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Clinical characteristics and endoscopic morphologic features of lower gastrointestinal toxicity induced by S-1, an oral fluoropyrimidine-based anticancer drug

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Objectives: Anticancer drugs may cause diarrhea, but the underlying endoscopic characteristics of lower gastrointestinal toxicity remain unclear. This study aimed to clarify the clinical characteristics and endoscopic morphologic features associated with diarrhea induced by S-1, a fluoropyrimidine-based anticancer drug.
Methods: Patients with gastrointestinal cancer who received S-1 alone or S-1-based combined chemotherapy from September 2000 through January 2006 were included. We examined demographic characteristics related to the risk of diarrhea. We also assessed the lower gastrointestinal endoscopic findings in patients with grade 3 or higher gastrointestinal toxicities.
Results: Among 327 patients with gastrointestinal cancer, 90 patients (27.5%) had diarrhea. With regard to clinical characteristics, diarrhea was associated with advanced age, female sex, a history of gastrointestinal surgery, the concomitant use of radiotherapy, a relatively high stool frequency before treatment, and the absence of peritoneal dissemination. Lower gastrointestinal endoscopy was performed in 8 patients with grade 3 lower gastrointestinal toxicities. All patients had lesions in the terminal ileum, and 1 patient had lesions in the rectum. Endoscopic findings were injury in a diffuse distribution pattern in an elongated segment of the small intestine.
Conclusions: We identified the risk factors and endoscopic characteristics of S-1-induced diarrhea.

Key words: anticancer drugs, adverse reaction, diarrhea, endoscopic morphology, S-1

Introduction

Anticancer drugs are commonly used worldwide. Most anticancer drugs cause gastrointestinal (GI) symptoms, including diarrhea. 5-Fluorouracil is converted into 5-fluoro-deoxyuridine monophosphate in the GI mucosal epithelium, which is accompanied by active cell division. This results in GI toxicities such as diarrhea, stomatitis, nausea, and vomiting.[1] A combination of leucovorin and 5-fluorouracil is sometimes used for biochemical modulation therapy; however, this causes severe diarrhea due to lower GI toxicity in 15% to 20% of patients.[2] Such toxicities are often a dose-limiting factor; and, therefore, a reduction in GI toxicity may lead to better antitumor effectiveness.

S-1 (TS-1, Taiho Pharmaceutical, Tokyo) is a relatively new oral fluoropyrimidine preparation that combines tegafur, a prodrug of 5-fluorouracil, with 5-chloro-2,4-dihydroxypyridine (gimeracil), a dihydropyrimidine dehydrogenase inhibitor, and potassium oxonate in a molar ratio of 1.0:0.4:1.0. Potassium oxonate inhibits the phosphorylation of 5-fluorouracil, specifically in GI mucosal cells, reducing GI toxicity, without compromising therapeutic effectiveness.[3] However, in a randomized phase III study of 5-fluorouracil alone versus a combination of cisplatin plus irinotecan versus S-1 alone in patients with unresectable gastric cancer in Japan, the incidences of grade 3 or 4 diarrhea were significantly higher with S-1 (7.0%) than were those with 5-fluorouracil (0.4%).[4]

A recent Japanese phase II study reported grade 4 colitis in only 1 patient treated with S-1, but the details were not specified.[5] In phase I studies performed in Europe and North America, S-1 treatment was associated

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with ileus in 1 to 2 patients[6-8] and rectal bleeding in 1 patient;[6] but whether or not lower GI endoscopy was performed was not reported. Oncologists rarely perform colonoscopy when prescribing anticancer drugs. Recent advances in colonoscopy, as well as endoscopy as a whole, have facilitated the detection and evaluation of lesions not only in the large intestine but also in the small intestine. However, very few studies have examined the endoscopic findings associated with the use of anticancer drugs. The objectives of this study, therefore, were to clarify the clinical characteristics and endoscopic morphologic features of lower GI toxicity induced by S-1.

