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A new regimen for S-1 therapy aiming at adverse reaction mitigation and prolonged medication by introducing a 1-week drug-free interval after each 2-week dosing session: efficacy and feasibility in clinical practice

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Abstract

Background. **The response rate of advanced or recurrent gastric cancer to S-1 (TS-1®) is 46.5%, which is higher than the response rate of this type of cancer to any other anticancer agent. However, the incidence of adverse reactions to this drug has also been reported to be as high as 83.2%. According to a postmarketing survey, adverse reactions to this drug begin to appear 2–3 weeks after the start of drug administration. With these findings in mind, we recently devised a new dosing regimen for the drug, by which the drug is administered for 2-week periods separated by 1-week drug-free intervals (the 2-week regimen). The aim of this retrospective study was to evaluate the efficacy and feasibility of the 2-week regimen in comparison with a 4-week dosing regimen with a 2-week interval between sessions (the 4-week regimen) as the historical control.**

Methods. **The subjects were 27 patients with advanced or recurrent gastric cancer who received S-1 therapy at our center between September 1999 and November 2001. Of these patients, 14 who received the 4-week regimen before January 2001 served as historical controls, and the results in these patients were compared with those of the remaining 13 patients, who received the 2-week regimen after February 2001. Patient backgrounds, adverse reactions, compliance, and efficacy were investigated retrospectively.**

Results. **The incidence of adverse reactions tended to be lower in the 2-week-regimen group (77%) than in the 4-week-regimen group (93%). The percentage of patients who received the drug for 6 months in complete compliance with the dosing schedule, as calculated by the Kaplan-Meier method, was 85% in the 2-week-regimen group and 40% in the 4-week-regimen group. The response rate to the drug was 23% in the 2-week-regimen group and 21% in the 4-week-regimen group.**

Conclusion. **These results suggest that this 2-week regimen may mitigate adverse reactions and prolong the medication period.**

Key words S-1 · 2-Week regimen · Gastric cancer

Introduction

5-FU is one of the most frequently used anticancer agents in the treatment of solid cancers, such as gastrointestinal cancer [1]. A number of regimens of 5-FU, devised based on the pharmacokinetic characteristics of the drug, have been studied. Continuous intravenous drip infusion of the drug for 4 weeks or more has been reported to yield higher response rates than a single intravenous injection, and has attracted close attention as a possible optimum dosing regimen of 5-FU [2]. However, gastrointestinal mucosal injury and the hand-foot syndrome have been identified as dose-limiting toxicities of this regimen [3]. Furthermore, continuous intravenous drip infusion involves complex manipulation, and the patient must be immobilized for long periods of time. In addition to these disadvantages, complications due to indwelling catheters must also be considered [4,5]. S-1 [6,7] is an oral anticancer preparation composed of a mixture of tegafur (FT, a prodrug of 5-FU), 5-chloro-2,4-dihydroxypyridine (CDHP, a biochemical modulator which inhibits the biodegradation of 5-FU) [8], and potassium oxonate (Oxo, added to reduce the gastrointestinal toxicity of 5-FU) [9]. It is a member of the DIF family of drugs (dihydropyrimidine dehydrogenase [DPD] inhibitory fluoropyrimidines) [10]. When S-1 was administered orally, the time course of changes in the blood 5-FU levels resembled that noted after intravenous drip infusion of 5-FU [11]. When this preparation was administered by a 4-week regimen, in which one cycle of treatment consisted of drug administration for 4 weeks, followed by a 2-week drug-free period, the response rate of advanced or recurrent gastric cancer was 46.5%, which was higher than that of this type of cancer to any other anticancer agent

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[12]. In premarketing clinical trials, the incidence of adverse reactions to this preparation was high (83.2%), and 20.3% of all adverse reactions were reported to be of grade 3 or greater severity [12,13]. In a postmarketing survey of S-1 [14], which included 3294 patients with advanced or recurrent gastric cancer, the incidence of adverse reactions following administration of the drug at the usual dose level (80 mg/m^2) as per the 4-week regimen was 74.1%, which was approximately equal to the incidence obtained in the premarketing trials. However, the percentage of patients who received three or more courses of the drug was 47% according to the postmarketing survey, which was lower than that (64%) recorded in the premarketing clinical trials. The major reasons for discontinuation of the drug during the first or second course of therapy were exacerbation of symptoms (43%) and adverse drug reactions (33%). Therefore, in order to be able to administer the drug for prolonged periods of time, the incidence of adverse reactions of the drug should be reduced.

