Pathological complete response induced by the combination therapy of S-1 and 24-h infusion of cisplatin in two cases initially diagnosed as inoperable advanced gastric cancer

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Abstract. We report on two patients, successfully treated by the combination therapy of S-1 and 24-h infusion of cisplatin (CDDP), who were initially diagnosed with unresectable stage 4 advanced gastric cancer. Each patient had a very good clinical response and underwent curative gastrectomy after completion of 14 and 10 courses of S-1/CDDP chemotherapy, respectively. A microscopically detailed examination of surgically obtained specimens showed the complete disappearance of malignant cells in the two cases. S-1/CDDP combination therapy can, therefore, be highly active in incurable advanced gastric carcinoma.

Introduction

Unresectable advanced gastric carcinoma has an extremely poor prognosis (1). Since randomized trials have demonstrated that fluorouracil-based regimens provide superior survival in patients with advanced gastric cancer when compared to the results of best supportive care (2), chemotherapy is the main treatment of choice for stage 4 advanced gastric cancer. A novel oral fluoropyrimidine anticancer agent, S-1, has recently been developed in Japan to enhance anticancer activity (3), by which a prodrug of 5-FU, tegafur (FT), has been combined with the two modulating substances of gimeracil (5-chloro-2,4-dihydroxypyrimidine) inhibiting dihydropyrimidine dehydrogenase, an enzyme for 5-FU degradation, and a potassium oxonate as a reducer of gastrointestinal toxicities. Phase II studies of S-1 monotherapy in patients with advanced gastric cancer showed overall response rates of 26-49% (4-6), which was higher than the continuous infusion of 5-FU. The antitumor effects of fluoropyrimidine are known to be enhanced through the biochemical modulation of folate metabolism modified by CDDP (7). Combination therapy, using S-1 and CDDP, has been reported to show high response rates in incurable advanced gastric cancer (8-10). The final results of a randomized control trial (SPIRITS) comparing S-1/CDDP with S-1 alone have recently been reported (11). The SPIRITS study clearly demonstrated the superiority of S-1/CDDP to S-1 monotherapy: overall survival was longer for patients receiving S-1/CDDP with a median survival time (MST) of 13.0 months than for those receiving S-1 alone (11.0 months; $p<0.05$). It has been suggested that a 24-h continuous infusion of CDDP may reduce the degree of nausea, vomiting and renal dysfunction, compared to the bolus injection of CDDP (12). Therefore, since 2002, our hospital has conducted a preliminary study of combination therapy using the continuous infusion of CDDP (13) for patients with inoperable highly advanced gastric cancer.

In response to this regimen, a marked tumor reduction was observed in two patients initially diagnosed as unresectable stage 4 gastric cancer. The patients were then able to undergo curative surgery.

Patients and methods

Eligibility. Patients were eligible if they signed the informed consent form and met all the following criteria: pathologically proven inoperable gastric cancer and at least one measurable lesion; age 20-80 years; Eastern Cooperative Oncology Group performance status of 0-3; no prior chemotherapy or one regimen that was completed >4 weeks before entry; a white blood cell count between 4000 and 12,000/mm^3, a platelet count of >10,000/mm^3 and haemoglobin of >8 g/dl; serum bilirubin <1.5 mg/dl, aspartate aminotransferase and alanine aminotransferase <3 times the upper limit of normal (ULN); and serum creatinin less than or equal to ULN. The main exclusion criteria were: symptomatic infectious disease; congestive heart failure; uncontrolled angina pectoris or arrhythmia; uncontrolled diabetes and hypertension; symptomatic brain metastasis and concomitant malignancy.

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Treatment and evaluation. S-1 was given orally twice daily based on the patients' body surface area (BSA): BSA <1.25 m^2, 40 mg; 1.25-1.50 m^2, 50 mg and BSA >1.50 m^2, 60 mg for two weeks followed by a two-week rest. CDDP at a dose of 70 mg/m^2 was administered by continuous infusion for 24 h on day 8 (13).