Materials and Methods

Eligibility

The study group comprised patients with GI cancer who received S-1 alone or S-1-based combined chemotherapy at the Kitasato East Hospital from September 2000 through January 2006. This was a retrospective study of patients who met the following criteria: 1. the presence of a malignant GI tumor; 2. S-1 alone or S-1-based combined chemotherapy administered as first- or second-line treatment (including preoperative or postoperative adjuvant chemotherapy); 3. the possibility of oral intake; 4. no diarrhea before S-1 treatment or underlying disease associated with diarrhea; 5. no ileus; 6. a performance status (PS) of 0 to 3 on the Eastern Cooperative Oncology Group (ECOG) scale; and 7. adequate hematological function (white blood cell count, $>4 \times 10^3/\mu l$ and platelet count, $>100 \times 10^3/\mu l$), hepatic function (serum total bilirubin level, <2 mg/dl), renal function (serum creatinine level, <1.5 mg/dl), cardiac function, and respiratory function. The institutional review boards reviewed and approved the protocol.

Treatment

S-1 was administered orally twice daily, after breakfast and dinner. The dose of S-1 was determined according to body surface area (BSA) as: BSA <1.25 m^2, 40 mg; BSA 1.25 to 1.5 m^2, 50 mg; and BSA >1.5 m^2, 60 mg. The following treatment regimens based on those used in clinical trials were used (1 standard course of therapy is described for each): S-1 alone, S-1 for 28 days followed by 2 weeks of rest;[9] S-1 plus irinotecan, S-1 for 21 days followed by 2 weeks of rest, with irinotecan (80 mg/m^2) on days 1 and 15;[6] S-1 plus cisplatin, S-1 for 21 days followed by 2 weeks of rest, with cisplatin (60 mg/m^2) on day 8;[10] S-1 plus gemcitabine, S-1 for 14 days followed by 2 weeks of rest, with gemcitabine (1,000 mg/m^2) on days 1 and 15;[11] S-1 plus docetaxel, S-1 for 14 days followed by 1 week of rest, with docetaxel (40 mg/m^2) on day 1;[8] and S-1 plus cisplatin and docetaxel, S-1 for 14 days, followed by 2 weeks of rest, with cisplatin (60 mg/m^2) and docetaxel (40 mg/m^2) on day 1;[12] and S-1 plus leucovorin, S-1 for 14 days, followed by 2 weeks of rest, with leucovorin given at a fixed dose of 25 mg each time.[13]

Diagnosis of diarrhea and follow-up

The differential diagnosis of lower GI toxicity requires the exclusion of diseases associated with diarrhea. The diagnostic workup should include an interview to ascertain the patient's dietary history, such as the intake of raw food, the date and time of onset and the duration of diarrhea, and the fecal properties; physical examination; fecal culture to exclude infectious disease; general blood testing, including white blood cell differential counts and viral antigen/antibody testing; and an overall assessment of the patient's condition. Lower GI endoscopy and histopathological biopsy were performed as needed. Follow-up physical examinations and blood tests were performed at least once every 1 to 2 weeks. Toxicity was assessed according to the National Cancer Institute-Common Toxicity Criteria, version 2.0.

Statistical analysis

We investigated the risk factors of the diarrhea to assess S-1 induced lower GI toxicities. The following demographic characteristics of the patients were assessed: age, sex, chemotherapeutic regimen (S-1 alone vs. S-1-based combined chemotherapy), concomitant use of radiotherapy, the presence or absence of peritoneal dissemination, a history of GI surgery, the regular use of laxatives or nonsteroidal anti-inflammatory drugs (NSAIDs), whether chemotherapy was first-line or not, and whether stool frequency was 7 or more times per week before treatment. The SPSS II for Windows software package was used for statistical analyses, including sample-size calculation. Values were expressed as medians and ranges. Multivariate logistic regression analysis with forward selection was then performed to estimate odds ratios with 95% confidence intervals. A two-sided test was used to examine the significance of differences between the groups. Chi-square P values of <0.05 were considered to indicate statistical significance.

