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Overview

Current topics of S-1 at the 74th Japanese Gastric Cancer Congress

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Abstract
S-1 (TS-1®)-related studies presented at the 74th Japanese Gastric Cancer Congress are reviewed. Of the papers presented at this conference, 35 were related to S-1. In the panel discussion on the therapeutic significance of oral fluoropyrimidines in gastric cancer, 9 papers were related to S-1 (sensitivities to oral fluoropyrimidines, 2 papers; clinical results of treatment with S-1, 5 papers; and combination therapy with S-1, 2 papers). In the general presentations, there were 26 papers on S-1 related-subjects (clinical studies or clinical practice of S-1, 12 papers; case reports, 3 papers; basic studies on animal models of peritoneal metastasis, 2 papers; and combination therapy with S-1, 9 papers). Several studies showed that S-1 was basically as effective against tumors in post-marketing surveillance in clinical practice as in phase II studies at the time of its development, including a report of a patient with complete response to S-1. Some reports suggested the possibility of using S-1 in neoadjuvant chemotherapy and postoperative adjuvant chemotherapy. The usefulness of S-1 in combination chemotherapy was also suggested in several reports. These results indicate that S-1 is a key drug that can be used in first-line treatment of gastric cancer. It will be necessary to accumulate evidence based on data from clinical trials and clinical applications in the future.

Key words 74th Japanese Gastric Cancer Congress · S-1 · Overview

Introduction

Oral fluoropyrimidines, which hold the most important position in chemotherapy on an outpatient basis for gastric cancer, are widely used for advanced disease and as adjuvant chemotherapy. S-1, a new oral antitumor agent, was designed based on the theory of biochemical modulation of 5-fluorouracil (5-FU) [1–4]. In S-1, tegafur (FT) is combined with two classes of enzyme inhibitor, 5- chloro-2, 4-dihydroxypyridine (CDHP) and potassium oxonate (Oxo), at a molar ratio of FT:CDHP:Oxo = 1:0.4:1 [5]. S-1 achieved a response rate of 44.6% (45/101) in gastric cancer patients in late phase II studies [6,7]. On the strength of such excellent results in phase II studies, gastric cancer as an indication for the use of S-1 was permitted, in March 1999, and its commercial use became possible.

The 74th Japanese Gastric Cancer Congress, chaired by Dr. Yosino, was held from February 7 to 9, 2002, in Tokyo. The conference included 7 special lectures, 2 symposia, 3 video symposia, 2 panel discussions, 3 workshops, and 300 general presentations (poster sessions). Of the papers presented at this conference, 35 were related to S-1. Particularly in the "Panel discussion on the therapeutic significance of oral fluoropyrimidines in gastric cancer", all the presentations were related to S-1. The following is an overview of S-1-related studies presented at this conference, with special reference to those at the panel discussion.

Panel discussion: the therapeutic significance of oral fluoropyrimidines in gastric cancer

The panel discussion for this conference was planned, and cochaired by the author and Dr. Maehara (Kyushu University). Nine papers at this symposium, all of them related to S-1, presented updated basic and clinical evidence on this agent (Table 1).

Sensitivity to oral fluoropyrimidines, mainly S-1, and related factors: two papers

Usuki reported that, in a study of 80 postoperative gastric cancer patients, both UFT (uracil + tegafar) and S-1, dihydropyrimidine dehydrogenase (DPD) inhibitory

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Table 1. S-1 related reports in Panel Discussion

No.	Title	Reporter
PD2-01	Dihydropyrimidine dehydrogenase activity in gastric cancer and DPD inhibitory fluoropyrimidines	Usuki
PD2-02	Prediction of oral fluoropyrimidine sensitivity by metabolic, catabolic and target enzymes	Fujiwara
PD2-03	Personalized chemotherapy in gastric carcinoma	Yoshida
PD2-04	Long-term control of advanced and recurrent gastric cancer by S-1	Cho
PD2-05	Efficacy and safety of S-1 in patients with advanced or recurrent gastric cancer	Imamura
PD2-06	Neoadjuvant chemotherapy for scirrhous gastric cancer — with special reference to S-1	Kinoshita
PD2-07	Clinical practice of S-1 for advanced gastric cancer	Kawai
PD2-08	Experimental approach for combination therapy of S-1 and docetaxel	Takahashi
PD2-09	Clinical significance of S-1 and S-1+CDDP for gastric cancer	Baba

S-1; Taiho Pharmaceutical (Tokyo, Japan); CDDP, cisplatin

Table 2. Response rates and median survival times (MSTs) of S-1 for gastric cancer in clinical practice (from Panel Discussion)

Reporter	Prior chemotherapy	No. of patients	Response rate (%)*	MST (days)
Kawai	No	51	43	337
Cho	No/Yes	69	38	336
Yoshida	No/Yes	40	44	NR

*Evaluable cases
NR, Not reported

fluoropyrimidines (DIF), were useful in the treatment of patients with low DPD activity and that S-1 was especially useful in patients with high DPD activity. Fujiwara, who conducted a basic study using nude mice, reported on the selection of indications for oral fluoropyrimidines in view of thymidylate synthase (TS), DPD, and thymidine phosphorylase (TP) enzyme activities.

