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Original Paper

Late Phase II Study of Novel Oral Fluoropyrimidine Anticancer Drug S-1 (1 M Tegafur–0.4 M Gimestat–1 M Otastat Potassium) in Advanced Gastric Cancer Patients

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S-1 is a novel oral anticancer drug, composed of tegafur (FT), gimestat (CDHP) and otastat potassium (Oxo) in a molar ratio of 1:0.4:1, based on the biochemical modulation of 5-fluorouracil (5-FU). CDHP inhibits dihydropyrimidine dehydrogenase (DPD), an enzyme which degrades 5-FU, and maintains prolonged 5-FU concentrations in the blood and tumours. Oxo is distributed in the gastrointestinal tract at a high concentration after oral administration and alleviates gastrointestinal toxicity due to 5-FU. S-1 improves the tumour-selective toxicity of 5-FU by the actions of two modulators, CDHP and Oxo. We conducted a late phase II clinical trial of S-1 as an open trial in patients with advanced gastric cancer, to confirm its antitumour effect and adverse reactions. 51 patients with advanced gastric cancer were enrolled in the trial. S-1 was administered orally twice daily after meals, at a standard dose of 80 mg/m^2/day. One course consisted of consecutive administration for 28 days and 14 days' rest. Administration was repeated over four courses. A complete response was obtained in 1 patient and partial responses in 24 patients, producing a response rate of 49% (25/51) (95% confidence interval (CI) 35.9–62.3%). The incidence of adverse reactions was 78% (40/51) and that of adverse reactions of grades 3 and 4 was 20%. Adverse reactions of grades 3 and 4 included a decrease in the haematocrit, leucopenia, granulocytopenia, diarrhoea, malaise and proteinuria. No serious unexpected adverse reactions were observed. In conclusion, S-1 was effective and well tolerated in patients with advanced gastric cancer. © **1998 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

FLUOROPYRIMIDINE ANTICANCER drugs have been widely used for the treatment of solid tumours since 5-fluorouracil (5-FU) was first synthesised in 1957. However, gastrointestinal cancers are considered less sensitive to chemotherapy despite the fact that many chemotherapeutic agents and administration methods have been reported, and limited clinical efficacy has been attained [1–3].

5-FU is currently widely used for the treatment of gastrointestinal cancers, and the clinical merits of administration by continuous intravenous (i.v.) infusion have been reported [4]. Its plasma concentration values reported in various studies have exhibited significant disparities and no consistent conclusion can be drawn [5, 6]. Dihydropyrimidine dehydrogenase (DPD), a 5-FU catabolising enzyme, is considered to contribute to the disparities [6]. Approximately 90% of 5-FU administered is metabolised by DPD to α-fluoro-β-alanine prior to exerting its antitumour effect [6]. The circadian rhythm of DPD activity may change the catabolism of 5-FU within a 24-h period [7]. DPD activity can exhibit differences of up to 100-fold, depending on the particular human cancer cells, and it is considered to be one of the main factors affecting the sensitivity of tumours to 5-FU [8].

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The dose-limiting toxicities with long-term continuous i.v. infusion methods are mucositis and diarrhoea [5]. Animal experiments have indicated that these toxicities are the result of phosphorylation of 5-FU by orotate pyrimidine phosphoribosyl transferase (ORTC) in the digestive tract [9]. Therefore, the concomitant administration of 5-FU and a DPD inhibitor may lead to a maximal antitumour effect of 5-FU. If phosphorylation of 5-FU is inhibited specifically in the digestive tract, the therapeutic index of 5-FU could possibly be enhanced.