Results

Patient characteristics

The study group was comprised of 327 patients with GI cancer. The total number of treatment courses was 1,362.

The median number of treatment courses per patient was 3 (range, 1－30). The clinical characteristics of the patients are shown in Table 1. The most common diagnosis was gastric cancer, followed by colorectal cancer. Other diagnoses included esophageal cancer in 11 patients (3.4%), duodenal cancer in 2 (0.6%), and pseudomyxoma peritonei in 1 (0.3%). The primary site was unknown in 1 patient (0.3%). Most patients had a good PS (0－2) on the ECOG scale. The most common regimen was S-1 alone (in more than half of the patients), followed by a combination of S-1 and cisplatin. The field of radiation was the rectum in 24 patients, the esophagus in 3, the stomach in 1, the duodenum in 1, and the liver in 1 patient. GI surgery was performed before treatment in 78 patients (23.9%): gastrectomy in 26, colectomy in 18, proctectomy in 15, gastrojejunostomy in 12, esophagectomy in 3, duodenectomy in 3, and gastrectomy and colectomy in 1 patient.

Table 1. Clinical characteristics of 327 patients with gastrointestinal cancer

	No. of patients (%)
Age (years)	
Median	65
Range	21－92
Sex	
Male	225 (68.8)
Female	102 (31.2)
Diagnosis	
Gastric cancer	203 (62.1)
Colorectal cancer	58 (17.7)
Hepatobiliary cancer	34 (10.4)
Pancreatic cancer	17 (5.2)
Others	15 (4.6)
PS	
0－1	288 (88.1)
2－3	39 (11.9)
4	0 (0)
Chemotherapeutic regimen	
S-1 alone	189 (57.8)
S-1 + cisplatin	68 (20.8)
S-1 + irinotecan	41 (12.5)
S-1 + gemcitabine	16 (4.9)
S-1 + docetaxel	6 (1.8)
S-1 + cisplatin + docetaxel	5 (1.5)
S-1 + leucovorin	2 (0.7)
Radiotherapy	
Yes	30 (9.2)
No	297 (90.8)
GI surgery	
Yes	78 (23.9)
No	249 (76.1)
First-line treatment	289 (88.4)
Second-line treatment	38 (11.6)
Stool frequency before treatment/week	
0－6	210 (64.2)
≥7	117 (35.8)

PS, performance status; GI, gastrointestinal

Diarrhea

Among the 327 patients, 90 (27.5%) had diarrhea, with 11 (3.4%) developing grade 3 diarrhea. No patient had grade 4 diarrhea. The median number of treatment courses at the onset of diarrhea was 1 (range, 1－12). Diarrhea most frequently occurred 14 days (range, 1－39) after the start of treatment. Diarrhea of grade 1 to 3 severity was significantly associated with an age of 75 years or older, female sex, the concomitant use of radiotherapy, a relatively high stool frequency before treatment, and a history of GI surgery (Table 2). The incidence of diarrhea was significantly lower in cases with peritoneal dissemination than in those without peritoneal dissemination.

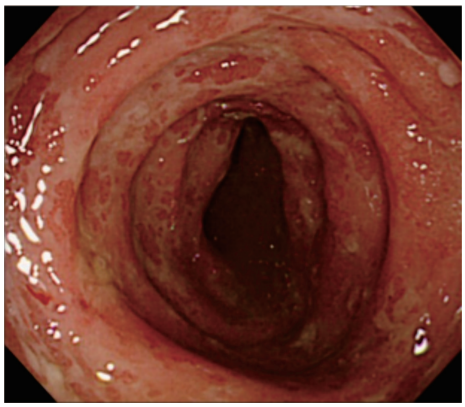
Details and clinical course of lower GI toxicity

