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Clinical efficacy of S-1 combined with cisplatin for advanced gastric cancer

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Abstract

Several chemotherapy regimens used against advanced gastric cancer have been studied extensively over the decades in an attempt to further improve the prognosis of patients. To date, no standard chemotherapeutic regimens have been established worldwide. S-1 (TS-1®), a combination of ftorafur and two modulators, gimestat (CDHP) and oxonic acid, in a molar ratio of 1:0.4:1, has been widely used in Japan for the treatment of advanced gastric cancer, and much attention has been paid to attempts to increase its antitumor effect by combining it with other chemotherapeutic drugs. We treated 12 patients with advanced gastric cancer with 80 mg/m² of S-1 for 21 days and 60 mg/m² of cisplatin (CDDP) on day 8 every 5 weeks. The treatment was continued until disease progression, unacceptable toxicity, or the patient's refusal. Eight out of 12 evaluable patients achieved a partial response (PR), with a response rate of 66.7%. The incidence of grade 3 or 4 adverse effects, including myelosuppression and gastrointestinal toxicities, was 16.6%. None of the patients treated with this regimen died of adverse effects and none required hospitalization for the toxicity. We conclude that the combination of S-1 and CDDP seems to have a high therapeutic index, enhancing the antitumor effect of S-1 while maintaining modest adverse effects, thus suggesting the possible use of this combination based at the outpatient clinic (apart from a short stay in hospital during the infusion of CDDP with hydration). Further study with a large number of patients may be needed to confirm the combination of S-1 and CDDP to be an appropriate first-line chemotherapy for gastric cancer.

Key words Chemotherapy · Gastric cancer · S-1 · CDDP

Introduction

More than 40 years after its development, fluorouracil (5-FU) remains the chemotherapeutic mainstay for the management of patients with gastrointestinal (GI) cancer [1]. Pharmacokinetic studies have demonstrated that about 85% of clinically administered 5-FU is inactivated and eliminated through the catabolic pathway in the liver [2]. The primary and rate-limiting enzyme related to the catabolism of 5-FU is dihydropyrimidine dehydrogenase (DPD), which metabolizes 5-FU into α-fluoro-β-alanine [3]. A number of clinical pharmacological studies with fluoropyrimidine drugs have shown the importance of DPD to the pharmacokinetics of 5-FU, its clinical toxicity, and its tumor resistance.

Various pharmacologic strategies have been undertaken to enhance the antitumor activity of 5-FU. One such approach is to use an inhibitor of DPD. S-1 is a newly developed oral fluoropyrimidine that is a combination of the 5-FU prodrug ftorafur and two modulators, gimestat (CDHP) and oxonic acid, in a molar ratio of 1:0.4:1, as reported before [4–7]. Ftorafur is converted to 5-FU through hepatic P-450s and through cytosolic enzymes [8]. CDHP is a competitive, reversible DPD inhibitor that prolongs the half-life of 5-FU. Oxonic acid is a pyrimidine phosphoribosyl transferase inhibitor that can reduce 5-FU-related GI toxicity by preventing the phosphorylation of 5-FU in the digestive tract.

In a phase I study, S-1 was administered orally for 28 days, with 2 weeks' rest. The dose-limiting factor was myelosuppression [9]. Other adverse reactions included anorexia, nausea/vomiting, and diarrhea. The pharmacokinetic profile of S-1 revealed that twice-daily ingestion could maintain the therapeutic 5-FU level without increasing Cmax in the blood.

A late phase II study of S-1 for advanced gastric cancer revealed a response rate of 49% (25/51) including 1 patient with a complete response (CR) and 24 patients with a partial response (PR), while the incidence of grade 3 and 4 adverse effects was less than 10% [10]. As there have been no single anticancer agents with such high antitumor effects without severe toxici-

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ties, and, moreover, as S-1 can be administered orally in an outpatient clinic, S-1 has been widely used for the treatment of advanced gastric cancer as a first-line chemotherapy in Japan [11,12].