Tumor response was evaluated by the criteria proposed by the Japanese Research Society for Gastric Cancer (14). The primary site was evaluated by the roentgenographic and endoscopic findings and, for metastatic lesions, a computed tomography (CT) scan was used. A complete response (CR) was defined as the disappearance of all evidence of cancer after 4 weeks. Partial response (PR) was defined as a >50% reduction of tumor volume. A new lesion or enlargement exceeding the original tumor size by 25% was defined as progressive disease (PD). All other patients were categorized as having stable disease (SD). The grading of histological responses to chemotherapy was based upon the General Rules for the Gastric Cancer Study in Surgery and Pathology (14). Overall survival was calculated from the start of treatment to death or the latest follow-up day. The Kaplan-Meier method was used to plot the overall survival curve. The National Cancer Institute common toxicity criteria version 3.0 was applied to evaluate the adverse effects of this therapy.

Results

In this pilot study we enrolled 20 patients with metastatic or recurrent gastric cancer from January, 2002 to December, 2004 (Table I). The overall response rate was 70% (14/20; CR 2, PR 12) (Table II). Among them, the pathological CR (grade 3) was demonstrated in two cases, which was confirmed by a histologically detailed evaluation of the resected specimens of the primary tumor and surrounding lymph nodes. The MST was 326 days (95% CI: 208-483) and the one-, two- and three-year survival rates were 35, 15 and 10.5%, respectively. With regard to the adverse effects in the 20 cases, the most frequently observed severe (grade 3 and 4) haematological toxicity was neutropenia (8 cases, 40%) (Table III). As for non-haematological toxicities, severe anorexia (grade 3 and 4) was observed in 4 cases (20%), while grade 3 mucositis and diarrhea were seen in 1 case (5%). Renal dysfunction and hand-foot syndrome were not observed.

Case 1. In a 65-year old man with upper abdominal pain, advanced gastric cancer type 5 was diagnosed by roentgenographic examination and gastrointestinal fiberscopy (GIF) (Fig. 1A and B). An abdominal CT scan did not show either lymph node swelling or ascites, indicating that the disease was resectable. Surgery was performed on September 12, 2002. However, severe peritoneal dissemination was identified (Fig. 2A and B), resulting in a conversion to open laparotomy. The histological diagnosis of the resected disseminated peritoneal tumor was poorly differentiated adenocarcinoma (Fig. 2C and D) and the cytological diagnosis from the small amount of ascites was also positive. Combination therapy of S-1/ CDDP was initiated and 14 cycles were completed. The re-evaluation showed only a fold convergence at the site of the primary gastric lesion by GIF (Fig. 1C and D) and no tumor by CT. Grade 3 leucopenia and thrombocytopenia were observed during chemotherapy. After obtaining written informed consent, a second surgery performed on December 1, 2004 showed that there was no dissemination to the peritoneum (Fig. 2E and F) and no evidence of a primary

Table I. Background of the patients.

Characteristics	No. of patients
Gender	
Male	14
Female	6
Age	42-79
Median	65
Performance status	
0	7
1	6
2	4
3	3
Pathology	
Intestinal	9
Diffuse	11
Target lesions	
Primary tumor	13
Lymph nodes	12
Liver	10
Bone	1
Peritoneum	6
(Ascites)	(5)
Total cycles	1-17
Median	4

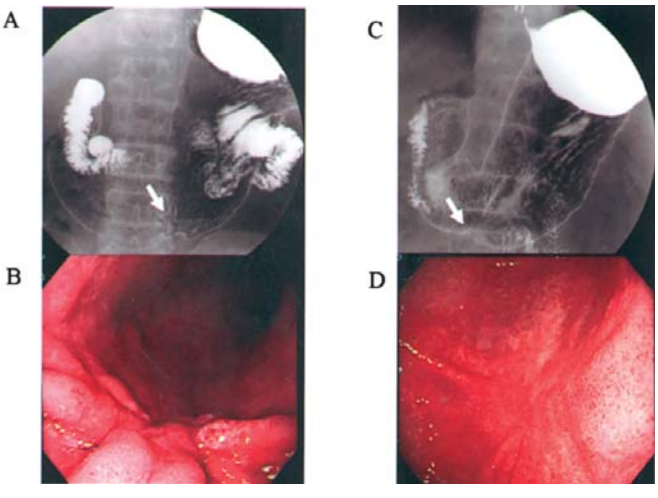

Figure 1. Roentgenological and endoscopic findings demonstrated that the depression in the greater curvature was accompanied by fold convergence before chemotherapy (A and B). After chemotherapy the depressed lesion was flattened (C and D).

Table II. Objective response rate.

