxicity or continuation rate of S-1 in elderly patients.

The aim of this study was to retrospectively investigate the safety and feasibility of adjuvant chemotherapy with S-1 in elderly patients compared to non-elderly patients.

Patients and methods

Patients

The patients were selected from the prospective database of the Kanagawa Cancer Center, Department of Gastrointestinal Surgery, Yokohama, Japan, according to the following criteria: (1) histologically proven gastric adenocarcinoma, (2) the patient had undergone a curative D2 resection for gastric cancer as a primary treatment between June 2002 and March 2010, (3) stage IIA, IIB, IIIA, IIIB, or IIIC disease was diagnosed pathologically according to the 14th edition of the *Japanese classification of gastric carcinoma* published by the Japanese Gastric Cancer Association [7], (4) the patient had a creatinine clearance of >50 ml/min, and (5) the patient's age was less than 80 years. The patients were classified into two groups according to their age: <70 years (group A) and ≥ 70 years (group B).

Treatment

The patients received S-1 chemotherapy and were followed on an outpatient basis. The patients who were registered to the ACTS-GC trial received 40 mg of S-1 per square meter of body-surface area twice a day for 4 weeks followed by 2 weeks' rest as one course (6 weeks' schedule), and this regimen was continued for 1 year after surgery. The patients who were registered to the Stomach Cancer Adjuvant Multi-institutional Trial Group (SAMIT) trial between February 2004 and April 2007 received the same dose as that in the ACTS-GC trial for 2 weeks followed by

1 week's rest (a 3-week schedule) and the regimen was continued for 6 months after surgery, while the patients who were registered to the SAMIT trial between May 2007 and September 2009 received the same 3 weeks' schedule of S-1 as that in the earlier cohort and the regimen was continued for 12 months, because the SAMIT protocol was amended in May 2007 based on the report of the ACTS-GC trial [8]. The remaining patients received S-1 at the dose that is used in clinical practice and the regimen was continued for 12 months following the ACTS-GC protocol after the results of the ACTS-GC trial were reported. Patients with a body-surface area of less than 1.25 m^2 received 80 mg of S-1 daily, those with a body-surface area of 1.25 m^2 or more but less than 1.5 m^2 received 100 mg daily, and those with a body-surface area of 1.5 m^2 or more received 120 mg daily. Reduction of the starting dose, suspension or delay, and dose reduction were determined by the protocol of each clinical trial in the patients registered to the ACTS-GC or the SAMIT trial [4, 8]. Reduction of the starting dose, delay, and dose reduction in the patients who received the S-1 dose used in clinical practice were determined according to the ACTS-GC trial protocol. Briefly, the treatment was delayed when patients had hematological adverse events of grade 3 or more, or non-hematological adverse events of grade 2 or more, until all adverse events recovered to grade 0 or 1, and the treatment was restarted at a reduced dose of 100, 80, or 50 mg based on the body surface area described above. Patients who started with the 6-week schedule of S-1 and experienced the adverse events described above at a reduced dose were switched from the 6-week schedule to the 3-week schedule. S-1 chemotherapy was terminated when the adverse events described above occurred in patients on the 3-week schedule.

Evaluation and statistical analyses

Toxicities were graded according to the National Cancer Institute common toxicity criteria version 3.0. Feasibility was evaluated by the continuation rate of S-1 chemotherapy. The date of S-1 discontinuation was defined as the last day on which S-1 was orally administered. The continuation rate was calculated using the Kaplan–Meier method and rates were compared by the log-rank test. The relative dose intensity (%) was defined based on the ratio of the change in the actual dose given for 6 months to the planned dose for 6 months. Treatment delay was defined when the new course could not be started or when the treatment was postponed during each course because of toxicity.

Comparisons of the two groups were performed using the unpaired χ^2 method or Student's *t*-test. A *P* value of <0.05 was defined as statistically significant. Laboratory data are expressed as means $\pm$ SD. An SPSS software

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

Results

Patient characteristics

A total of 240 patients underwent surgical resection and were pathologically diagnosed with stage IIA, IIB, IIIA, IIIB, or IIIC disease. A flow diagram of the treatment allocation in the 240 patients is shown in Fig. 1.