Several efforts have been conducted to enhance antitumor effects by combining oral fluoropyrimidines with cisplatin (CDDP) or other cytotoxic agents. Ohtsu et al. [13] conducted a preliminary phase I/II study of S-1 plus CDDP for patients with advanced gastric cancer. A standard dose of S-1 for 3 weeks and 70 mg/m^2 of CDDP on day 8 were determined to be the maximum tolerated dose (MTD), and the recommended dose of CDDP was 60 mg/m^2. The overall response rate was 76%. Toxicity induced by S-1 combined with CDDP was slightly increased compared with that induced by S-1 alone, but the regimen could be given safely in the outpatients clinic.

We conducted the present phase II study, using 80 mg/m^2 of S-1 from day 1 through day 21, with 60 mg/m^2 of CDDP on day 8, to evaluate the antitumor effect and toxicity profile of this combination for advanced gastric cancer.

Patients and methods

Eligibility

Patients with histologically proven metastatic or recurrent gastric cancer were eligible for the study. Further eligibility criteria included measurable or evaluable lesions; performance status equal to or better than 2 on the Eastern Cooperative Oncology Group scale, with a life expectancy of 3 months or longer; no prior chemotherapy or radiotherapy, except for adjuvant chemotherapy; age less than 75 years; and adequate organ function (WBC, $\geqq$4000/mm^3 but less than 12000/mm^3; platelets $\geqq$100000/mm^3; hemoglobin, $\geqq$9.0 g/dl; total bilirubin, $\leqq$1.5 mg/dl; transaminases, $\leqq$100 U/l; and creatinine, $\leqq$ upper limit of normal range). All patients provided their written informed consent.

Chemotherapy regimens

All patients were treated with S-1 combined with CDDP. S-1 was administered orally twice daily for 21 days. The dose of S-1 was based on the body surface area (BSA) as follows: 80 mg/day for BSA less than 1.25 m^2, 100 mg/day for BSA 1.25 m^2 to less than 1.50 m^2, and 120 mg/day for BSA 1.5 m^2 or more. CDDP, 60 mg/m^2, was infused over 2 h on day 8. Before and after CDDP administration, adequate hydration was given. This treatment schedule was repeated every 5 weeks.

Treatment administration was regulated by evaluation of blood cell count before the start of the treatment cycle. Treatment was administered if the granulocyte count was 3000/μl or more and the platelet count was 100000/μl or more.

Evaluation of response

The measurement and evaluation of lesions were conducted by the use of X-ray, gastrofiberscopy, computed tomography, and ultrasonography. Response was defined according to the following criteria [14]. A CR was defined as the complete disappearance of all measurable and assessable lesions for a minimum of 4 weeks. A partial response (PR) was defined as a 50% or more reduction in the sum of the products of the perpendicular diameters of measurable lesions for a minimum of 4 weeks. Progressive disease (PD) was defined as a 25% or more increase in the sum of the products of the perpendicular diameters of measurable lesions or the appearance of new lesions. Stable disease (no change; NC) was defined as other than CR, PR, or PD.

Toxicity assessment

Hematologic, mucosal, gastrointestinal, and skin toxicities were assessed before each course according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC).

No prophylactic antiemetic therapy was recommended. When patients had nausea or vomiting, metoclopramide was administered. Clinical examination and blood determinations were repeated before each treatment course. Hematology laboratory evaluation was also performed weekly.

Results

During the period from March 2001 to October 2002, a total of 12 patients were enrolled. All patients had histologically proven metastatic gastric cancer, and were considered to be eligible. The characteristics of the patients are shown in Table 1. The mean age of the patients was 57.2 years. There were 3 patients with prior therapy (2 patients with surgery and 1 patient with chemotherapy). Differentiated and undifferentiated adenocarcinoma were found in 6 and 6 patients, respectively. Sites of metastasis included lymph node in 10 patients, liver in 6 patients, and peritoneum in 4 patients. The mean number of treatment courses given to patients was 4.3 (range, 2–10).