	CR	PR	SD	PD	Response rate (%)	CR rate (%)
Overall	2	12	3	3	70	10
Primary lesion	2	1	8	2	25	18
Lymph nodes	2	6	1	3	51	17
Liver	1	7	1	1	80	10
Bone	0	0	1	0	0	0
Ascites	0	2	2	1	40	0

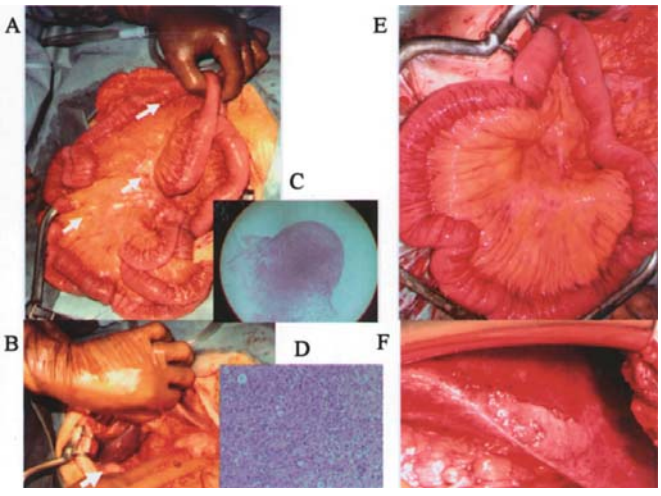

Figure 2. Performed on September 12, 2002, the peritoneal dissemination was evident in the omentum and mesocolon and was scattered (A and B). The histological diagnosis of the resected peritoneal tumor was poorly differentiated adenocarcinoma (C and D) and cytology of the peritoneal washing was also positive. No peritoneal dissemination was noted at the second operation on December 1, 2004 (E and F).

gastric lesion by palpation. Distal gastrectomy was performed. A histological microscopic examination revealed the complete absence of cancer cells in the site of the primary gastric lesion as well as the lymph nodes, evaluated as grade 3 (Fig. 3).

Case 2. Advanced gastric cancer type 3 was diagnosed by GIF in a 53-year old man who complained of body weight loss and abdominal pain. An abdominal CT showed a large tumor and liver metastasis, and a diagnosis of stage 4 (T4, N3 and M1) gastric carcinoma was established (Fig. 4A). A re-evaluation after 10 courses of S-1/CDDP therapy showed a small erosion in the primary gastric lesion with no swollen lymph nodes and only a cystic lesion in the liver (Fig. 4B). Grade 2 leucopenia, nausea and anorexia were observed during chemotherapy. Consequently, the chemotherapeutic efficacy was diagnosed as PR and surgical curative resection was deemed possible. Curative surgery performed after PR was induced by chemotherapy may suggest a poor prognosis for stage 4 gastric cancer patients. Although the patient was well informed that surgery may not provide any benefit, he underwent surgery in the hope of cure or extension of survival. We performed total gastrectomy with D2 lymph node dissection

Table III. Toxicity incidence.

	Grade		
Toxicity (n=20)	2	3	4
Haematological toxicity			
Leucopenia	5	5	0
Neutropenia	6	7	1
Thrombocytopenia	1	3	0
Anemia	3	4	0
Non-haematological toxicity			
Skin rash	1	1	0
Mucositis	2	1	0
Diarrhea	1	1	0
Anorexia	4	3	1
Nausea	5	3	0
Vomiting	7	0	0
Liver dysfunction	1	0	0

Grading is based on the National Cancer Institute common toxicity criteria, version 3.0.

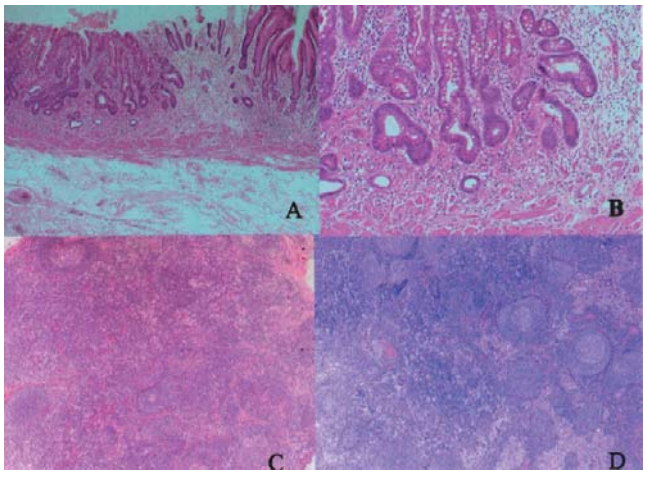

Figure 3. A detailed histological examination of surgically resected specimens showed that no malignant cells were observed at the site of the gastric primary lesion (A and B) and regional lymph nodes (C and D).