S-1 is a novel oral antimalignant tumour drug, based on a biochemical modulation of 5-FU, and containing tegafur (FT), gimestat (CDHP) and otastat potassium (Oxo) in a molar ratio of 1:0.4:1 [10]. This drug was developed to improve the tumour-selective toxicity of 5-FU by means of modulating the actions of CDHP and Oxo [11, 12]. FT, a prodrug of 5-FU, is absorbed well after oral ingestion and is converted into 5-FU. *In vitro*, CDHP has been shown to exert DPD inhibition activity 180-fold higher than that of uracil, which has been confirmed to be a DPD inhibitor in the form uracil/tegafur (UFT) [13]. Concomitant use of CDHP with FT, a prodrug of 5-FU, enables high 5-FU concentrations to be maintained in blood for long periods of time [11]. Oxo, which inhibits ORTC, decreases the levels of 5-fluorouridine 5′-monophosphate (FUMP) and 5-FU incorporated into RNA (F-RNA) by approximately 70% only in the small intestine, while the decrease is limited to 0–20% in bone marrow and tumour regions [14]. This suggests that Oxo is distributed at high levels in the digestive tract after oral administration and, thus, reduces the gastrointestinal toxicity of 5-FU [14].

Phase I [15] and early phase II clinical trials [16] have already been conducted. In a phase I clinical study, it was deduced that the maximum tolerable dose was 150 mg/day once daily and 75 mg/body twice daily (as FT) and the dose-limiting factor was myelosuppression, mainly leucopenia [15]. In an early phase II clinical trial, a course consisted of administration at 75 mg/body or 50 mg/body twice daily for 28 consecutive days followed by 14 days' rest. The response rate was 53.6% (15/28) and the median survival period was 298 days for advanced gastric cancer patients. Major adverse reactions were gastrointestinal symptoms and myelosuppression. The incidence of adverse reactions of grades 3 and 4 was 35.7% (10/28) [16]. The rate of discontinuation of administration due to adverse reactions was markedly lower for patients given doses of 90 mg/m^2/day or less. Thus, 80 mg/m^2/day was recommended as the standard dose.

We conducted two pivotal late phase II trials in patients with advanced gastric cancer to confirm the efficacy and safety observed in the early phase II trial. The results of one of these studies are described below, the other will be described elsewhere.

PATIENTS AND METHODS

Patients

All patients from the sites shown in the Appendix had to have histologically proven gastric cancer with measurable or evaluable lesions. Additional criteria included age ≥ 20 years, but < 75 years, performance status (PS) of WHO grade ≤ 2, life expectancy ≥ 3 months, adequate marrow function (white blood cells (WBC) $\geq 4000/mm^3$ but less than $12\,000/mm^3$; platelets $\geq 100\,000/mm^3$; haemoglobin ≥ 9.0 g/dl), adequate liver function (total bilirubin ≤ 1.5 mg/dl; transaminases ≤ 100 U/l; alkaline phosphate (Al-P) $\leq 2\times$ the upper limit of normal range) and adequate renal function (serum creatinine $\leq$ upper limit of normal range). Patients were excluded if there was a history of drug hypersensitivity, serious complications, symptoms attributable to brain metastasis and active secondary cancer. Patients with experience of prior chemotherapy, radiation therapy and hormone therapy were not permitted to enrol in the study. Patients who had completed adjuvant chemotherapy 6 months or more before study entry were included. Pregnant or lactating women were excluded. This study was approved by the institutional review board at each site, and all patients provided written informed consent.

Methods

S-1 (Taiho Pharmaceutical Co., Tokyo, Japan) was administered orally at 40 mg/m^2 (standard dose) twice daily after meals. Three initial doses of S-1 were established according to body surface area (BSA) as follows: BSA < 1.25 m^2; 80 mg/day; $1.25\,m^2 \leq BSA < 1.5\,m^2$, 100 mg/day; and $1.5\,m^2 \leq BSA$, 120 mg/day (Table 1). One course consisted of consecutive administration for 28 days followed by 14 days' rest. This therapy was administered for four courses in repeated administration, if there was no disease progression. The patients in whom efficacy was observed, at the time of completion of the fourth course, were transferred to the long-term administration study. Dose modifications were effected in accordance with the following guidelines: when adverse reactions at grades 2–4 appeared, the dose was reduced from 120 to 100 mg/day, from 100 to 80 mg/day, respectively, or administration was temporarily discontinued. When no adverse reactions appeared, the dose was increased gradually in steps from 80, 100, 120, to 150 mg/day (Table 1). The rest period was shortened to 1 week, unless adverse reactions appeared, and was extended to 4 weeks at the longest, if adverse reactions appeared. If a rest period of longer than 4 weeks was required, the patient was withdrawn from the study. The number of patients to be enrolled in this study was calculated at 50, which was required for dismissing the assumption that the 95% confidence interval (CI) would be 20% under the conditions of $\alpha = 0.05$ (one side) and $\beta = 0.2$, assuming an expected response rate of 40%.