Seventy-five of these 240 patients were eligible for the present study. Nine patients had been registered to the ACTS-GC trial between June 2002 and June 2004, and 20 had been registered to the SAMIT trial between August 2004 and February 2009. Forty-six patients received the S-1 treatment used in clinical practice after the results of the ACTS-GC trial were reported, while 5 patients in this study rejected S-1 adjuvant chemotherapy between August 2006 and March 2010. One of these 5 patients was under 70 years old, while 4 were more than 70 years old.

Fifty-five patients were classified into group A, and 20 into group B. The median follow-up period was 24.3 months. The median duration of adjuvant S-1 administration was 8.4 months.

Table 1 shows the background of the patients, which was similar in the two groups. Table 2 shows the patients' baseline characteristics just before starting the S-1 therapy. Creatinine clearance was significantly lower in group B compared to group A. However, this difference was small.

Toxicity

All 75 patients were evaluated for toxicities of grade 3 or 4 (Table 3). There were no grade 4 toxicities. The incidences of grade 3 hematological and non-hematological toxicities were less than 5% in both groups, and the differences in toxicities were not significantly different between the two groups.

Continuation rates and treatment events

Figure 2 demonstrates the continuation curves calculated by the Kaplan–Meier method. The curves for the two groups were similar, and no significant difference was shown between the groups as determined by the log-rank test ($P = 0.6498$). The continuation rates at 2, 4, and 6 months were not significantly different, as indicated by the χ^2 method (Table 4). Table 5 shows the details of the patients who stopped S-1 because of adverse events. There was no difference in the toxicities associated with withdrawal between groups A and B. Table 5 shows that 7 patients terminated the treatment because of hematological toxicities and 10 because of non-hematological events. Six of these 10 patients experienced grade 1–2 non-hematological toxicities and rejected the treatment within only 30 days. On the other hand, only 1 of the 7 patients experienced grade 1–2 hematological toxicities and rejected the treatment within 30 days.

The incidences of treatment delay and dose reduction tended to be higher in group B (40.0 and 45.0%) than in group A (27.3 and 38.2%), but the differences did not reach

Fig. 1 Flow diagram of treatment allocation in 240 patients

statistical significance ($P = 0.290$ and 0.697 , respectively). No difference was observed in the alterations of the treatment schedule between the two groups (12.7% in group A and 10.0% in group B, $P = 0.748$). There was also no difference in the relative dose intensity between the two groups (0.758 in group A and 0.757 in group B, $P = 0.992$).

Discussion

This is the first report to demonstrate that the toxicities and continuation rates of adjuvant chemotherapy with S-1 were similar in patients aged ≥ 70 years and those aged < 70

years. Moreover, the dose intensity was almost the same in the two groups. Our results suggested that S-1 adjuvant chemotherapy was safe and feasible even for elderly patients who underwent a D2 gastrectomy for gastric cancer and were diagnosed with pathological stage II or III disease.

Elderly patients often have comorbidities and age-related physiological problems, such as organ dysfunction. The present study showed that creatinine clearance was significantly lower in the patients aged ≥ 70 years than in those aged < 70 years. A previous study showed that creatinine clearance was an important factor for the safety and feasibility of S-1 therapy. Yamanaka et al. reported that baseline renal impairment was a significant risk factor for grade 3–4 adverse events caused by S-1 chemotherapy. They showed that the incidences of key severe adverse events, such as neutropenia, nausea/vomiting, diarrhea, stomatitis, rash, and pigmentation were significantly higher in patients who had a creatinine clearance level of less than 50 ml/min than in those who had a creatinine clearance level of more than 80 ml/min [hazard ratio (HR), 1.46; 95% confidence interval [CI], 1.16–1.82; $P < 0.001$] [9]. S-1 is an oral fluoropyrimidine, consisting of tegafur (a prodrug of fluorouracil), 5-chloro-2,4-dihydropyrimidine (CDHP), and potassium oxonate. CDHP is an inhibitor of dihydropyrimidine dehydrogenase (DPD), which is the rate-limiting enzyme for the degradation of fluorouracil [10]. It is known that the clearance of CDHP is reduced by renal dysfunction, resulting in a high blood concentration of 5-fluorouracil (5-FU) due to decreased DPD activity [11, 12]. Renal function is affected by aging; thus, the frequency and grade of adverse events may be increased in elderly patients. In the present study, the frequencies of grade 3 or higher toxicities were $< 5\%$, and there were no significant differences between the two groups, although the renal function was decreased in the elderly patients. However, treatment events such as delay and dose reduction occurred more frequently in the elderly patients than in the non-elderly patients. Thus, our results also suggest the need for careful monitoring of treatment events in elderly patients during the continuation of S-1 adjuvant chemotherapy.

