Feasibility Study of Supportive Care Using Lafutidine, a Histamine H2 Receptor Antagonist, to Prevent Gastrointestinal Toxicity During Chemotherapy for Gastric Cancer

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Abstract. *The present study evaluated the efficacy of lafutidine, a histamine H2 receptor antagonist, for reducing gastrointestinal toxicities during adjuvant chemotherapy using oral fluorouracil anticancer drugs for gastric cancer. Patients and Methods: Patients with stage II (T1 cases excluded) or stage III gastric adenocarcinoma who underwent gastrectomy with D2 lymphadenectomy achieving R0 resection from 2011 to 2013 were prospectively enrolled in the study. Patients were randomly assigned to either S-1 treatment or S-1 plus lafutidine treatment. Quality of life and gastrointestinal toxicity were evaluated before chemotherapy and at 2, 4, and 6 weeks after the beginning of treatment. Results: The incidence of diarrhea during chemotherapy was significantly lower in the S-1 plus lafutidine group than in the group treated with S-1 alone (10% vs. 83%, respectively; p=0.002). The grades of diarrhea and nausea during chemotherapy were also significantly lower compared to those before chemotherapy in patients receiving S-1 plus lafutidine than in those administered S-1 alone. The rate of patients requiring a dose reduction or interruption of S-1 was significantly lower in the S-1 plus lafutidine group than in the group treated with S-1 alone (30% vs. 83%, respectively; p=0.027). Conclusion: Lafutidine might be useful not only for preventing gastrointestinal toxicities during adjuvant chemotherapy for gastric cancer, but also for improving compliance with taking oral fluorouracil anticancer drugs. However, this indication needs to be confirmed in a larger, prospective, randomized, controlled trial.*

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Gastric cancer is the third most common cancer and the second most common cause of cancer-related death worldwide. It is also the most common malignancy in Asia, South America, and Eastern Europe (1). Based on results from the Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC), postoperative administration of S-1 for one year is now considered the standard adjuvant treatment for curatively resected stage II/III gastric cancer in Japan (2). S-1 is an oral anticancer drug that combines the pro-fluorouracil drug tegafur, an inhibitor of dihydropyrimidine dehydrogenase, and potassium oxonate, in a molar ratio of 1:0.4:1. However, treatment with S-1 was continued for at least three months in 87.4%, at least six months in 77.9%, and 12 months in 65.8% of patients in the S-1 group (n=529) of the ACTS-GC study, with the most important reason for withdrawal of treatment cited as adverse events, including gastrointestinal toxicity (2).

Such adverse events due to anticancer drugs, including gastrointestinal toxicity, could therefore mediate a decrease in patients' quality of life and compliance with taking drugs. Recent reports of biomarkers being used to predict such gastrointestinal toxicities during chemotherapy may lead to a reduction in these adverse events caused by anticancer drugs (3, 4). Indeed, lafutidine, a histamine H2 receptor antagonist, not only reduces acid secretion and 5-fluorouracil-induced mucosal injury, but also strengthens the mucosal barrier of human gastric mucosa (5, 6), and therefore, may also help reduce drug-related gastrointestinal side-effects.

This study, thus, evaluated the efficacy of lafutidine in reducing gastrointestinal toxicities such as stomatitis, loss of appetite, nausea, vomiting and diarrhea, during adjuvant chemotherapy for gastric cancer using oral fluorouracil anticancer drugs.

Patients and Methods

Patients and procedures. From March 1, 2011 to July 30, 2013, 22 patients were enrolled at the Kochi Medical School Hospital. Eligibility criteria for patient inclusion in this study were as follows:

gastrectomy (excluding total gastrectomy) with D2 lymphadenectomy for stage II (excluding T1 cases) or stage III gastric adenocarcinoma achieving R0 resection, 20-90 years of age, an Eastern Cooperative Oncology Group performance status of 0-1, and adequate function of principal organs. Stage classification and assessment of resected specimens accorded with the International Union against Cancer TNM classification (7) and the TNM Supplement (8). Exclusion criteria were synchronous or metachronous cancer in other organs; contraindication for administration of S-1 or lafutidine; past illness from drug allergy greater than grade 3; grave underlying disease such as paresis of the intestine, bowel obstruction, interstitial pneumonia, pulmonary fibrosis, difficult-to-control diabetes mellitus, heart, renal or hepatic failure; watery diarrhea; pregnancy; lactation; planning pregnancy (both men and women); and as deemed unsuitable by the doctors responsible for this study. After the above eligibility and exclusion criteria were confirmed by the surgeon immediately following the initial laparotomy, patients were randomized to either the S-1 alone or the S-1 plus lafutidine treatment group. Randomization was performed using blinded envelopes to avoid selection bias. All patients gave their written informed consent before undergoing randomization.

All patients received 80 mg of S-1 per square meter of body surface area per day orally, for four weeks, followed by two weeks of no chemotherapy. In patients assigned to receive S-1 plus lafutidine, 10 mg of lafutidine was given orally once daily in addition to S-1.

Quality of life and gastrointestinal toxicities were evaluated before chemotherapy and at 2, 4, and 6 weeks after the beginning of treatment, using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (9) and the Gastrointestinal Symptom Rating Scale (GSRS) (10).

The study was approved by the Institutional Review Board at the Kochi Medical School Hospital (Approval number: 21-65), and was undertaken in accordance with the Helsinki declaration and the Japanese Good Clinical Practice Guidelines.

Statistical analysis. We used the Mann–Whitney *U*-test to evaluate differences in the ordinal and continuous variables between groups and the chi-square test to compare the categorical variables. A *p*-value of less than 0.05 was considered to indicate statistical significance. Statistical analysis was performed using SPSS for Windows version 13.0 (SPSS, Inc., Chicago, IL, USA).

Results

Clinical characteristics. Table I summarizes the clinical characteristics of all 22 patients in this study. Our cohort comprised of 18 men and 4 women, with a median age of 68 years (range=56-80 years). The patients included six cases of stage II, eight cases of stage IIIA, and eight cases of stage IIIB adenocarcinoma. There were no significant differences in clinical characteristics between the groups treated with S-1 alone and with S-1 plus lafutidine.

Gastrointestinal toxicities during chemotherapy. The incidence of gastrointestinal toxicities during the first cycle of adjuvant chemotherapy is presented in Table II. There were no patients with grade 3 or 4 gastrointestinal toxicities in either group, but the frequency of gastrointestinal toxicities, including stomatitis, loss of appetite, nausea, vomiting, and diarrhea, was higher in the group treated with S-1 alone than in the S-1 plus lafutidine group. The incidence of diarrhea was significantly lower in the S-1 plus lafutidine group than in the group treated with S-1 alone (10% *vs*. 83%, $p=0.002$) (Table II).

Table I. *Patients' characteristics*.

	S-1 alone (n=12)	S-1 + Lafutidine (n=10)	*p*-Value
Age, median (range), years	68 (56-80)	67 (57-78)	0.706
Gender			
Male	10	8	0.724
Female	2	2	
Stage			
II	4	2	0.974
IIIA	4	4	
IIIB	4	4	

The CTCAE grade for gastrointestinal toxicities experienced during chemotherapy was expressed as the change in grade from that assessed before the start of chemotherapy. Table III shows the CTCAE grades at two and six weeks after the start of chemotherapy in the two groups. The median grade for diarrhea at two and six weeks after the beginning of chemotherapy was significantly lower in the S-1 plus lafutidine group than in the group treated with S-1 alone ($p=0.009$ and $p=0.001$, at two and six weeks, respectively) (Table III). Similarly, the grade for nausea at two weeks after chemotherapy was significantly lower in the S-1 plus lafutidine group than in the group treated with S-1 alone ($p=0.019$) (Table III). All grades were lower for those treated with S-1 plus lafutidine compared with those treated with S-1 alone; however, there were no significant differences for stomatitis, loss of appetite, and vomiting between the groups.