The measurement and evaluation of lesions were conducted repeatedly by X-ray, computed tomography (CT), and ultrasonography. During the administration period, haematological tests, such as WBC counts, biochemical tests, such as liver and renal function tests and urinalysis were conducted repeatedly. Responses and safety were reviewed by external authorities. The major endpoints of this study were

Table 1. *Dosage schedule*

Body surface area (m^2)	Initial dosage (mg/body/day)	Dose modification	
		Reduced*	Increased†
$- < 1.25$	80	Rest	100
$1.25 \leq - < 1.50$	100	80	120
$1.50 \leq -$	120	100	150

The patients were assigned on the basis of body surface area. S-1 was administered orally after breakfast and dinner twice daily for 28 days, followed by 2 weeks of no treatment. *In patients with grade 3 haematological or grade 2 non-haematological toxicity. †In patients with no toxicity.

Table 2. Patients' characteristics

Patients *n*	51
Median age, years (range)	62 (30–74)
Male/female	37/14
Performance status	
0	27
1	22
2	2
Median first dose, mg/m^2 (range)	72.9 (64.5–79.8)
Extent of disease	
Locoregional	4
Primary not excised, metastatic	32
Primary excised, metastatic	15
Sites of primary disease	36
Sites of metastatic disease*	
Distant lymph nodes	37
Liver	16
Other	10

*Some patients had more than one site of metastasis.

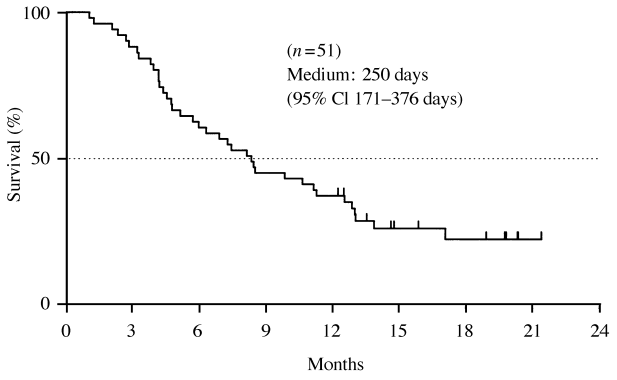

Figure 1. Overall survival.

response rates (ratio of patients attaining response (complete response (CR) + partial response (PR)) and incidence of adverse reactions. The antitumour effects and adverse reactions were evaluated in accordance with the criteria of the Japan Society for Cancer Therapy [17], which were established based on criteria established by the WHO. The criteria for the evaluation of antitumour effects were as follows: CR, eradication of all cancers and maintenance of the condition for 4 weeks or more; PR, 50% or more reduction in size of lesions and maintenance of the condition for 4 weeks or more; no change (NC), less than 50% reduction in size of lesions or enlargement of lesions within 25% and maintenance of the condition for 4 weeks or more; progressive disease (PD), 25% or more enlargement of lesions or appearance of new lesions. Primary gastric lesions can be classified into three types as follows; (a) measurable lesions; (b) evaluable but not measurable lesions; (c) diffused infiltrating lesions. Measurable lesions can be measured during a gastrographic examination of the same position. Evaluable but not measurable lesions can be evaluated by improvements of gastrographic and/or endoscopic findings that can clearly differ from those in the pretreatment examinations, e.g. showing a marked regression of tumours and ulcerations or marked flattening of elevated lesions which can be estimated to be a regression of more than 50%. Diffused infiltrating lesions can be evaluated by the expansion of the affected gastric lumen and can be measured by planimeter during a gastrographic examination or computer image analysis, which compares the image before and after treatment. The gastrographic examination must be performed in the same position using the same volume of barium and ingested air. In a comparison with the data before treatment, a PR can be confirmed by the enlargement of 50% or more of the affected area [18]. The survival rate was calculated by statistical analysis using the Kaplan–Meier method.

