

# Feasibility and Efficacy of Combination Chemotherapy with S-1 and Fractional Cisplatin for Advanced Gastric Cancer

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**Abstract.** *Background:* There is a great need for effective outpatient chemotherapy for advanced gastric cancer in patients with good performance status. The present pilot study evaluated the use of combination chemotherapy with S-1 and fractional CDDP for unresectable–recurrent gastric cancer in an outpatient setting. *Patients and Methods:* A total of 41 patients with unresectable or recurrent gastric cancer were treated with this combination chemotherapy. S-1 was administered orally every day on days 1-28 and CDDP was infused on days 1, 15, and 29. *Results:* Thirty-six patients had measurable lesions and 19 patients had partial responses, resulting in an overall response rate of 52.8%. The median survival time was 494 days. There was no grade 4 haematological toxicity, no grade 3 or more non-haematological toxicity, and no treatment-related death. *Conclusion:* This combination chemotherapy has no serious toxicities in patients with unresectable and recurrent gastric cancer and can be used effectively in an outpatient setting.

Gastric cancer is one of the most frequent causes of death from malignant disease worldwide, especially in East Asia, Eastern Europe, and parts of Central and South America (1). Although the prognosis of highly advanced gastric cancer is poor, several clinical trials established that systemic chemotherapy provides a significant benefit over best supportive care (2-4). Recently, development of novel anticancer drugs such as camptothecins, taxanes, third-generation platinum, and new oral fluoropyrimidines has improved the clinical outcomes of patients with unresectable and recurrent gastric cancer (5-13). Especially in Japan, S-1 is recognised as a key agent for treating unresectable and recurrent gastric cancer (8). S-1 is a

synthetic compound containing tegafur, gimeracil (which inhibits the 5-fluorouracil (5-FU) degradation enzyme), and oteracil (which reduces gastrointestinal toxicity) (9-11). Phase II studies of S-1 for advanced gastric cancer demonstrated a favorable outcome, with a response rate of approximately 40%; the low incidence of adverse reactions permits its use on an outpatient basis (12, 13). In addition, since cisplatin (CDDP) modulates the anticancer effect of 5-FU, CDDP can be used for the treatment of gastric cancer, and combination chemotherapy with S-1 and CDDP is well-known to result in high efficacy and tolerable toxicity (14, 15). According to a recent clinical trial, combination chemotherapy with S-1 and CDDP prolongs survival (median survival time, 13.0 months) compared with S-1 alone, and is now recognised as one of the standard regimens for patients with advanced gastric cancer (16). However, before this regimen is administered, the patients are hydrated with 5% glucose to avoid CDDP-induced renal damage and therefore should be hospitalised at the time of CDDP administration. In addition, high dose CDDP ( $\geq 50$  mg/m<sup>2</sup>) is highly emetogenic and negatively impacts the patient's quality of life (QOL). The clinical efficacy and safety of S-1 and fractional low-dose cisplatin (TSLD regimen) if hydration and severe gastrointestinal toxicity is avoided was previously reported (17). However, the patients need to be hospitalised because the low-dose CDDP is administered on 5 consecutive days each week. For patients with good performance status, there is a great need for an effective chemotherapy regimen that can be administered in an outpatient setting. The present pilot study examined the efficacy, toxicity, and effect on prognosis of combination chemotherapy with S-1 and fractional CDDP for unresectable and recurrent gastric cancer in outpatients.

## Patients and Methods

*Patients.* From August 2004 to December 2009, 42 patients with unresectable or recurrent gastric cancer were treated with combination chemotherapy of S-1 and fractional CDDP. Eligibility requirements for study entry included adequate bone marrow, heart, liver, and renal function at the initiation of chemotherapy and also a

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*Key Words:* Gastric cancer, S-1, cisplatin, outpatient setting.

Table I. Patient characteristics.

Age (years)	
Median (range)	60.8±8.9 (20-84) years
Gender	
Male/female	29/12
ECOG performance status	
0/1/2	31/9/1
Disease status	
Recurrent/unresectable	19/22
Number of metastatic site	
1/2/3	30/9/2
Metastatic site	
Peritoneal dissemination	20
Lymph node	17
Liver	7
Lung	4
Ovary	2
Other	4

performance status score of 2 or higher on the Eastern Cooperative Oncology Group scale. Informed consent was obtained from each individual before initiating treatment.