Based on the knowledge that adverse reactions to oral S-1 therapy begin to appear 2–3 weeks after the start of dosing, we recently devised a new dosing regimen for the drug by which the drug is administered for 2-week periods separated by 1-week drug-free intervals (the 2-week regimen). This regimen was devised based on the expectation that providing a 1-week drug-free period in the third week of the dosing cycle (when adverse reactions are the most likely to occur) would reduce the incidence of adverse reactions to the drug and allow the patients to tolerate the drug for longer periods of time, while the antitumor activity of the 4-week regimen would be maintained. The usefulness of this new regimen (2-week regimen) was evaluated retrospectively in comparison with that of the conventional 4-week regimen.

Subjects and methods

Subjects

The subjects of the study were 27 patients with advanced or recurrent gastric cancer who received S-1 therapy at our center between September 1999 and November 2001. Informed consent was obtained from each patient prior to the start of S-1 therapy. The 14 patients, who began to receive treatment between September 1999 and January 2001 were treated with the 4-week regimen of S-1, by which they received the drug for 4-week periods followed by 2-week drug-free intervals (4-week regimen group; 4 W/2 W). The remaining 13 patients, who began to receive treatment after February 2001, were treated with the 2-week regimen, by which the patients received the drug for 2-week periods followed by a drug-free interval for 1 week (2-week regimen group; 2 W/1 W). Patients who satisfied all of the following requirements were included in the study: (1) patients with inoperable gastric cancer or recurrent gastric cancer; (2) patients with adequate marrow, liver, and kidney functions; (3) patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) between 0 and 2; (4) patients expected to survive for 3 months or more after the start of the treatment; and (5) patients who gave informed consent for the therapy.

Methods

S-1 was administered at a daily dose of 80–120 mg/body, determined from the body surface area. One cycle of treatment in the 4-week regimen consisted of 4 weeks of drug administration followed by a 2-week drug-free period. Each course of treatment in the 2-week regimen consisted of 2 weeks of drug administration followed by a 1-week drug-free period. If a grade 3 or higher hematologic toxicity or a grade 2 or higher nonhematologic toxicity was observed, administration of S-1 was discontinued until recovery from these adverse events.

Evaluation and observations

Adverse drug reactions, compliance with the dosing schedule, reasons for discontinuation of medication, and drug efficacy in patients with lesions that allowed valid evaluation were compared retrospectively between the two regimen groups. Adverse reactions were evaluated according to the National Cancer Center Common Toxicity Criteria (NCC-CTC). Metastatic lesions were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) [15]. For primary lesions, responses were evaluated according to the Japanese Research Society for Gastric Cancer criteria, using either gastroscopy or barium gastrography [16]. With the scheduled dosing period set at 3 months (the period considered as the mean survival time for patients with advanced gastric cancer), the ratio of the actual cumulative dose to the planned cumulative dose was calculated to yield the relative performance (RP). Patients in whom the drug was discontinued for reasons other than adverse drug reactions (e.g., recurrence, death, surgery, or patient's refusal) were deemed to be dropouts. The percentage of patients who received the drug regimen for at least 6 months after the start of dosing was calculated by the Kaplan-Meier method.

Results

Patient characteristics

The characteristics of the patients in each group are shown in Table 1. There were no significant inter-

Table 1. Patient characteristics

		2 W/1 W (n = 13) February to November 2001	4 W/2 W (n = 14) September 1999 to January 2001
Age in years (median)		36–79 (67)	36–77 (65)
Sex (M : F)		9 : 4	10 : 4
Performance status	0	5	5
	1	5	7
	2	3	2
Prior gastrectomy	(−) Unresectable	4	3
	(+)	9	11
Prior chemotherapy	(−)	6	4
	(+)	7	10
	Intravenous	2	6
	Per os	5	3
	Intraperitonial	2	1
	Intraarterial	1	0
Dose (mg/day)	80	2	5
	100	8	6
	120	3	3
No. of treatment courses or cycles (median)		0.5–11 (4.0)	0.25–10 (2.8)
	Total weeks (W) (median)	1 W–22 W (8 W)	1 W–40 W (11 W)
Duration of follow-up; months (median)*		2.5–10.1 (5.7)	2.4–17.5 (7.5)
Treatment	Inpatient	1	1
	Inpatient + outpatient	5	3
	Outpatient	7	10
Histopathological type	Intestinal	8	8
	Diffuse	5	6