RESULTS

Response rate

Between July 1995 and July 1996, 51 patients with advanced gastric cancer were enrolled in this study. All patients were eligible and subjected to evaluation for antitumour effects and adverse reactions. The patients' characteristics are shown in Table 2. Evaluation was made for primary lesions in 4 patients, for both primary and metastatic lesions in 32 and for only metastatic lesions in 15. The number of patients who completed the first course was 46/51 (90%) and the second course was 44/45 (98%). Patients' compliance during all the courses was 95%. The doses were modified in 11 patients. Two doses were reduced, five were increased and four were increased initially and then reduced.

Table 3. Response

	Response: *n* patients (%)					
	CR	PR	NC	PD	NE	Total
All patients	1 (2.0)	24(47.1)	11 (21.7)	13 (25.5)	2	51
Extent of disease						
Locoregional	0	1	2	1	0	4
Primary not excised, metastatic	1	14	8	8	1	32
Primary excised, metastatic	0	9	1	4	1	15
Sites of primary disease	1	13	15	6	1	36
Sites of metastatic disease*						
Distant lymph nodes	2	19	11	2	3	37
Liver	0	4	5	6	1	16
Other	1	3	3	2	1	10

CR, complete response; PR, partial response; NC, no change; PD, progressive disease; NE, not evaluable. *Some patients had more than one site of metastasis.

Table 4. Adverse reaction

	Grade				Incidence of grades 3–4	
	1	2	3	4	(%)	*n*
Haematological						
Haemaglobin	5	8	3	0	6	(3/51)
Leucocytes	15	4	1	0	2	(1/51)
Granulocytes	6	9	3	0	6	(3/51)
Gastrointestinal						
Diarrhoea	5	0	1	0	2	(1/51)
Stomatitis	10	2	0	0		
Nausea/vomiting	6	0	0	0		
Skin						
Dermatitis*	5	3	0	0		
Pigmentation	11	0	0	0		
Renal						
Proteinuria	0	0	0	1	2	(1/51)
Malaise	4	1	1	0	2	(1/51)

*Hand–foot syndrome indicated 1 case at grade 2.

The reasons for reduced doses were adverse events. The responses to the therapy are shown in Table 3. A CR was obtained in 1 patient and PRs in 24, with a response rate of 49% (25/51) and 95% CI of 35.9–62.3%. As to efficacy by sites, the response rate was 39% (14/36) for primary lesions; and 25% (4/16) for liver metastases and 57% (21/37) for distant lymph node metastases. 17 patients were transferred to the long-term administration study. In 1 patient, who previously exhibited a PR, this response changed to a CR after the fifth course. The median response period was 68 (29–330) days and the median total response period (from the start of administration to the onset of progression) was 158 (64–372) days. The median survival period was 250 days (95% CI 171–376 days). 19 patients (37%) survived for 1 year or more (Figure 1).

Adverse reactions

Major adverse reactions are shown in Table 4. Adverse reactions appeared in 78% (40/51) of the patients. The incidence of adverse reactions at grades 3 and 4 was 20% (10/51). The incidences of major adverse reactions were 31% for decreased haemoglobin level, 39% for leucopenia, 12% for diarrhoea, 24% for stomatitis, 12% for nausea/vomiting, 16% for dermatitis, 22% for pigmentation and 12% for malaise. The incidences of adverse reactions at grades 3 and 4 were 6% for a reduction in haemoglobin level, 2% for a decrease in leucocyte counts, 6% for a decrease in granulocyte counts, 2% for diarrhoea and 2% for malaise. Proteinuria at grade 4 was observed in 1 patient, but no nephrosis or renal functional disorders were observed in the patient. It was judged not to be serious. Hand–foot syndrome was observed in 1 patient. There were no irreversible adverse reactions at grades 3 and 4 nor any serious unexpected adverse reactions. There were no toxic deaths. In all other patients, adverse reactions were within the acceptable range (grade 2 or less).