Table IV. Patients showing pathological complete response.

Case	Before chemotherapy	Pathology	Cycles	Postoperative chemotherapy	Survival 1	Survival 2
Age 47, male	Peritoneal dissemination (stage 4: T4 N3 H0 P1)	Diffuse	2	S-1	7	N.D.
Age 61, male	Locally advanced (stage 3a: T3 N1 H0 P0)	Intestinal	2	None	12	N.D.
Age 57, female	Peritoneal dissemination (stage 4: T3 N0 H0 P1)	Diffuse	7	S-1	12	21
Case 1	Peritoneal dissemination (stage 4: T3 NX H0 P1)	Intestinal	14	None	36	62
Case 2	Liver and massive lymph node metastasis (stage 4: T4 N3 H1 P0)	Diffuse	10	None	12	51

Survival 1, months after curative surgery and survival 2, months after the initiation of S-1/CDDP combination therapy. N.D., not described.

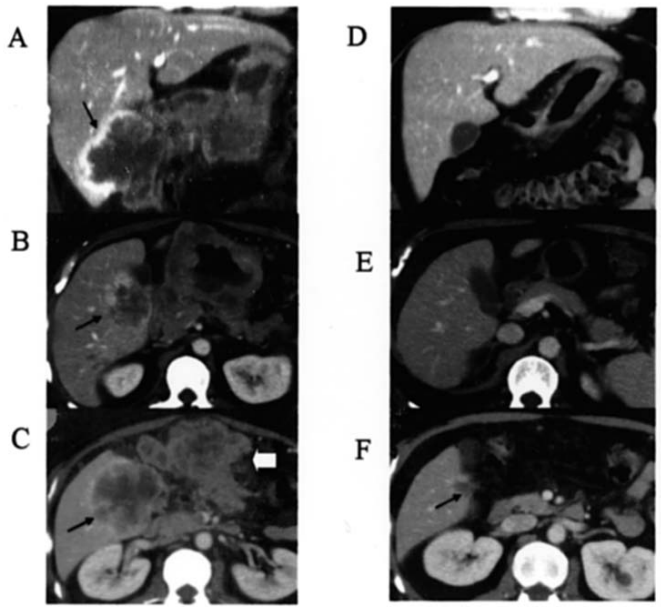

Figure 4. Computed tomography (CT) scans demonstrated a marked thickening of the gastric wall, bulky mass (arrow head) and metastatic liver tumor (arrow) before chemotherapy (A-C). Complete disappearance of the abdominal mass and the cystic lesion in the liver was observed after 10 cycles of chemotherapy (D-F).

on November 27, 2006. The intraoperative histological examination of the hepatic lesion detected on the CT showed fibrosis alone. Therefore, we cauterized the liver tumor. A microscopic examination of the resected specimens revealed the complete disappearance of cancer cells at the site of the primary gastric lesion as well as the lymph nodes, evaluated as grade 3 (Fig. 5).

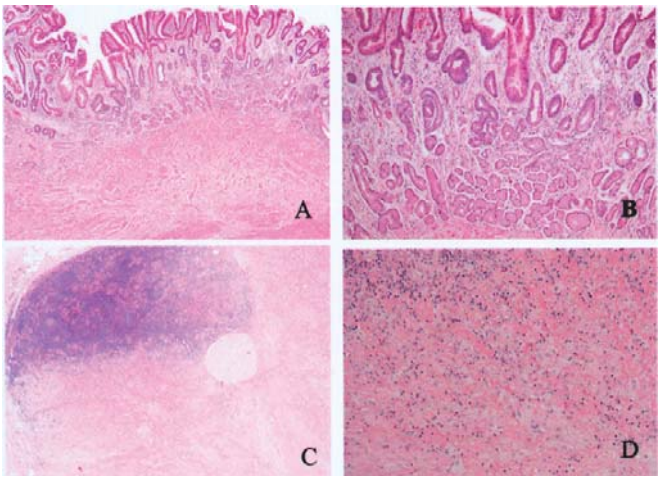

Figure 5. Microscopically, no malignant cells were observed in the gastric primary lesion (A and B) nor the regional lymph nodes (C and D).

