Feasibility Study of S-1 and Intraperitoneal Docetaxel Combination Chemotherapy for Gastric Cancer with Peritoneal Dissemination

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Abstract. *Background: Gastric cancer with cancer cells on peritoneal cytology has very poor prognosis because of the existence of simultaneous peritoneal metastasis. Here we performed a dose-escalation study of intraperitoneal docetaxel (DTX) combined with S-1 to determine the maximum-tolerated dose (MTD) and recommended dose (RD) in gastric cancer with peritoneal dissemination. Patients and Methods: Twelve gastric cancer patients with positive cytology were enrolled in this study. Peritoneal lavage specimens were obtained under local anesthesia or staging laparoscopy before treatment and the combination chemotherapy was applied in patients with positive cytology. DTX was administered on day 1 intraperitoneally with initial dose of 40 mg/m^2, stepped up to 50 or 60 mg/m^2. S-1 was administered at a fixed dose of 80 mg/m^2/day on days 1-14, followed by 7 days of rest. After two cycles of the combination chemotherapy, staging laparoscopy was performed to evaluate the effect of the chemotherapy. Simultaneous gastrectomy was performed in cases without peritoneal deposits at staging laparoscopy. Results: The MTD of intraperitoneal DTX was not determined and the RD was defined as 60 mg/m^2 because dose-limiting toxicity occurred in only one patient at level II (DTX: 50 mg/m^2). Out of twelve patients given the combination chemotherapy, nine had cytologically negative peritoneal lavage and had no peritoneal metastases at surgery after chemotherapy. Conclusion: The combined chemotherapy of S-1 plus intraperitoneal DTX was revealed to be safe and may be effective for gastric cancer with peritoneal dissemination.*

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Although the incidence of gastric cancer has been declining, it remains the second most frequent cause of cancer-related mortality worldwide (1). The prognosis of patients with advanced gastric cancer, especially of those with serosa-invaded tumors (T3 or T4) remains poor even after curative resection, and peritoneal dissemination is one of the most common types of recurrence in such cases (2, 3).

Cytological examination of peritoneal lavage is performed to predict peritoneal recurrence and simultaneous peritoneal dissemination of cancer cells (4-6). Most cases with positive cytology on peritoneal lavage develop peritoneal recurrence and are classified as stage IV and non-curative disease according to the Japanese Classification of Gastric Cancer (7).

Recently, a multidisciplinary approach to treatment of advanced gastric cancer including chemotherapy, radiation and surgery has been developed and the survival benefit has been investigated (8, 9). Furthermore, several novel chemotherapeutic agents including the taxanes (paclitaxel, PTX, and docetaxel, DTX), irinotecan, oxaliplatin, S-1, and capecitabine, have shown activity in gastric cancer (10-15).

Recently, the intraperitoneal administration of taxanes such as PTX and DTX has been investigated as a promising therapy for peritoneal dissemination of gastric cancer (16, 17).

Combination therapy with intravenous DTX and oral intake of S-1 have been investigated for unresectable gastric cancer patients (18). Yoshida *et al*. reported on a tri-weekly regimen of DTX and S-1, and the response rate was 56.3% and the median overall survival prolonged to 14.3 months,

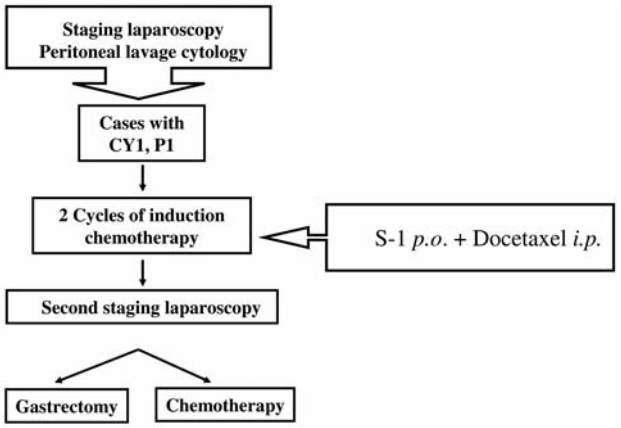

Figure 1. *Flowchart outlinig the diagnosis and treatment pathway. CY1: Positive on peritoneal cytology; P1: the existence of macroscopic peritoneal dissemination.*

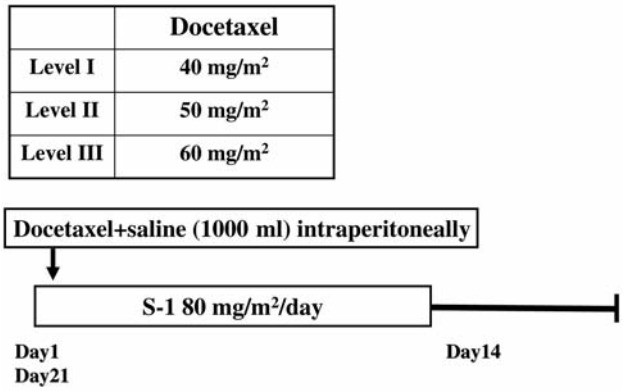

Figure 2. *Treatment protocol of the combination chemotherapy with intraperitoneal administration of docetaxel and oral-intake of S-1. The dosage of docetaxel was escalated from 40 mg/m^2 to 60 mg/m^2.*

which indicates this as a promising combination regimen for gastric cancer.

