

A patient with stage IV type 4 advanced gastric cancer who had a complete pathological response to short-term treatment with S-1 alone

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An 81-year-old woman presented with dysphagia. Stage IV (cT3, cN3, cM0, cM1) type 4 advanced gastric cancer was diagnosed. The left adrenal gland and the paragastric, mediastinal, and abdominal para-aortic lymph nodes were enlarged. Ascites was present. The patient started to receive S-1 (100 mg/day), given orally for 4 weeks followed by 2 weeks of rest. During the first course of treatment, grade 2 anorexia, grade 2 vomiting, and grade 2 diarrhea developed. Treatment with S-1 was therefore discontinued on day 27. The tumor had shrunk and was severely deformed. There was marked narrowing of the pyloric antrum. Abdominal computed tomography revealed that ascites and enlargement of the left adrenal gland and paragastric lymph nodes had resolved. To ensure adequate oral intake and improve the patient's quality of life, a total gastrectomy with a limited (D1) lymph node dissection was performed. The primary gastric tumor, resected lymph nodes, and a peritoneal-lavage specimen were all negative

for tumor. Histologically, the tumor had a complete pathological response to S-1. Two years after surgery, the patient is alive, with no evidence of metastasis or recurrence. *Anti-Cancer Drugs* 19:921–925 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Guidelines of the Japan Gastric Cancer Association recommend treatment according to disease stage. Endoscopic mucosal resection and laparoscopic surgery are recommended for early gastric cancer. Standard surgical procedures, neoadjuvant chemotherapy, and extended operations are the treatments of choice for advanced gastric cancer [1].

Stage IV advanced gastric cancer has a higher risk of peritoneal dissemination and lymph node metastasis than other types of advanced gastric cancer, leading to poor outcomes. Even if surgery is performed, curative resection is often not feasible, requiring systemic chemotherapy to prolong survival.

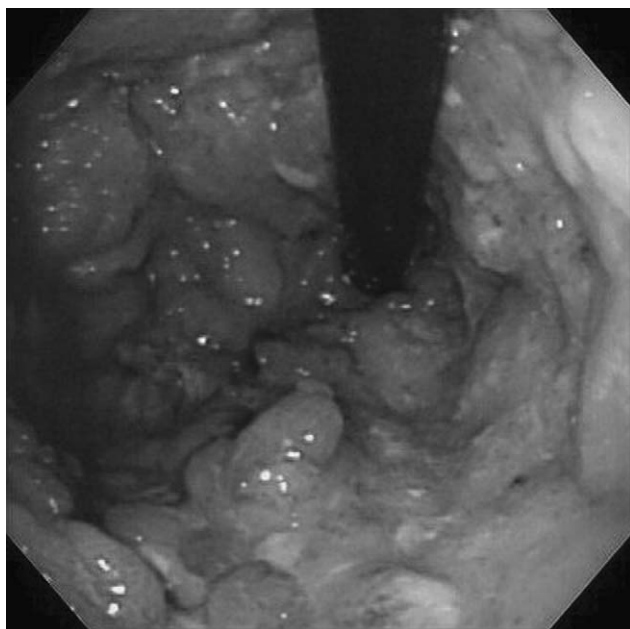
The development of S-1 (a combination of tegafur, gimeracil, and potassium oteracil) [2], a new oral anti-cancer drug approved in Japan in 1999, has led to new treatment strategies for type 4 advanced gastric cancer. Many studies have reported that S-1 is therapeutically useful for type 4 advanced gastric cancers and poorly differentiated adenocarcinomas associated with peritoneal dissemination [3–5].

We describe our experience with a patient who received systemic chemotherapy with S-1 alone. Despite the short treatment period, the patient was confirmed to have had a complete pathological response to S-1 on subsequent surgery.