Among the 14 patients with grade 3 GI toxicity (diarrhea, 11; ileus, 2; melena, 1), 6 patients with diarrhea were able to be followed-up in the outpatient department and other 8 patients required hospitalization for anemia, hypoproteinemia, dehydration, and electrolyte abnormalities. And among the latter 8 patients, 5 patients (62.5%) received S-1 alone, and 3 patients (37.5%) received S-1-based combined chemotherapy. One patient had elevated peripheral blood eosinophils, and 1 patient had been administered NSAIDs. The cytomegalovirus antigenemia assay for peripheral blood leukocytes was performed in 5 of 8 patients, and the results were negative in all 5 patients. After admission, food was withheld and intravenous infusion was conducted to allow the bowel to rest. Octreotide, antibiotics, and steroids, were administered to treat diarrhea. Ileus occurred in 2 patients. An ileus tube was inserted as needed. One patient with massive melena received blood transfusions and underwent embolization of the culprit artery. All the patients responded to treatment and were discharged. Diarrhea improved in the patient with eosinophilia on discontinuation of S-1, but the peripheral eosinophil count did not return to normal. Ileus was noted after repeated S-1 administration in patients who had used NSAIDs even though administration had been discontinued because of diarrhea. There were no treatment-related deaths.

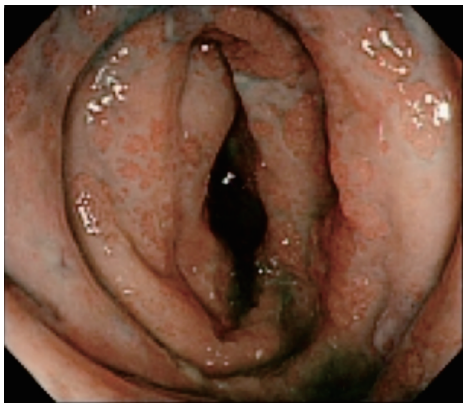
Table 2. Clinical characteristics of patients with diarrhea who received S-1-based chemotherapy

	Grade 1－3 diarrhea				Grade 3 diarrhea	
	No. of patients (%)	P value	OR	95% CI	No. of patients (%)	P value
Age (years)						
21－74	70 (25.7)				9 (3.3)	
75－92	20 (36.4)	0.021	2.118	1.126－4.227	2 (3.6)	NS
Sex						
Male	54 (24.0)				6 (2.6)	
Female	36 (35.3)	0.024	1.872	1.085－3.225	5 (4.9)	NS
PS						
0－1	79 (27.4)				9 (3.1)	
2－3	11 (28.2)	NS	-	-	2 (5.1)	NS
S-1-based regimen						
S-1 alone	43 (22.7)				5 (2.6)	
Combination therapy	47 (34.0)	NS	-	-	6 (4.3)	NS
Radiotherapy						
No	77 (25.8)				11 (3.6)	
Yes	13 (44.8)	0.034	2.438	1.069－5.560	0 (0)	NS
Peritonitis carcinomatosis						
No	80 (29.9)				10 (3.7)	
Yes	10 (10.6)	0.049	0.460	0.212－0.996	1 (1.6)	NS
GI surgery						
No	59 (23.7)				8 (3.2)	
Yes	31 (39.7)	0.003	2.375	1.335－4.219	3 (3.8)	NS
Regular use of laxatives						
No	41 (24.4)				5 (2.9)	
Yes	49 (30.8)	NS	-	-	6 (3.7)	NS
Regular use of NSAIDs						
No	69 (25.6)				8 (3.5)	
Yes	21 (36.2)	NS	-	-	3 (3.1)	NS
Treatment line						
First-line	80 (27.7)				8 (2.6)	
Second-line	10 (26.3)	NS	-	-	3 (11.1)	NS
Stool frequency/week						
0－6	43 (20.4)				9 (4.2)	
≥7	47 (40.1)	< 0.001	2.695	1.592－4.566	2 (1.7)	NS