Dose reduction or interruption of S-1. Dose reduction or interruption of S-1 was needed in 13 patients during chemotherapy because of adverse events, including gastrointestinal toxicities. The percentage of patients requiring dose reduction or interruption of S-1 was significantly lower in the S-1 plus lafutidine group than in the group treated with S-1 alone (30% *vs*. 83%, respectively; $p=0.027$).

Assessment of quality of life. Quality of life was assessed using GSRS scores, measured before and during chemotherapy, and expressed as the change in score. The results for the two groups are given in Table IV. In interpreting GSRS results, a higher score indicates a higher level of symptom or problem.

Table II. *Incidence of gastrointestinal toxicities during the first cycle of chemotherapy (for all grades).*

Toxicity	S-1 alone, n (%)	S-1+Lafutidine, n (%)	*p*-Value
Stomatitis	3 (25)	2 (20)	0.994
Loss of appetite	9 (75)	5 (50)	0.378
Nausea	6 (50)	1 (10)	0.074
Vomiting	2 (17)	0	0.481
Diarrhea	10 (83)	1 (10)	0.002

The median scores for reflux at two and six weeks after the beginning of chemotherapy were significantly lower in the S-1 plus lafutidine group than in the group treated with S-1 alone (p=0.027 and p=0.019, for two and six weeks, respectively) (Table IV). There were no significant differences in the other scores between the groups.

Discussion

We found that supportive care using lafutidine was useful for preventing gastrointestinal toxicities during chemotherapy for gastric cancer. Specifically, our findings demonstrated a lower grade of diarrhea in patients administered lafutidine than in those given S-1 alone during adjuvant chemotherapy. Furthermore, the rate of dose reduction or interruption of S-1 was significantly reduced by the addition of lafutidine.

Proton pump inhibitors (PPIs), which are strong antisecretory agents that act on the (H^+/K^+) ATPase of gastric parietal cells, and histamine H2 receptor antagonists are now widely used for the therapeutic control of acid-related disorders, including gastroesophageal reflux disease and peptic-ulcer diseases caused by stress, non-steroidal anti-inflammatory drugs, and *Helicobacter pylori* infection (11, 12). In rat, the PPIs lansoprazole and omeprazole protected the small intestine against indomethacin-induced mucosal damage (11, 13), with the effect attributed to these anti-inflammatory and antioxidative mechanisms of these drugs (11, 14). However, other studies have reported that PPIs, including lansoprazole and omeprazole, and other histamine H2 receptor antagonists, such as cimetidine, have no effect on mucin biosynthesis in the rat gastrointestinal mucosa (6).

Mucin, a major component of mucus, is considered a principal factor in the physiological defense mechanisms of the gastrointestinal mucosa. Lafutidine stimulates mucin accumulation and has a protective effect against gastric mucosal damage induced by hydrochloric acid in the rat (15, 16). Murashima *et al*. also demonstrated that a delay in healing of acid-induced gastric mucosal lesions induced by 5-fluorouracil infusion could be reversed by the administration of lafutidine in the rat (17). These authors suggested that mucin accumulation by lafutidine was associated with amelioration of gastric mucosal blood flow mediated by capsaicin-sensitive afferent neurons, because this effect was attenuated by the chemical ablation of these neurons (17, 18). Indeed, stimulation of capsaicin-sensitive sensory neurons by lafutidine releases the neurotransmitter calcitonin gene-related peptide into the vascular bed of the gastrointestinal tract, causing vasodilation and mucin production (15, 19-21). Therefore, lafutidine may promote goblet cell mucus function *via* such neuronal stimulation, and in turn, an increased production of mucin. Furthermore, in addition to the stomach, lafutidine ameliorates mucosal damage and decreased mucin accumulation induced by 5-fluorouracil in the rat jejunum and ileum (6, 22). Together with the results of these animal studies, our clinical results suggested that lafutidine could be effective in reducing gastrointestinal mucosal damage induced during cancer chemotherapy. However, further studies are

Table III. *Assessment of gastrointestinal toxicities using Common Terminology Criteria for Adverse Events (9).*

	Weeks after chemotherapy					
	S-1 alone (n=12)		S-1+Lafutidine (n=10)		*p*-Value	
Toxicity	2	6	2	6	2	6
Stomatitis	0.17	0.25	0.10	0.20	0.669	0.831
Loss of appetite	0.67	0.58	0.30	0.40	0.157	0.487
Nausea	0.42	0.25	0.00	0.10	0.019	0.388
Vomiting	0.08	0.17	0	0	0.374	0.193
Diarrhea	0.67	1.00	–0.10	–0.10	0.009	0.001

Values are medians and are expressed as the change in grade from the start of chemotherapy.