In the light of these results, we introduced preoperative chemotherapy including intraperitoneal administration for gastric cancer patients with peritoneal dissemination of cancer cells, diagnosed preoperatively by peritoneal lavage cytology or staging laparoscopy. After the combination chemotherapy, staging laparoscopy was performed to examine the therapeutic effect on peritoneal dissemination. Gastrectomy was performed for cases with no peritoneal deposits.

In this study, we performed a phase I study of intraperitoneal DTX and S-1 for gastric cancer patients with peritoneal dissemination in order to assess its feasibility and efficacy as induction chemotherapy.

Patients and Methods

Study design. Figure 1 shows the therapeutic strategy of this study. Patients who had serosa-invaded tumors were investigated for peritoneal dissemination of cancer cells by mean of peritoneal lavage cytology or staging laparoscopy. Patients with positive cytology or peritoneal deposits and without any other non-curative factors were enrolled in this trial. Two cycles of combination therapy with intraperitoneal DTX and S-1 was introduced for these patients. Staging laparoscopy was performed after chemotherapy to assess the chemotherapeutic effect in the peritoneal cavity. In cases with no macroscopic residual disease, gastrectomy with lymph node dissection was performed under laparotomy. The cases with residual disease went on to systemic chemotherapy including S-1 and taxanes without surgery.

Patients. Patients were required to have pathologically proven gastric cancer and positive pretreatment peritoneal lavage cytology. The eligibility criteria were as follows: age: 20-75 years; no prior chemotherapy; ECOG performance status 1-2; adequate function of major organs; no other active malignancy; estimated life expectancy of more than 3 months; provision of written informed consent. Patients ineligible for inclusion were those with severe comorbid conditions, infectious diseases, brain metastasis, severe pleural effusion, severe pericardial effusion, peripheral neuropathy or a past history of drug allergy. Pregnant and breast-feeding women were also excluded.

Pre-operative peritoneal lavage diagnosis. Preoperative peritoneal lavage diagnosis was performed as follows. After making a small incision (20 mm) under local anesthesia and aseptic conditions, a drainage tube was inserted into the pelvic cavity through the anterior abdominal wall. Next, 500 ml of saline were introduced into the abdominal cavity, and about 100 ml of peritoneal lavage were collected. The lavage specimen was subjected to cytological examination.

Treatment protocol. The protocol was as follows (Figure 2): the abdominal cavity was irrigated with DTX dissolved in 1l of saline on day 1 every three weeks, which was applied through the drainage tube placed for the collection of peritoneal lavage diagnosis or staging laparoscopy (19). The dose of DTX was escalated from 40 mg/m^2 (level I), 50 mg/m^2 (level II), and 60 mg/m^2 (level III). Oral S-1 was administered at a fixed dose of 40 mg/m^2 twice daily on days 1-14 every three weeks (one cycle). Patients were treated for two cycles before staging laparoscopy and subsequent gastrectomy unless unacceptable toxicities or patient unwillingness was observed.

At least three patients were treated at each dose level. If no dose-limiting toxicity (DLT) was observed in the first three patients, the dose was escalated to the next level. If one of the three patients developed any DLT, an additional three patients were added at the same dose level. If none of the additional patients developed DLT, the dose was escalated. The maximum-tolerated dose (MTD) was defined as the dose level at which two or more patients developed DLTs. The recommended dose (RD) was defined as one dose level under the MTD or as the final level III, if the MTD was not defined.

Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. DLTs were defined as grade 4 hematological toxicity and grade 3 nonhematological toxicity.

Table I. *Patient characteristics*.

No. of patients		12
Male/female		9/3
Average age, years (range)		64.3 (51-73)
ECOG Performance status	0/1/2	9/3/0
Borrman type	3/4	3/9
Histological type		
Intestinal/diffuse		2/10
Type of resection		
Total/distal		8/2
Patients registered		
Level I		3
Level II		6
Level III		3

Surgery. All surgical treatments were performed in the Department of Gastroenterological Surgery, Osaka University Hospital. After 2 cycles of chemotherapy, staging laparoscopy was performed immediately before surgery to avoid needless laparotomy and gastrectomy in the presence of peritoneal dissemination. Patients underwent gastrectomy with D2 or more extensive lymph node dissection according to the Japanese Classification of Gastric Cancer (7).

Results

Patient characteristics. Between May 2006 and April 2008, twelve patients were enrolled in this study. All patients were proven to have cytologically positive results with peritoneal lavage and no patient had received prior therapy. All patients were assessable for toxicity and response. Table I shows the characteristics of patients enrolled in this study. Nine out of twelve patients had type 4 tumors and histological findings showed diffuse cell type in ten cases. All patients had completed two cycles of the combination chemotherapy except one who had only one cycle because of grade 3 fever before staging laparoscopy.