Table 1 Baseline characteristics of the treated patients

Characteristics	Group A (< 70 years)	Group B (≥ 70 years)	<i>P</i> value
No. of patients	55	20	
Age, years (range)	62 (36–69)	72.5 (70–80)	
Gender			
Male	37	13	0.854
Female	18	7	
Site of tumor			
Entire	3	1	0.868
Upper third	11	5	
Middle third	25	7	
Lower third	16	7	
Type of gastrectomy			
Distal gastrectomy	22	7	0.694
Total gastrectomy	33	13	
Stage			
IIa	1	0	0.694
IIb	17	4	
IIIa	6	1	
IIIb	16	7	
IIIc	15	8	

Table 2 Comparison of the patient characteristics in the two groups before starting S-1

	Group A (< 70 years)	Group B (≥ 70 years)	<i>P</i> value
Performance status			
0	47	18	0.609
1	8	2	
Serum AST (IU/l)	24.7 $\pm$ 9.0	22.1 $\pm$ 7.6	0.267
Serum ALT (IU/l)	31.7 $\pm$ 18.1	25.3 $\pm$ 26.3	0.252
Serum BUN (mg/dl)	14.5 $\pm$ 7.0	14.2 $\pm$ 3.5	0.871
Serum Cr (mg/dl)	0.72 $\pm$ 0.13	0.70 $\pm$ 0.12	0.531
Creatinine clearance (mL/min)	93.7 $\pm$ 20.3	73.0 $\pm$ 15.7	< 0.001

AST aspartate aminotransferase, ALT alanine aminotransferase, BUN blood urea nitrogen, Cr creatinine

Table 3 Comparison of patients experiencing toxicities in the two groups

Toxicity	Group A <70 years (<i>n</i> = 55)			Group B ≥70 years (<i>n</i> = 20)			<i>P</i> value
	Grade			Grade			
	3 No. of patients	4 No. of patients	3 or 4 (%)	3 No. of patients	4 No. of patients	3 or 4 (%)	
Hematological							
Leukopenia	1	0	1.8	1	0	5	0.449
Anemia	1	0	1.8	0	0	0	0.544
Thrombocytopenia	0	0	0	0	0	0	NS
Nonhematological							
Elevated AST/ALT level	0	0	0	0	0	0	NS
Elevated serum bilirubin	0	0	0	0	0	0	NS
Elevated creatinine level	0	0	0	0	0	0	NS
Stomatitis	0	0	0	0	0	0	NS
Nausea/vomiting	1	0	1.8	0	0	0	0.544
Diarrhea	2	0	3.6	0	0	0	0.387
Rash	0	0	0	0	0	0	NS
Anorexia	0	0	0	1	0	5	0.095
Fatigue	0	0	0	1	0	5	0.095
Pigmentation	0	0	0	0	0	0	NS
Body weight loss	1	0	1.8	1	0	5	0.449

NS not significant

Fig. 2 Comparison of the treatment continuation rates between the patients who were aged 70 years or more and those who were younger than 70