Case report

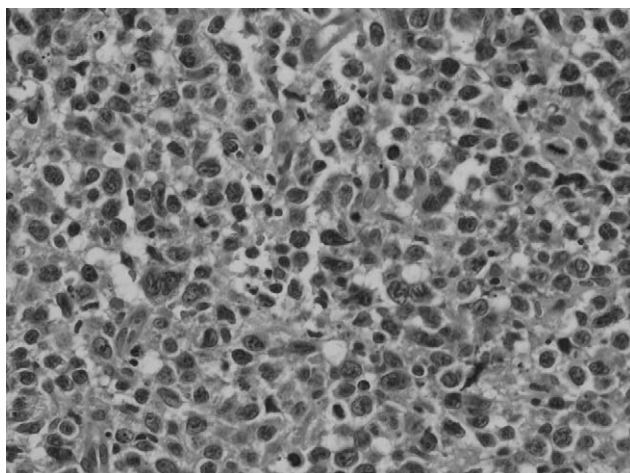
An 81-year-old woman presented with dysphagia and a body weight loss of 15 kg over the course of 6 months. An endoscopic examination performed by a local physician revealed type 4 advanced gastric cancer. The patient was referred to our hospital in October 2005. The endoscopic examination showed irregular, uneven, enlarged, and coarse mucosa, extending circumferentially along the stomach from the esophagogastric junction to the duodenal bulb. A circumferential ulcer was seen in the pyloric antrum, which was markedly narrowed (Fig. 1). A biopsy revealed poorly differentiated adenocarcinoma (group V) (Fig. 2). An upper gastrointestinal series showed irregularity and hardening of the entire gastric wall, poor distensibility, and marked narrowing of the pyloric antrum. The tumor directly invaded the esophagogastric junction and duodenal bulb (Fig. 3). Computed tomography of the chest and abdomen revealed no evidence of liver metastasis or lung metastasis.

Fig. 1



Upper gastrointestinal endoscopy showed irregular, uneven, enlarged, and coarse mucosa, circumferentially occupying the entire stomach.

Fig. 2



A biopsy specimen showing medullary growth of a poorly differentiated adenocarcinoma (hematoxylin and eosin, $\times 50$).

However, there was marked thickening of the gastric wall, and the left adrenal gland and paragastric, mediastinal, and abdominal para-aortic lymph nodes were enlarged. Ascites was present. Peritoneal dissemination was suspected (Fig. 4). Blood tests revealed no elevation of tumor-marker values (CEA, 1.5 U/ml and CA19-9, 21.3 U/ml). No abnormalities were evident, except for mild anemia and undernutrition. Stage IV (cT3, cN3, cH0, cM1) type 4

Fig. 3



An upper gastrointestinal series showed an irregular, hardened wall extending throughout the stomach, poor distensibility, and marked narrowing of the pyloric antrum.

Fig. 4



An abdominal computed tomographic scan, showing marked thickening of the gastric wall and an enlarged left adrenal gland.

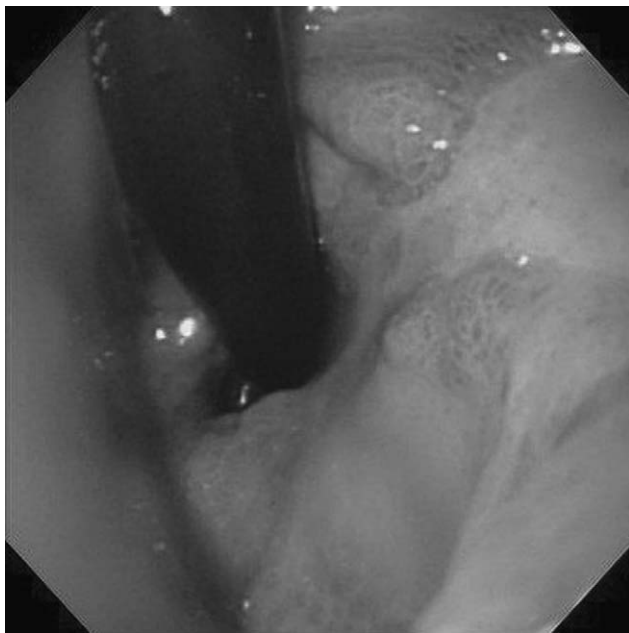
advanced gastric cancer was diagnosed [6]. The patient started to receive a 6-week course of S-1 at a dose of 100 mg/day (80 mg/m²/day), given orally for 4 weeks followed by 2 weeks of rest.