Discussion

The clinical response rate in our regimen using a 24-h continuous infusion of CDDP combined with S-1 was 70% (14/20). The MST of 326 days (95% CI: 208-483) was relatively good, considering that our study included patients >75 years old and with a PS of 3. The incidence of severe (grade 3-4) haematological and non-haematological toxicities were 40 and 20%. These results were compatible with previous reports on S-1/CDDP combination therapy using a bolus injection of CDDP. Two out of 14 responders in this pilot study were successfully treated with surgery, both of whom showed a pathological CR (CR rate: 10%).

In Japan, oral fluoropyrimidine anticancer agents, such as FT, uracil in combination with FT (UFT), and 5'-deoxy-5-fluorouridine, have been used to make chemotherapy more convenient and less toxic. The combination of 5-FU with CDDP exerts a synergistic anti-tumor activity through a biochemical modulatory mechanism (7) and it was reported that an objective response by the primary gastric lesion was achieved in 50% of patients with advanced scirrhous type gastric cancer treated by combination chemotherapy using the continuous infusion of CDDP and UFT (15). Suga *et al* (15) reported that histological effects were evaluated as grade 2 in 4 out of 10 patients undergoing total gastrectomy.

The newly developed oral fluoropyrimidine agent, S-1, has replaced UFT for use in combination therapy with continuous infusion of CDDP (13). Since gimeracil used in S-1 is almost 200-fold more potent in DPD inhibitory activity than uracil in UFT (3), it is reasonable to imagine that the S-1/CDDP combination therapy will be more effective in advanced gastric cancer than the UFT/CDDP regimen. Several clinical trials of S-1/CDDP combination therapy have yielded high response rates of up to 76% (8-10). Recent phase III trials have shown that S-1/CDDP combination treatment can significantly prolong overall survival compared to S-1 monotherapy (11). In addition, a combination of S-1 for 14 days plus a 24-h infusion of CDDP on day 8 of every 28-day cycle is a candidate for neo-adjuvant chemotherapy because this treatment enabled radical operation in 3 patients with locally advanced gastric cancer (13).

Simultaneous combination therapy with S-1 and CDDP can be regarded as one of the first-line treatment options for advanced gastric cancer. Although preoperative chemotherapy with S-1/CDDP is suspected to be effective in controlling the micrometastasis as well as down-staging the disease (9), its indications as neo-ajduvant chemotherapy are still controversial (16). A thorough literature search revealed that there have been only 3 other cases of highly advanced gastric cancer showing pathological CR (grade 3 effects in histology) in response to S-1/CDDP combination therapy (Table IV) (17-19). Among the 5 cases, including our 2 cases, only one case was locally advanced gastric cancer (stage 3a), while the other four cases were initially diagnosed as inoperable highly advanced gastric cancer.

Since the cycles of preoperative chemotherapy varied between 2 and 14, there is no basis on which to establish the best timing of a potential curative resection during effective chemotherapy (20,21). Nishiura *et al* recommended that chemotherapy be continued until peritoneal dissemination disappears (19). However, it is very difficult to diagnose the precise extent of peritoneal involvement by conventional modalities such as a CT scan. In Case 1, before the first surgery, the CT scan showed no evidence of peritoneal spread and the preoperative diagnosis was T3, N2, H0 and P0, indicating that the disease was resectable. On the initial surgery, extensive peritoneal dissemination was identified, resulting in open laparotomy. Therefore, the second surgery was not performed until the gastric primary lesion macroscopically disappeared after 14 cycles of S-1/CDDP therapy. In Case 2 an abdominal CT scan showed residual liver tumor with the complete disappearance of a huge lymph node and the gastric primary tumor even after 10 cycles of S-1/CDDP combination therapy. According to the wish of this patient, surgical curative resection was performed after PR was induced by chemotherapy. A histologically detailed examination of the resected specimens of our two cases revealed pathological CR in the site of the gastric primary lesion and metastatic lesions. Therefore, no postoperative adjuvant therapy was performed. The two cases are free of recurrence at 36 and 12 months after the gastrectomy and at 62 and 51 months after the initiation of the combination therapy, respectively.

In conclusion, S-1/CDDP combination therapy can be extremely effective in the treatment of inoperable advanced gastric cancer.

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