OR, odds ratio; 95% CI, 95% confidence interval; NS, no significant difference; PS, performance status; GI, gastrointestinal

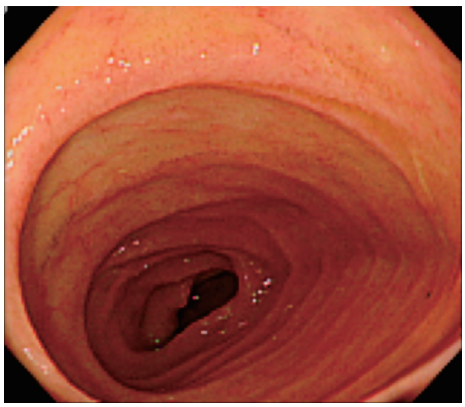


A. The mucosa was highly edematous and an irregularly shaped, diffuse ulcer was found.

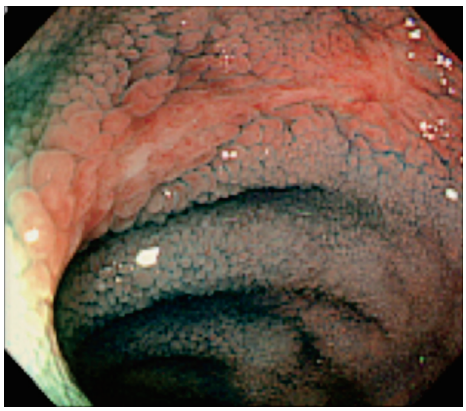


B. Mucosal defluvium is clearly seen in this indigo carmine dispersal image.

Figure 1. A 56-year-old woman with gastric cancer, multiple metastases to the abdominal lymph nodes, and peritoneal dissemination, received chemotherapy with S-1+cisplatin. She presented with abdominal pain, diarrhea, and vomiting that developed 17 days after the second course of treatment was started. Endoscopic findings in the terminal ileum 2 days after admission.



A. The mucosal villus displayed atrophic changes and the capillaries were transparent.



B. The mucosal ulceration scars are clearly seen in this indigo carmine dispersal image.

Figure 2. A 65-year-old man with rectal cancer, multiple metastases to the lung, and lymph node metastasis received chemotherapy with S-1+leucovorin. He presented with abdominal pain, vomiting, and ileus that developed 7 days after start of the second course of treatment. Endoscopic findings in the terminal ileum 18 days after admission.

Table 3. Endoscopic and pathologic findings of the ileum

Duration after admission	Endoscopic finding	Pathologic finding
≤1 week Range: 2－7 (days) Number of patients: 6	First: erythema and edema	Edema and marked infiltration of inflammatory cells
	Second: erosions and ulcers	Degenerative desquamation of the superficial mucosal epithelium
≥2 weeks Range: 15－70 (days) No. of patients: 4	First: capillary transparency	Villous atrophy
	Second: erosions and ulcer scars	Fibrosis

Lower GI endoscopy and histopathology

All 8 patients who were admitted underwent lower GI endoscopy and had lesions in the terminal ileum. Among those 8 patients, 1 patient also had lesions in the rectum. The terminal ileum mucosa of 6 patients who underwent lower GI endoscopy within 1 week after admission showed erythema and edema in a diffuse distribution pattern in an elongated segment of the small intestine. Irregularly shaped erosions and ulcers were diffusely found in the terminal ileum mucosa (Figure 1). Atrophy and ulcer scars were found within the terminal ileum mucosa of 4 patients who had undergone lower GI endoscopy more than 2 weeks after admission, when the symptoms had already improved (Figure 2).

Histopathological examination of endoscopic biopsy specimens of the ileal mucosa showed degenerative desquamation of the superficial mucosal epithelium, villous atrophy, and crypt shortening. Edema and marked infiltration of inflammatory cells such as neutrophils and eosinophils were noted in the lamina propria mucosae. Inflammation was extensive and affected the submucosa as well as the mucosa (Table 3). Granuloma formation and extensive fibrosis were also present in some areas. Biopsies showed no cytomegalic inclusion bodies or amoeba.