The responses of the patients treated with S-1 and CDDP are listed in Table 2. The overall response rate was 66.7%, including eight PRs and four NCs, while there were no PDs. Response rates with regard to the site of lesions were 80% for lymph node metastasis,

Table 1. Background of the patients treated with S-1 and CDDP

No of patients	12
Sex	
Male	11
Female	1
Mean age; years (range)	57.2 (44–75)
PS	
0	8
1	3
2	1
Prior treatment	
None	9
Surgery	2
Chemotherapy	1
Histology	
Differentiated	6
Undifferentiated	6
Sites of metastasis	
Lymph node	10
Liver	6
Peritoneum	4
Average number of treatment courses (range)	4.3 (2–10)

CDDP, Cisplatin; PS, performance status

Table 2. Response of patients treated with S-1 and CDDP

	CR	PR	NC	PD	RR (%)
	0	8	4	0	66.7
Sites of lesions					
Primary ($n = 10$)	1	4	5	0	50.0
Liver ($n = 6$)	0	3	3	0	50.0
Lymph node ($n = 10$)	2	6	2	0	80.0
Peritoneum ($n = 4$)	0	1	3	0	25.0
Local ($n = 1$)	0	0	1	0	0

CR, Complete response; PR, partial response; NC, no change; PD, progressive disease; RR, response rate

50% for the liver metastasis, 50% for the primary lesion, and 25% for peritoneal seeding. There were three CRs (one in the primary lesion, and two in lymph node metastases).

Hematologic and nonhematologic adverse effects are listed in Table 3. Hematologic toxicities were often seen, but most patients demonstrated mild to moderate toxicity, of grade 1 or 2. Two patients showed grade 3 anemia. GI toxicities, such as appetite loss, nausea, vomiting, and diarrhea were also seen; however, there were no patients with grade 3 GI toxicities.

The clinical outcome of the patients is summarized in Table 4. Three patients were treated by surgery after the treatment with S-1 and CDDP (one patient with subtotal esophagectomy, one patient with total gastrectomy, and one patient with gastrojejunostomy). Of the12 patients four patients died of the disease and the other eight patients were still alive at the time of writing. There was no toxicity-related death.

Table 3. Toxicities in patients treated with S-1 and CDDP

	NCI-CTC Grade				
	1	2	3	4	G3 or more (%)
Leukopenia	3	5	0	0	0
Neutropenia	3	4	0	0	0
Anemia	1	7	2	0	16.6
Thrombocytopenia	3	1	0	0	0
Appetite loss	6	2	0	0	0
Nausea	1	1	0	0	0
Vomiting	1	1	0	0	0
Diarrhea	0	0	0	0	0
Fatigue	3	0	0	0	0
Fever	0	0	0	0	0
Dermatitis	2	0	0	0	0

NCI-CTC, National cancer Institute Common Toxicity Criteria; G, grade

Discussion

5-FU is one of the most commonly prescribed anticancer agents for gastrointestinal malignancy. Among several methods of administration of 5-FU, continuous i.v. infusion is superior to i.v. bolus with regard to both antitumor effects and adverse effects [15]. S-1 has been developed to increase the antitumor effect (by inhibiting DPD activity with gimestat), and also to decrease the adverse effects (by protecting the gastrointestinal tract with otastat potassium), thus resulting in a pharmacokinetic profile similar to that of continuous venous infusion of 5-FU, but with less toxicity and improved patient quality of life [4–7]. Because it is an oral preparation of fluoropyrimidine, S-1 has several advantages over the continuous venous infusion of 5-FU; the inconvenience and morbidity associated with the indwelling catheters and infusion pumps that are used with the latter treatment are avoided. Thus, S-1 is now attracting considerable attention from oncologists [7], and it has been used for the treatment of advanced gastric cancer throughout Japan as a first-line chemotherapy.