Anorexia developed about 3 weeks after starting the first course of treatment. S-1 was discontinued on day 27 because of grade 2 anorexia, grade 2 vomiting, and grade 2

diarrhea. As for hematologic toxicity, grade 2 neutropenia was noted on day 15 but it gradually improved. After the withdrawal of S-1, anorexia and vomiting did not resolve. Endoscopic examination was thus performed. The tumor had shrunk and was severely deformed. There was marked narrowing of the pyloric antrum (Fig. 5). An upper gastrointestinal series showed that the distensibility of the gastric body had improved, but the pyloric antrum remained markedly narrowed and deformed because of tumor shrinkage (Fig. 6). Computed tomography of the abdomen showed that the ascites and enlargement of the left adrenal gland and paragastric lymph nodes had resolved; the enlarged abdominal para-aortic lymph nodes were unchanged (Fig. 7). The patient had severe gastric stenosis. Total gastrectomy with a limited (D1) lymph node dissection was performed in December 2006 to improve oral intake and the patient's quality of life. There was no evidence of liver metastasis, ascites, or peritoneal dissemination. Cytologic examination of a peritoneal-lavage specimen revealed no tumor cells. However, the abdominal para-aortic lymph nodes (no. 16b1) remained enlarged. The resected stomach showed marked thickening and shortening of the wall. The resected primary tumor, dissected lymph nodes, and a peritoneal-lavage specimen were all negative for tumor cells. All layers of the stomach were replaced by fibrous connective tissue. Histologically, the tumor was confirmed to have had a complete pathological response (Fig. 8).

Two weeks after surgery, treatment with S-1 was resumed at a decreased dose of 80 mg/day. However, grade 3

Fig. 5



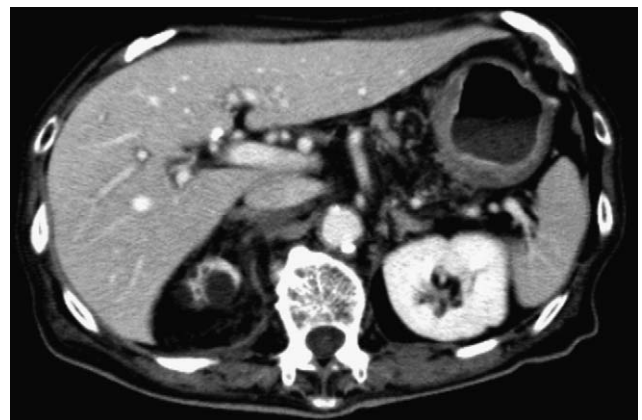
Upper gastrointestinal endoscopy (after the administration of S-1) showed that the tumor had shrunk and was severely deformed.

Fig. 6



An upper gastrointestinal series (after the administration of S-1) showed that the distensibility of the gastric body had improved, but the pyloric antrum remained markedly narrowed, with deformation owing to tumor shrinkage.

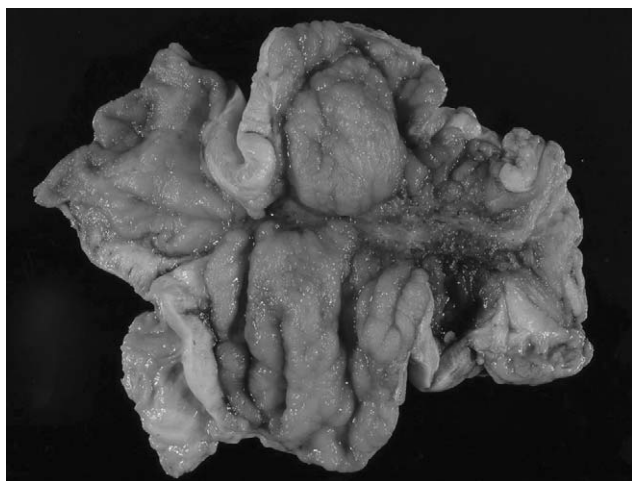
Fig. 7



Abdominal computed tomography (after the administration of S-1) revealed that the gastric wall had become thin and that the enlarged left adrenal gland and ascites had resolved.