Discussion

In this study, advanced age, female sex, a history of GI surgery, the concomitant use of radiotherapy, and a relatively high stool frequency before treatment were found to be risk factors for S-1-induced diarrhea. Furthermore, the incidence of diarrhea was significantly lower in cases with peritoneal dissemination. Studies have identified female sex and advanced age as risk factors for fluorouracil-induced diarrhea.[14,15] Another study showed that chemotherapy is increasingly combined with radiotherapy as a radiosensitizer but that chemotherapy can also sensitize normal tissues to radiation toxicity.[16] In the present study, both S-1 alone and S-1-based combination therapy were included with varied radiation fields; therefore, the treatment plans were not unified. Furthermore, because this was a retrospective study, we were unable to verify whether or not patients actually received the drug amounts prescribed according to the chemotherapy regimen, due to the difficulty to verify compliance factors related to oral administration compared with instillation. Nevertheless, our results may be reliable as they are similar to those of other studies.[14-16]

Regarding history of GI surgery, a study comparing the pharmacokinetics of S-1 between patients who had and those who had not undergone gastrectomy reported only minimal differences.[17] However, in a Japanese study of patients with gastric cancer who received adjuvant chemotherapy after gastrectomy, the overall incidence of diarrhea was 59.8%, and the incidence of grade 3 or higher diarrhea was 3.1%,[18] indicating that gastrectomy was clinically associated with an increased incidence of mild diarrhea, which is in agreement with our results. Contrastingly with irinotecan, constipation and peritoneal dissemination, which are thought to decrease intestinal peristalsis, decreased the risk of diarrhea in patients treated with S-1.

In the present study, the endoscopic findings of S-1 induced GI toxicities were revealed to be mucosal erythema, edema, erosion, and ulcers, occurring in a diffuse distribution pattern in an elongated segment of the small intestine. To our knowledge, this is the first study on the endoscopic findings associated with the use of anticancer drugs. Cancer chemotherapy-induced intestinal mucositis is characterized by the shortening of villi and disruption of crypt cell homeostasis.[19-21] Although this is not completely understood, the pathogenesis is considered to be multifactorial, including factors such as abnormal inflammation, apoptosis, cell hypoproliferation, and direct cytotoxicity.[19-21] Apoptosis is a particularly critical event in intestinal mucositis induced by cancer chemotherapy.[22-24] Chemotherapy-induced GI toxicity is more frequent in the small intestine than in the large intestine. This difference is apparently related to the location of stem cells.[25] In the present study, histopathological examination of endoscopic biopsy specimens showed degeneration and desquamation of the surface layer of the mucosal epithelium, villous atrophy, and crypt shortening, suggesting that apoptosis has a role in tissue toxicity, although the presence of apoptotic tumor cells was not confirmed by *in situ* end labeling or terminal deoxynucleotidyl transferase-mediated nick-end-labeling techniques.[26] The other conditions considered in the differential diagnosis of the lesions in the terminal ileum were excluded, as the findings of various clinical examinations and the clinical course were not characteristic. Because the lesions developed following cancer chemotherapy and improved on treatment withdrawal, we concluded that S-1 was the most conceivable cause of the lesions in the terminal ileum observed on colonoscopy. However, because of the small number of cases evaluated for the endoscopic morphologic features associated with S1-induced diarrhea, the accumulation of additional cases is necessary.

In conclusion, the risk factors for S-1-induced diarrhea were advanced age, female sex, a history of GI surgery, the concomitant use of radiotherapy, and a relatively high stool frequency. The endoscopic findings of S-1-induced GI toxicities were mucosal erythema, edema, erosion, and ulcers present in a diffuse distribution pattern in an elongated segment of the small intestine.

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