**Treatment schedule and evaluation.** S-1 and CDDP were purchased from Taiho Pharmaceutical Co., Ltd. (Tokyo, Japan) and Yakult Honsya Co., Ltd. (Tokyo, Japan), respectively. The chemotherapy schedule consisted of one cycle given every 6 weeks. S-1 was administered orally every day on days 1-28 and the total dose was based on the patient body surface area (BSA) as follows: less than 1.25 m<sup>2</sup>, 80 mg; 1.25-1.5 m<sup>2</sup>, 100 mg; and greater than 1.5 m<sup>2</sup>, 120 mg. CDDP was infused at a dose of 20 mg/m<sup>2</sup>/day for 1 hour on days 1, 15, and 29. Treatment was discontinued upon the occurrence of unacceptable toxicity (any adverse effect of more than grade 3) or disease progression.

Primary and metastatic lesions were examined by gastrointestinal endoscopy and imaging examinations including abdominal computed tomography (CT), and upper gastrointestinal series. The effect of chemotherapy was evaluated by an extramural review committee and according to Response Evaluation Criteria in Solid Tumors (RECIST) (18). The adverse effects of treatment were evaluated according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2. Survival time was calculated from the initial date of the first course of chemotherapy to the date of the last confirmation of survival, or the date of death. Overall survival was estimated using the Kaplan-Meier product-limit method.

## Results

**Patient characteristics.** Patient characteristics are summarised in Table I. The mean age of patients was 60.8±8.9 years (range, 20-84 years). Forty-one patients had good performance status (PS0) at the initiation of chemotherapy. Of the 41 patients, 19 patients had recurrent and 22 patients had unresectable gastric cancer. Thirty patients (73%) had one

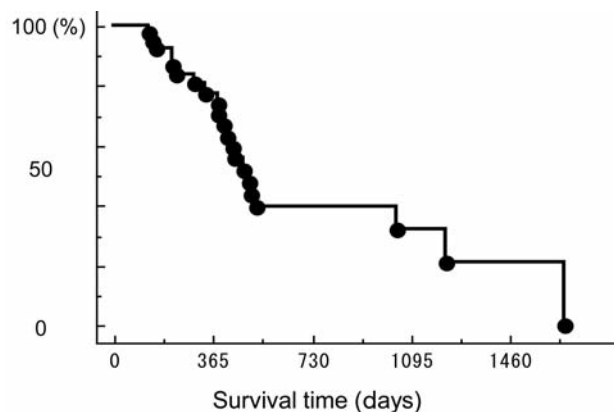


Figure 1. Overall survival of patients treated with combination chemotherapy consisting of S-1 and fractional cisplatin.

metastatic site and the remaining 11 patients (27%) had multiple metastatic sites. Metastatic sites included peritoneum (20 patients; 49%), abdominal lymph nodes (17 patients; 41%), and liver (7 patients; 17%). The diagnosis of peritoneal dissemination was made only when massive ascites or peritoneal tumours were observed by abdominal CT.

**Response rate and survival outcome.** The median number of treatment courses was 4 (range: 1-7). Of the 41 patients, 36 patients had measurable lesions. Gastrointestinal endoscopy and imaging examinations determined that 19 of the 36 patients had partial responses (PRs), while no patients had a complete response (CR) (Table II), resulting in an overall response rate of 52.8%. Progressive disease (PD) occurred in 5 patients (12%). Thirty-three patients (80%) received the second-line chemotherapy including camptothecins or taxanes. The median survival time (MST) of these patients was 494 days (Figure 1).

**Adverse reactions.** The major adverse reactions are shown in Table III. The most frequent adverse events were haematological toxicities, including leukocytopenia (51%), neutropenia (46%), anaemia (54%), and thrombocytopenia (46%). Grade 3 haematological toxicities were observed in 5 patients (12%). Non-haematological toxicity was observed in 10 patients (24%). Among non-haematological toxicities, ALT or AST elevation was the most frequent event (5 cases, 12%). Other frequently observed non-haematological toxicities were induced general fatigue (4 cases, 10%), anorexia (4 cases, 10%), nausea (4 cases, 10%), and renal-related events (4 cases, 10%). Gastrointestinal toxicities such as anorexia, nausea, and vomiting were manageable by administering anti-emetic drugs. There was no grade 4 haematological toxicity, no grade 3 or more non-haematological toxicity, and no treatment-related death.