anorexia occurred, and S-1 was withdrawn after about 2 months. Subsequently, the patient's appetite gradually improved, and the body weight increased by about 5 kg as compared with the value at admission. Thereafter, the patient was followed up with no further treatment because of advanced age (81 years). Two years after surgery, the size of the abdominal para-aortic lymph

Fig. 8



Macroscopic examination of the resected stomach revealed marked thickening and shortening of the gastric wall.

nodes remains unchanged. Enlargement of the mediastinal lymph nodes, other lymph nodes, and the adrenal gland has disappeared. The patient is alive, with no evidence of metastasis or recurrence.

Discussion

Recently, mortality from gastric cancer has decreased [7], but advanced gastric cancer continues to have poor outcomes. Multidisciplinary treatment including systemic chemotherapy is the treatment of choice for advanced gastric cancer.

A rising incidence of cancer among elderly patients has become a serious problem. Older patients are more likely to have decreased organ function, concurrent diseases, and adverse effects than adults generally. Elderly patients with cancer thus often receive less intensive, symptomatic treatment to maintain a good quality of life in view of their expected survival, domestic environment, and socioeconomic factors.

In phase II clinical trials, chemotherapy with S-1 alone yielded response rates of 44–54% and a median survival of 207–224 days in patients with advanced or recurrent gastric cancer, comparing favorably with conventional chemotherapy [3,8,9]. The incidence of grade 3 or higher toxicity was only 5%, suggesting that S-1 is safe [3,9].

Tanaka *et al.* [10] examined the response to S-1 in elderly patients with gastric cancer and found that it is safe and effective, even in patients 75 years or older. Many elderly patients have decreased renal function. When such patients receive S-1, serum gimeracil concentrations

increase because this component is excreted mainly via the kidney [11]. Serum 5-fluorouracil concentrations thus become higher than those in patients with normal renal function, increasing the risk of toxicity [12]. Therefore, the glomerular filtration rate and 24-h creatinine clearance should be monitored during treatment with S-1 [13].

Although our patient was 81 years old, the 24-h creatinine clearance was maintained at 58 ml/min. The patient initially received S-1 in the recommended dose of 100 mg/day (80 mg/m²/day). However, grade 2 anorexia, grade 2 diarrhea, and grade 2 vomiting developed. Treatment was thus discontinued before completing the first course [13,14].

After oral administration of S-1, serum 5-fluorouracil concentrations and dihydropyrimidine dehydrogenase activity, required for the metabolism of 5-fluorouracil, differ considerably among patients, even when liver and renal functions are normal. Adverse events may be caused by overtreatment with 5-fluorouracil despite a complete response to S-1, similar to our elderly patient [15].

Although the patient received less than one course of treatment, the tumor shrank markedly because of a complete response to S-1. Subsequently, no tumor cells were found at surgery. Histologically, the tumor was confirmed to have had a complete pathological response.

Patients with distant metastasis or unresectable disease, who had a complete response to S-1, have been reported sporadically [15–17]. Previously, only a few patients, who received one course of S-1 monotherapy, were histopathologically confirmed to have had a grade 3 complete pathological response after total gastrectomy. One such case was reported by Yamamoto *et al.* [18].

In our patient, treatment with S-1 was resumed at a decreased dose after surgery. However, grade 3 severe anorexia developed. Thereafter, the patient was followed up on an outpatient basis, with no further treatment. Two years after surgery, the patient is still alive, with no metastasis or recurrence. We hope that our experience will contribute to the improved treatment of elderly patients with advanced gastric cancer.

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