In the study by Tsushima et al. [6] cited earlier, those authors examined the toxicities of S-1 monotherapy for patients with metastatic gastric cancer, and reported that the elderly patients showed higher incidences of severe toxicities than the younger patients. In that study, however, several points were different from the present study. First, the renal function was different; the median creatinine clearance in that study was 59.9 ml/min, but it was 73.0 ml/min in the present study, and this difference could

have affected the severity of the toxicities. Second, the disease status in the two studies was different. Patients with advanced metastatic disease may more easily develop tumor-related symptoms, which are sometimes difficult to distinguish from S-1-related toxicities, while the patients in our study who underwent gastrectomy had no residual macroscopic disease. Third, the definition of elderly patients was different. Tsushima and colleagues defined elderly patients as those aged more than 75 years, because patients with advanced or recurrent gastric cancer who were aged more than 75 years were not included in Japanese phase III trials. They did not compare the feasibility and the safety profiles between patients aged 70 to 75 years and those aged more than 75 years. However, in the present study, the patient characteristics, continuation rates, and treatment modifications were almost the same in the 70- to 75-year-old group and the 76- to 80-year-old group (data not shown). We therefore defined elderly patients as those aged ≥70 years in this study.

When comparing our present findings to the results of the ACTS-GC trial, the continuation rate and the frequencies of non-hematological toxicities tended to be lower in our study. The clinical trial had strictly defined the rules for discontinuation of S-1, while daily clinical practice did not. Because the quality of life of the patient is affected more by non-hematological toxicity than by hematological toxicity, in our study S-1 could be

Table 4 Continuation rates and reasons for withdrawal of treatment in the two groups

Duration (months)	Group A <70 years (<i>n</i> = 55)				Group B ≥70 years (<i>n</i> = 20)				<i>P</i> value
	Continuation rate (%)	Reasons for withdrawal			Continuation rate (%)	Reasons for withdrawal			
		Any adverse event	Recurrence	Others		Any adverse event	Recurrence	Others	
2	83.6	8	0	1	90	2	0	0	0.245
4	69.0	5	3	0	80	1	1	0	0.179
6	69.0	0	0	0	70	1	1	0	0.428

Table 5 Details of withdrawals because of any adverse event

Case no.	Group A (<70 years)			Case no.	Group B (≥70 years)		
	Reasons for withdrawal				Reasons for withdrawal		
	Day	Type of event	Grade		Day	Type of event	Grade
1	7	Palpitations	1	1	21	Stomatitis	2
2	11	Anorexia	2	2	28	Herpes infection	2
3	21	Neutropenia	2	3	63	Neutropenia	3
4	28	Nausea	2	4	154	Anorexia	3
5	29	Anorexia	2				
6	38	Duodenal fistula	3				
7	42	Neutropenia	3				
8	42	Thrombocytopenia	2				
9	63	Anorexia	2				
10	63	Neutropenia	3				
11	68	Neutropenia	3				
12	98	Leukopenia	3				
13	104	Vestibular disorder	2				

discontinued due to grade 1–2 non-hematological toxicities such as anorexia, fatigue, and nausea, even though a physician explained the details of the ACTS-GC trial to the patients. In fact 4 non-elderly and 2 elderly patients rejected S-1 chemotherapy within 30 days because of grade 1–2 non-hematological toxicity, while only 1 non-elderly patient in this study rejected this regimen because of grade 1–2 hematological toxicity. These 7 patients could have had the chance of continuing S-1 treatment if the treatment had been delayed and/or the dose had been reduced. Moreover, some patients in our series were registered to the SAMIT trial, in which the duration of S-1 was defined as 6 months before amendment. This may account, at least in part, for the lower toxicity rates observed in our study.

When interpreting our results, special attention is required, because there were some limitations associated with this study. First, this was a retrospective single-center study with a small sample size. Second, some patients in this study received S-1 adjuvant chemotherapy as a test

arm of the SAMIT trial, which is a 2 × 2 phase III trial for surgical serosa-positive tumors. The SAMIT trial prescribed adjuvant chemotherapy with S-1 for 6 months before amendment. Therefore, the precise continuation rate at 12 months in the present study is unknown. Third, there is a possibility of selection bias in this series, as shown in Fig. 1. (1) All patients who were registered to the adjuvant phase III trial (i.e., the ACTS-GC or SAMIT trial) were randomly assigned to surgery alone, S-1, or other chemotherapeutic regimens; therefore, there was no selection bias among these patients. (2) After August 2006, 68 patients were not registered to the clinical trial. Of these, 5 patients rejected S-1 chemotherapy although S-1 is a standard treatment. These 5 patients may have produced a selection bias, but this proportion is very low. (3) Before August 2006, 69 patients were not registered to the phase III trial. None of these 69 patients received S-1 because the standard treatment was surgery alone. On the other hand, 65 patients were registered to the phase III trial and 17 were assigned to S-1. There may have been a selection bias in