The adverse effects of S-1 in the clinical phase I/II studies showed an incidence of less than 10% of grade 3/4 toxicities [9–12], and it therefore seems that the antitumor tumor effect of S-1 can be further enhanced by combining it with other antitumor drugs. Ohtsu et al. [13] reported a significantly high response rate of S-1 in combination with CDDP in their phase I/II study. They recommended 80 mg/m^2 of S-1 for 21 consecutive days, with 60 mg/m^2 of CDDP on day 8 as an appropriate dose of this combination.

We showed, in this study, a response rate of 66.7%, with minimal adverse effects, with combination chemotherapy of S-1 with CDDP. Although the response rates in our study were not as high as in the previous report, this combination of S-1 and CDDP was confirmed to

Table 4. Outcomes of patients treated with S-1 and CDDP

Case no.	Sex	Age (years)	PS	No. of treatment cycles	Response	Subsequent treatment	Survival time (days)	Prognosis
1	M	51	0	10	PR		558	Alive
2	M	61	0	6	PR	Surgery	541	Alive
3	M	57	0	3	PR	Surgery	243	Alive
4	M	44	0	3	PR		127	Alive
5	M	75	2	3	PR		233	Died
6	M	70	1	3	NC		168	Died
7	M	64	0	3	NC		215	Died
8	M	64	1	2	NC	Surgery	184	Alive
9	F	46	0	3	NC		609	Alive
10	M	47	0	4	PR		185	Died
11	M	46	0	6	PR		260	Alive
12	M	61	0	4	PR		145	Alive

have a significant therapeutic index, enhancing the antitumor effects of S-1 while maintaining modest adverse effects, thus suggesting the possible use of this combination based at the outpatient clinic (except for a short stay in the hospital during the infusion of CDDP with hydration).

The combination of S-1 and CDDP seems to be suitable for neoadjuvant chemotherapy, as well as for the treatment of metastatic gastric cancer, because it has high response rates, shown within one or two courses of administration, with minimal adverse effects that may not compromise consecutive surgery. As a response to neoadjuvant chemotherapy was reported to be able to predict prognosis in patients with advanced gastric cancer [16], the establishment of an effective neoadjuvant regimen may lead to further improvements of the prognosis. In our study, three patients were surgically treated after the chemotherapy with S-1 and CDDP; however, we did not encounter increased morbidity due to the prior chemotherapy, and we found that S-1 and CDDP could be safely administered as neoadjuvant chemotherapy. The feasibility of S-1 and CDDP as neoadjuvant chemotherapy may need to be appropriately evaluated for patients with advanced gastric cancer with bulky primary tumor or lymph nodes in future.

The disadvantages of the combination of S-1 and CDDP may include the short hospital stay during CDDP administration and the associated increase in costs and adverse effcts, as well as the difficulty of selecting second-line chemotherapy.

A clinical phase III trial comparing S-1 alone with S-1 and CDDP for advanced gastric cancer has now been conducted in Japan, and the efficacy, adverse effects, and prognoses of these regimens will be evaluated appropriately in the near future.

To date, no definitive standard regimen has yet been drawn from randomized clinical trials of chemotherapy for gastric cancer, because few studies have shown a significant positive impact on survival as compared with 5-FU alone. A phase III study by the Japan Clinical Oncology Group (JCOG) has been conducted to evaluate the clinical efficacy of S-1, irinotecan (CPT-11) plus CDDP, and 5-FU alone for advanced gastric cancer. As a result of this study, the clinical usefullness of S-1 may be clarified.

We conclude that the combination of S-1 and CDDP seems to have a high therapeutic index, enhancing antitumor effects while maintaining modest adverse effects. Further study with a large number of patients may be needed to confirm the combination of S-1 and CDDP or other newly developed agents to be an appropriate first-line chemotherapy for gastric cancer.

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