Toxicity. The toxicity profile is shown in Table II. At dose level I and III, no patient developed grade 3 or grade 4 toxicities. At dose level II, DLT was observed in one of six patients. The patient developed grade 3 fever, which resulted in the protocol failure. Another patient at dose level II showed grade 3 leukopenia and neutropenia.

Clinical response to induction chemotherapy. After the chemotherapy, staging laparoscopy was performed to assess the status of the peritoneal dissemination. Nine patients (2 out of 3 cases in Level I, 5 of 6 cases in Level II, and 2 out of 3 cases in Level III) showed no cancer cells on peritoneal cytology and also no peritoneal deposits. Gastrectomy with lymph node dissection was performed in these nine cases and in one case with positive cytology and no peritoneal deposits.

Table II. *Toxicity profile according to the dose level of intraperitoneal docetaxel*.

	Level I (n=3)			Level II (n=6)			Level III (n=3)		
	Grade								
Adverse event	1	2	3	1	2	3	1	2	3
Non hematological toxicity									
Fatigue	0	2	0	2	1	0	2	1	0
Anorexia	0	1	0	3	2	1	1	2	0
Diarrhea	0	1	0	0	0	0	0	0	0
Rash	0	0	0	2	0	0	1	0	0
Alopecia	0	0	0	1	0	0	1	0	0
Fever	0	0	0	0	0	1	0	0	0
Hematological toxicity									
Leukocytopenia	1	0	0	0	0	1	0	0	0
Neutropenia	1	0	0	0	0	1	0	1	0
Anemia	1	0	0	1	0	0	0	1	0
AST	1	0	0	0	0	0	0	0	0
ALT	0	0	0	1	0	0	1	0	0
Creatinine	0	0	0	1	0	0	0	0	0
Total events	4	4	0	11	3	4	6	5	0

AST: Aspartate aminotransferase; ALT: alanine aminotransferase.

Discussion

In advanced gastric cancer, peritoneal dissemination is the most frequent type of recurrence and it is generally accepted that peritoneal dissemination originates from peritoneal cancer cells that exfoliate from the serosa of primary tumors (20, 21). Cytological examination of peritoneal lavage is performed to predict peritoneal recurrence and simultaneous peritoneal dissemination of cancer cells (4-6). Most cases with positive cytology on peritoneal lavage develop peritoneal recurrence and show poor prognosis even after gastrectomy.

Intraperitoneal chemotherapy is a promising therapy for local control of floating cancer cells in the peritoneal cavity and of early-stage cancer cells attached to the peritoneal surface in the abdominal cavity (22, 23). Recently, taxanes such as PTX and DTX, have been studied as promising intraperitoneal drugs for peritoneal metastasis by maintaining a high concentration of the drugs in the peritoneal cavity for a long period (16, 17). Furthermore, several clinical trials have verified the clinical significance of intraperitoneal administration of taxanes (22, 24).

Furthermore, we also demonstrated that oral S-1 was a promising chemotherapy for peritoneal dissemination of gastric cancer because higher concentration of 5-FU was confirmed in peritoneal nodules than in plasma (25).

Therefore, we developed a novel combination chemotherapy with intraperitoneal administration of DTX and an oral anticancer agent S-1. In this study, we introduced the combination regimen as an induction chemotherapy for gastric cancer patients with cancer cells on peritoneal cytology. The present study was performed as a dose-escalation study to determine the MTD and the RD in preoperative gastric cancer patients. At dose Level II, one patient showed grade 3 fever, which was the only DLT. However, an additional three cases enrolled showed no DLT. At dose level I and III, no DLT was observed. Therefore, the RD of intraperitonal. DTX was determined to be level III, 60 mg/m^2. Yoshida *et al*. reported on a combination chemotherapy with intravenous DTX and S-1. The regimen was the same as ours except for the difference in the means of administration of DTX, intravenous *versus* intraperitoneal (18). The phase I study of Yoshida *et al*. showed the RD of DTX was 40 mg/m^2 because of a high incidence of leukopenia and neutropenia (26). Our results revealed intraperitoneal administration of DTX to be less toxic, which might be caused by pharmacokinetics of DTX: with low concentration in systemic circulation and a higher concentration in the abdominal cavity on intraperitoneal administration (16, 17).

The clinical response of the combination regimen is also promising: nine out of twelve patients enrolled showed no cancer cells on peritoneal cytology nor macroscopic peritoneal deposits after chemotherapy; further clinical trials are warranted to examine the clinical significance of this regimen.

In conclusion, our phase I study provides evidence that a combination chemotherapy of S-1 plus intraperitoneal DTX is a safe regimen and warrants further clinical trials to clarify the significance of the regimen for gastric cancer with peritoneal dissemination of cancer cells.

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