these 17 patients, because only patients who fulfilled the strict eligibility criteria were entered into the trial. However, this proportion is not so high. Fourth, there was a selection bias in the elderly patients in this series. Surgeons often avoid performing D2 in elderly patients, because D2 gastrectomy itself potentially has 0.8% mortality and 20.9% morbidity [13]. Thus, the fact that the elderly patients in this study received D2 could itself be a bias. In addition, our hospital is a specialized cancer center. The elderly patients treated at general hospitals usually have more serious comorbidities than those treated at most Japanese cancer centers.

In summary, both the safety and the feasibility of S-1 adjuvant chemotherapy were almost equal in the elderly and the non-elderly patients in this study. Therefore, it is unnecessary to avoid chemotherapy or to reduce the dose of S-1 at least in elderly patients who could be candidate for clinical trials simply because of their age.

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Conflict of interest None declared.

References

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, Smigal C, et al. Cancer statistics, 2006. *CA Cancer J Clin*. 2006;56:106–30.
2. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol*. 2006;24:2137–50.
3. Yancik R, Ries LA. Cancer in older persons. Magnitude of the problem—how do we apply what we know? *Cancer*. 1994;74:1995–2003.
4. Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med*. 2007;357:1810–20.
5. Bonadonna G, Valagussa P. Dose-response effect of adjuvant chemotherapy in breast cancer. *N Engl J Med*. 1981;304:101–5.
6. Tsushima T, Hironaka S, Boku N, Machida N, Yamazaki K, Yasui H, et al. Safety and efficacy of S-1 monotherapy in elderly patients with advanced gastric cancer. *Gastric Cancer*. 2010;13:245–50.
7. Japanese Gastric Cancer Association. Japanese Classification of Gastric Carcinoma 14th Japanese Edition. Tokyo: Kanehara-shuppan; 2010. p. 5–17.
8. Tsuburaya A, Sakamoto J, Morita S, Kodera Y, Kobayashi M, Miyashita Y, et al. A randomized phase III trial of post-operative adjuvant oral fluoropyrimidine versus sequential paclitaxel/oral fluoropyrimidine; and UFT versus S1 for T3/T4 gastric carcinoma: the Stomach Cancer Adjuvant Multi-institutional Trial Group (Samit) Trial. *Jpn J Clin Oncol*. 2005;35:672–5.
9. Yamanaka T, Matsumoto S, Teramukai S, Ishiwata R, Nagai Y, Fukushima M. Safety evaluation of oral fluoropyrimidine S-1 for short- and long-term delivery in advanced gastric cancer: analysis of 3, 758 patients. *Cancer Chemother Pharmacol*. 2008;61:335–43.
10. Shirasaka T, Shimamoto Y, Ohshimo H, Yamaguchi M, Kato T, Yonekura K, et al. Development of a novel form of an oral 5-fluorouracil derivative (S-1) directed to the potentiation of the tumor selective cytotoxicity of 5-fluorouracil by two biochemical modulators. *Anticancer Drugs*. 1996;7:548–57.
11. Tatsumi K, Fukushima M, Shirasaka T, Fujii S. Inhibitory effects of pyrimidine, barbituric acid and pyridine derivatives on 5-fluorouracil degradation in rat liver extracts. *Jpn J Cancer Res*. 1987;78:748–55.
12. Hirata K, Horikoshi N, Aiba K, Okazaki M, Denno R, Sasaki K, et al. Pharmacokinetic study of S-1, a novel oral fluorouracil antitumor drug. *Clin Cancer Res*. 1999;5:2000–5.
13. Sasako M, Sano T, Yamamoto S, Kurokawa Y, Nashimoto A, Kurita A, et al. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. *N Engl J Med*. 2008;359:453–62.