* $P < 0.05$
2 W/1 W, Two-week drug administration followed by 1-week washout period; 4 W/2 W, 4-week drug administration followed by 2-week washout period

Table 2. Number of patients who experienced toxic effects

	2 W/1 W (n = 13)						4 W/2 W (n = 14)					
	Grade						Grade					
Toxic effects	0	1	2	3	4	Overall (%)	0	1	2	3	4	Overall (%)
Blood												
Leucocytes	8	4	1	0	0	5 (38%)	8	3	3	0	0	6 (43%)
Hemoglobin	9	3	1	0	0	4 (31%)	10	1	2	1	0	4 (29%)
SGOT	13	0	0	0	0	0	10	2	2	0	0	4 (29%)
Bilirubin	13	0	0	0	0	0	13	0	1	0	0	1 (7%)
Stomatitis	12	1	0	0	0	1 (8%)	12	1	1	0	0	2 (14%)
Nausea	11	2	0	0	0	2 (15%)	13	1	0	0	0	1 (7%)
Anorexia	10	2	0	1	0	3 (23%)	10	2	1	1	0	4 (29%)
Diarrhea	11	1	1	0	0	2 (15%)	9	3	2	0	0	5 (36%)
Fatigue	10	1	1	1	0	3 (23%)	10	0	3	1	0	4 (29%)
Skin lesion	9	4	0	0	0	4 (31%)	10	2	1	1	0	4 (29%)
Overall toxicities						10 (77%)						13 (93%)
Grade 1 toxicities						5 (38%)						2 (14%)
Grade 2 toxicities						4 (31%)						9 (64%)
Grade 3 or 4 toxicities						1 (8%)						2 (14%)

group differences in terms of the median age, male-to-female ratio, PS, history of prior treatment, type of previous treatment received, or the histological type of the cancer. The follow-up period was significantly longer in the 4-week regimen group. Combination therapy of 5-FU and low-dose cisplatin (CDDP) was the most frequent intravenous regimen administered before S-1 therapy. Oral anticancer agents other than S-1 had also been used for oral drug therapy prior to the present therapy. Intraoperative operative CDDP

Table 3. Rate of medication completion

Duration of administration (W) (No. of courses)	2 W/1 W (n = 13)				Duration of administration (W) (No. of cycles)	4 W/2 W (n = 14)			
	No. (%)	Cause of discontinuance				No. (%)	Cause of discontinuance		
		Toxicity	PD No.	Continue			Toxicity	PD No.	Continue
~4 W (~2 courses)	2 (15%)	2	0	0	~4 W (~1 cycle)	4 (29%)	4	0	0
~8 W (~4 courses)	5 (38%)	0	3	2	~8 W (~2 cycles)	2 (14%)	1	1	0
8 W~ (5 courses~)	6 (46%)	0	2	4	8 W~ (3 cycles~)	8 (57%)	2	5	1
Total No. (%)	13	2 (15%)	5 (38%)	6 (46%)	Total No. (%)	14	7 (50%)	6 (43%)	1 (7%)
Median (W)	8 W (1 W–22 W)				Median (W)	11 W (1 W–40 W)			

PD, Progressive disease

Fig. 1. Rate of medication completion in the 2-week-(*2 W/1 W*) and 4-week (*4 W/2 W*)-regimen groups for 6 months, calculated by the Kaplan-Meier method. Discontinuance of S-1 administration because of adverse events was treated as the event. Patients in whom the drug was discontinued for reasons of recurrence, death, surgery, or patient's refusal were deemed to be dropouts. *W*, Weeks

(100 mg) was the major intraperitoneal drug therapy administered before S-1 therapy.

Adverse reactions

Table 2 summarizes the data concerning adverse reactions observed among the 27 patients. The incidence of adverse reactions was 77% in the 2-week-regimen group and 93% in the 4-week regimen group. Unlike in the 4-week-regimen group in which grade 2 or more severe adverse reactions were predominant, grade 1 adverse reactions were predominant in the 2-week-regimen group (difference not significant).

Compliance with the dosing schedule

The percentage of patients who received oral S-1 therapy for 8 weeks or more was 46% in the 2-week- and 56% in 4-week-regimen groups. In all patients in whom the drug was discontinued, it was discontinued for reasons of adverse reactions in 15% in the 2-week-regimen group and 50% in the 4-week-regimen group (Table 3). The RP, as calculated for the scheduled dosing period of 3 months, was 84% in the 2-week-regimen group and 72% in the 4-week-regimen group. The percentage of patients in whom the drug could be continued for 6 months, as calculated by the Kaplan-Meier method, was 85% in the 2-week-regimen group and 40% in the 4-week-regimen group (Fig. 1).