Table II. *Clinical responses.*

Median number of courses	4 (1-7)	
Efficacy (Evaluable cases: n=36)	CR/PR/SD/PD	0/19/12/5
Response rate	19/36 (52.8%)	
Median survival (range)	494 (56-1631) days	

## Discussion

Although several chemotherapy regimens have a survival benefit compared with best supportive care, the prognosis of patients with unresectable or recurrent gastric cancer is still poor (2-4). Recently, treatment with novel anticancer agents has extended the survival of these patients (5-13). S-1 is a novel oral anticancer drug that combines tegafur, a prodrug of 5-FU, with 5-chloro-2, 4-dihydropyrimidine (CDHP), and potassium oxonate. S-1 has several advantages, including high efficacy, excellent tolerability, low side-effect profile, and the convenience of outpatient administration (9-13). Recently, the Japan Clinical Oncology Group (JCOG) study (JCOG9912) reported that S-1 was well-tolerated and associated with a median survival as long as that of 5-FU alone (control treatment) in advanced gastric cancer (8). Therefore, in Japan, S-1 is recognized as a first-line agent for treating unresectable highly advanced gastric cancer.

CDDP is another key chemotherapeutic agent used for the treatment of gastric cancer, and combination chemotherapy with CDDP and S-1 results in high efficacy and tolerable toxicity (16, 17). A recent randomized control trial showed that combination chemotherapy with CDDP and S-1 offers a survival benefit over S-1 alone to patients with advanced gastric cancer (16). However, patients treated with this regimen must be hospitalized before the administration of CDDP in order to receive hydration and thereby avoid renal damage and severe emetogenesis. It was previously reported that the antitumour activity of CDDP *in vitro* and *in vivo* depends on its area under the curve (AUC) (19, 20). Therefore, it was suggested that low-dose daily bolus infusions of CDDP would be useful in reducing renal damage and gastrointestinal toxicity, without reducing the AUC which is important for antitumour activity (21). On the basis of these data, the feasibility and efficacy of combination chemotherapy with S-1 and low dose cisplatin was previously reported (17). The TSLD regimen permits the administration of CDDP without the need for hydration and risk of severe gastrointestinal toxicity; however, the patients must also be hospitalised to administer low-dose CDDP on 5 consecutive days per week.

The use of novel chemotherapy agents has the potential to improve the survival of patients with advanced gastric cancer. Outpatient chemotherapy would be expected to improve their QOL. Therefore, it is necessary to establish chemotherapy regimens that can be administered in an

Table III. *Toxicities.*

	Grade				Total	3/4
	1	2	3	4		
<b>Haematological toxicity</b>						
Leukocytopenia	11	8	2	0	21 (51%)	2 (5%)
Neutropenia	7	9	3	0	19 (46%)	3 (7%)
Anaemia	14	7	1	0	22 (54%)	1 (2%)
Thrombocytopenia	17	2	0	0	19 (46%)	0
<b>Non-haematological toxicity</b>						
General fatigue	2	2	0	0	4 (10%)	0
Anorexia	2	2	0	0	4 (10%)	0
Nausea	2	2	0	0	4 (10%)	0
Vomiting	3	0	0	0	3 (7%)	0
Diarrhoea	1	1	0	0	2 (5%)	0
ALT/AST elevation	4	1	0	0	5 (12%)	0
Creatinine	2	2	0	0	4 (10%)	0
Eruption	0	3	0	0	3 (7%)	0
Other	2	0	0	0	2 (5%)	0

outpatient setting. This study evaluated the feasibility, efficacy, and survival benefit of combination chemotherapy with S-1 and CDDP administered in an outpatient setting for unresectable or recurrent gastric cancer. The most frequent adverse events were haematological toxicities including leukocytopenia (51%), neutropenia (46%), anaemia (54%), and thrombocytopenia (46%). However, grade 3 haematological toxicities were observed in only 5 patients (12%). All non-haematological toxicities (*i.e.* renal-related events in 4 cases [10%]) and all gastrointestinal toxicities (anorexia, nausea, or vomiting) were grade 2 or less. The latter were manageable by administering anti-emetic drugs. There was no grade 4 haematologic toxicity, grade 3 or more non-haematological toxicity, or treatment-related death. These results suggest that this S-1 and fractional CDDP combination is effective and suitable for outpatient treatment. All courses of this combination chemotherapy were provided at the outpatient chemotherapy center of Keio University Hospital. As a result, all patients had better QOL insofar as they could continue to work, engage in hobbies, or engage in daily life activities without hospitalization.

In this study, comparatively good efficacy was observed (52.8% clinical response rate), with a median survival time of 494 days. Compliance with treatment was good because toxicities were tolerable (no grade 4 haematological toxicity, no grade 3 or more non-haematological toxicity, and no treatment-related death). In addition, the patients in this study had a relatively good performance status; therefore, 35 out of 41 patients were able to receive subsequent chemotherapy which might prolong MST.

In conclusion, although its efficacy should be evaluated prospectively, outpatient combination chemotherapy with S-1

and fractional CDDP has no serious toxicities in patients with unresectable and recurrent gastric cancer and therefore may lead to a better QOL.

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