DISCUSSION

In this study, responses were observed in 25 patients (1 CR and 24 PRs), with a response rate of 49% (25/51) and 95% CI of 35.9–62.3%. This is considered to satisfy the conditions assumed prior to the study that the response rate should not be lower than 40% and the 95% CI not lower than 20%. The response rate was 54% (15/28) in the early phase II clinical trial. A similar response rate was obtained in this trial, so the efficacy observed in the early phase II clinical trial was confirmed. The response rates of major drugs used alone have been reported to be 21% for 5-FU, 30% for mitomycin C (MMC), 17% for doxorubicin (DOX), 19% for cisplatin (CDDP) [1], 18% for irinotecan hydrochloride (CPT-11) [19] and 22% for docetaxel (Taxotere) [20]. The response rates of combination therapy in gastric cancer have been reported to be 9–42% for 5-FU + DOX + MMC (FAM) [1, 2, 21, 22], 33–59% for 5-FU + DOX + methotrexate (FAMTX) [1, 2, 21, 23], 33–64% for etoposide + DOX + CDDP (EAP) [1, 2, 23], 41–43% for 5-FU + CDDP (FP) [2, 24], and 11–48% for 5-FU/leucovorin [1, 2, 25]. The response rate in administration of S-1 alone indicated that it had efficacy comparable with that of combination therapy and the efficacy of 5-FU was considered to be able to be adequately demonstrated by S-1.

The median survival period was 8 months. Median survival periods of patients with advanced gastric cancer were 3–4 months under best supportive care [2], 7 months for 5-FU [22, 26], 6–7 months for FAM [1, 2, 21, 22], 6–10 months for FAMTX [1, 2, 21, 23], 6–10 months for EAP [1, 2, 23], 7–10.6 months for FP [2, 24] and 5.5–7 months for 5-FU/leucovorin [1, 2, 25]. In this study, despite the fact that 71% of patients (36/51) had a primary lesion, the survival period was comparable with that achieved by combination therapy.

In Japan, oral anticancer drugs are frequently administered in out-patient departments. The response rates of major drugs for gastric cancer have been 28% (52/188) for UFT [27] and 14% (20/140) for 5′-deoxy-5-fluorouridine (5′-DFUR) [28]. The response rates of combination regimens have been 25% (20/79) for UFT + MMC [29] and 50% (14/28) for 5′-DFUR + CDDP [30]. The median survival periods were 6 months for UFT [27], 6 months for UFT + MMC [29] and 8.3 months for 5′-DFUR + CDDP [30]. Even compared with the above, S-1 exhibited remarkable results. Therefore, S-1 is expected to be a drug for induction therapy rather than a drug used as part of combination therapies. A study on the effects in combination study will be required in the future.

In this study, the incidence of adverse reactions was 78% and that of adverse reactions at grades 3 and 4 was 20%. In the early phase II clinical trial, the incidence of adverse reactions was 82% and that of adverse reactions at grades 3 and 4 was 36% [16]. The incidence was reduced in this study. This was considered to be due to the adoption of a standard dosage of 80 mg/m^2/day compared with 150 or 100 mg/body/day in the early phase II clinical trial. The incidence of major adverse reactions in long-term continuous i.v. infusion of 5-FU for gastric cancer have been reported as 86% for leucopenia and 43% for diarrhoea, and adverse reactions at grades 3 and 4 were 35% for leucopenia and 3% for diarrhoea ($n = 69$) [26]. In addition, there is a study which reports the incidence of adverse reactions at grades 2–4 as 1.2% for leucopenia (cycles = 426) and 5.3% for diarrhoea ($n = 94$) [22]. The incidences of major adverse reactions associated with the administration of UFT in the phase II trials in various carcinomas were 4% for leucopenia and 11% for diarrhoea ($n = 551$) [27]. Therefore, the incidence of adverse reactions in our S-1 study was lower than that observed in continuous i.v. infusion of 5-FU, but phase III trials should be conducted

to confirm this result. Further, the incidence of diarrhoea in our study was similar to that for oral UFT, although the incidence of myelosuppresion was higher. In total, there was only 1 case of grade 4 toxicity which was not serious, indicating acceptable safety in the administration of S-1.

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APPENDIX

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