Table IV. *Assessment of symptoms using the Gastrointestinal Symptom Rating Scale (10).*

	Weeks after chemotherapy					
	S-1 alone (n=12)		S-1+Lafutidine (n=10)		*p*-Value	
Symptom	2	6	2	6	2	6
Reflux	–0.08	0.08	–1.61	–1.60	0.027	0.019
Abdominal pain	0.25	0.08	–0.70	–0.10	0.251	0.160
Indigestion	–0.83	0.32	0.73	–0.18	0.490	0.428
Diarrhea	0.80	0.89	1.25	0.50	0.809	0.507
Constipation	–0.98	–0.75	1.73	–0.18	0.166	0.847
Change in total score	–1.09	0.35	2.74	–2.29	0.711	0.296

Values are medians and are expressed as the change in score from the start of chemotherapy.

required to clarify the detailed mechanism for cancer chemotherapy-induced intestinal injury.

Although adjuvant chemotherapy after complete resection for gastric cancer is therapeutically useful, adverse events caused by anticancer drugs, including gastrointestinal tract toxicities, may result in disturbance or even discontinuation of chemotherapy. Therefore, preventing such gastrointestinal toxicities during chemotherapy is extremely important for improving the prognosis of patients with cancer. Some biomarkers may be useful for predicting chemotherapy tolerability and adverse events due to anticancer drugs, including gastrointestinal toxicities (3, 4). In addition, some biological substances, such as glutamine, medium-chain triglycerides, and soluble dietary fiber, may protect against intestinal barrier dysfunction and improve mucosal injury-enhanced mucus secretion from the goblet cells in the small intestine (4, 23, 24). However, these previous studies included animal models, while our study demonstrated the clinical advantage of lafutidine in significantly lowering the number of patients requiring a dose reduction or interruption of adjuvant chemotherapy during clinical treatment for gastric cancer.

The present study also showed that the grade of diarrhea using CTCAE was significantly lower in patients receiving S-1 plus lafutidine than in those not receiving lafutidine. However, no significant difference between the groups was evident for the diarrhea score using GSRS. According to the CTCAE, diarrhea is defined as a disorder characterized by frequent and watery bowel movements, with the defined grade depending on the frequency of stools per day over baseline. On the other hand, the GSRS includes 15 items, each rated on a seven-point Likert scale ranging from no discomfort to very severe discomfort. The diarrhea score was calculated by taking the mean of the individual scales for the items of diarrhea, loose stools, and urgent need for defecation. Thus, the differences in these definitions may underlie the discrepancy between the diarrhea scores for CTCAE and GSRS.

We recognize the following limitations of the present study. Firstly, the sample size was insufficient to clarify any definitive or long-term changes in gastrointestinal toxicities during chemotherapy. Secondly, the present study was carried out only in the first cycle of chemotherapy using S-1, while continuation of S-1 administration for one year is recommended. Further studies with adequate statistical power and a larger number of patient subgroups are needed to examine the reliability and accuracy of assessing lafutidine efficacy during chemotherapy for gastric cancer.

In conclusion, lafutidine might be useful, not only for preventing gastrointestinal toxicities during adjuvant chemotherapy for gastric cancer, but also for improving patient compliance with taking oral fluorouracil anticancer drugs. However, further investigations, including a larger-sized prospective study, are expected to confirm these findings, especially the relationship between lafutidine and the reduction of diarrhea during adjuvant chemotherapy for gastric cancer.

Conflicts of Interest

The Authors declare no conflicts of interest.

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