Table 4. Response to treatment

		CR	PR	SD	PD	NE	RR
2 W/1 W	Overall	0	3	6	3	1	23% (3/13)
	Metastatic site	0	3	6	3	1	23% (3/13)
	Lymph node	0	3	4	1	0	38% (3/8)
	Liver	0	0	0	1	0	0%
	Others	0	1	2	1	1	20% (1/5)
	Primary	0	2	2	0	0	50% (2/4)
4 W/2 W	Overall	0	3	5	3	3	21% (3/14)
	Metastatic site	0	3	5	3	3	21% (3/14)
	Lymph node	0	2	4	3	0	22% (2/9)
	Liver	0	1	0	1	1	33% (1/3)
	Others	0	1	1	0	2	25% (1/4)
	Primary	0	1	2	0	0	33% (1/3)

CR, Complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; RR, response rate

Efficacy

The response rate was 23% in the 2-week-regimen group and 21% in the 4-week-regimen group (Table 4). Prior chemotherapy did not affect the efficacy either in the 2-week; or in the 4-week-regimen group (data not shown).

Discussion

It is more difficult for effective blood levels of 5-FU to be achieved following oral 5-FU administration than following continuous intravenous drip infusion. Even when effective blood 5-FU levels are achieved following oral 5-FU administration, adverse reactions (e.g., in the digestive tract) are frequent. S-1 is a preparation of 5-FU designed to reduce its gastrointestinal toxicity. In a phase II clinical study, the response rate of advanced or recurrent gastric cancer to this drug preparation was 46.5% [12], higher than that of this cancer to conventional oral anticancer agents such as uracil plus tegafur (UFT) and 5′-deoxy-5-fluorouridine (5′-DFUR) [17,18]. However, the incidence of adverse events following S-1 therapy is high (83.2% in premarketing clinical trials [12,13]). In the postmarketing survey, conducted on 3294 patients, evaluation of the drug's hematological toxicity revealed that the median time for the WBC, RBC, and platelet counts to reach their lowest levels was 22 days [14]. In the same study, the median time to the onset of nonhematological adverse reactions (diarrhea, skin symptoms, stomatitis, etc.) was 14–15 days. In regard to the duration of therapy, the percentage of patients in whom a third cycle of therapy could be started (i.e., the percentage of patients who tolerated 8 weeks of the oral regimen) was 64% in premarketing clinical trials and 47% in the postmarketing survey. The reason for discontinuation of the drug was exacerbation of symptoms in 43% of all patients and adverse reactions in 33%. A new regimen for administering S-1 was therefore sought that could replace the conventional 4-week regimen and reduce the incidence of adverse reactions, but have comparable antitumor activity. The 2-week regimen evaluated in this study appears to be promising. The incidence of adverse events was lower with this regimen than with the conventional 4-week regimen. Both hematological and nonhematological adverse reactions tended to be less severe. Considering that the median time required for maximal marrow suppression (a sign of hematological toxicity) and the median time required for the onset of diarrhea and skin symptoms (a sign of nonhematological toxicity) in the postmarketing survey were determined to be 22 days and 15 days, respectively, the provision of a drug-free interval in the third week of the drug cycle (the time when adverse reactions are the most likely to develop) should reduce the incidence of adverse reactions. Furthermore, among the patients in whom oral S-1 administration had to be discontinued midway, the percentage of patients in whom the discontinuation was due to adverse reactions was much lower in the 2-week-regimen group (15%) than in the 4-week regimen group. The percentage of patients in whom the oral treatment could be continued for 6 months was as high as 85% in the 2-week-regimen group, higher than that in the 4-week regimen group, although the difference was not significant. While further follow-up of patients who received the 2-week-regimen of S-1 therapy is necessary, because the follow-up period in these patients was not adequate, the data collected from these patients receiving therapy at our center indicate that many of them showed improved appetite, reduction in the severity of the symptoms of cancer, and a lower incidence of gastrointestinal adverse reactions. The response rate of these patients to the 2-week regimen of S-1 therapy was comparable to that recorded in the postmarketing survey (26%).

We concluded that the 2-week regimen of S-1 may mitigate adverse reactions and prolong the medication period. A multicenter collaborative study of this S-1 regimen as a phase II clinical study is currently ongoing at Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG).

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