Clinical results of treatment with S-1 alone: five papers

Cho, Kawai, and Yoshida reported the results of clinical practice in the treatment of gastric cancer with S-1 alone. Cho reported a survival benefit among patients who received longterm administration of S-1. Kawai reported that patients who received an initial dose of S-1 showed a 2-year survival rate of 35%, indicating the high efficacy of S-1. Yoshida emphasized that treatment with S-1 alone produced better results than treatment with a low dose of cisplatin (CDDP) plus 5-FU at his facility. Yoshida also indicated the possibility of personalized chemotherapy, based on an efficacy prediction model using a statistical technique. Table 2 shows a summary of the response rates and median survival times (MSTs) of these three reports.

Imamura reported on the results of a clinical study for curing gastric cancer with S-1 alone and suggested a modified schedule to reduce adverse reactions. Kinoshita reported a pilot study of preoperative chemotherapy with S-1 for scirrhous gastric cancer. Given these study results, the Japan Clinical Oncology Group (JCOG) is currently carrying out a phase II study of S-1 preoperative chemotherapy for scirrhous gastric cancer.

S-1 therapy combined with other drugs: two papers

Takahashi reported the results of a study on the antitumor effect and toxicity of combination chemotherapy of S-1 with docetaxel using nude rats. An increased antitumor effect in the slight toxicity range was demonstrated. Baba reported the therapeutic outcome for advanced gastric cancer patients treated with a combination of S-1 and CDDP. According to the Ohtsu regimen [8], S-1 was administered orally at 80 mg/m^2 per day twice a day for 21 consecutive days and CDDP was infused at 60 mg/m^2 over 2 h on day 8. An assessment of nine evaluable cases showed a response rate of 56%. Baba stated that this combination therapy was the first choice for patients with advanced or recurrent gastric cancer and that it was suitable for preoperative chemotherapy.

Finally, Kaibara gave a special lecture. He reported an investigation of the relationship between the prognosis of patients who received oral fluoropyrimidines as postoperative adjuvant chemotherapy and the prognosis of those who also received 5-FU metabolic and catabolic enzymes. He presented results for some patients who responded to S-1 and also described the prospects for future S-1 chemotherapy.

General presentations

In the "General presentations," 26 papers on S-1 related subjects were presented in posters (Table 3). Twelve papers were about the clinical study of S-1 alone or the results of clinical practice with S-1. Three papers were case reports, including the report of a patient with a complete response to S-1. Nearly all the papers described the clinical effects of S-1 on advanced or recurrent gastric cancer, suggesting the usefulness of S-1 in

Table 3. S-1 related reports in General Presentations

No.	Title	Reporter
P-042	Experience of chemotherapy using S-1 for advanced and recurrent gastric cancer	Nakamura
P-063	A case of advanced gastric cancer improved by S-1	Nagai
P-064	Clinical efficacy of S-1 for treatment of advanced gastric cancer	Nakamura
P-065	A case of advanced gastric cancer treated with S-1 and CPT-11	Yamashita
P-075	Preoperative chemotherapy with S-1 and low dose CDDP for advanced gastric cancer	Saikawa
P-078	Effect of administration of CPT-11 combined with CDDP on S-1 tolerated gastric cancer	Sugiura
P-079	FLEP/S-1 therapy for advanced gastric cancer	Mochizuki
P-080	Effectiveness of S-1 for gastric cancer: emphasis on effective cases	Sato
P-081	Clinical effect and adverse reactions of S-1 administration before surgery for advanced gastric cancer	Chochi
P-082	S-1/CDDP therapy for advanced gastric cancer	Nakamura
P-083	Chemotherapy with S-1 and CDDP for advanced gastric cancer	Michiura
P-084	The effect of S-1 and combined chemotherapy of CDDP/S-1 for highly advanced gastric cancer	Konno
P-090	New therapeutic experience of S-1 for reduction of adverse reactions	Kimura
P-091	A case of gastric cancer with liver metastasis and LN metastasis treated with S-1/CDDP	Maruyama
P-167	Evaluation of the efficacy of S-1 on peritoneal metastasis of gastric cancer using an animal model	Mori
P-168	Inhibition of peritoneal micrometastasis of GFP-tagged gastric cancer cells by S-1	Mochizuki
P-175	Effects of S-1 on recurrent gastric cancer and consideration of the indications for administration	Yamada
P-185	Umbilical metastasis of gastric cacer	Nakasato
P-187	A case in which S-1+CDDP therapy worked effectively on DIC due to multiple bone metastasis of gastric cancer	Yoshioka
P-238	Home therapy using S-1 in combination with enteral nutrition support for gastric cancer patients	Sano
P-279	Successful treatment for gastric cancer associated with multiple liver metastases with S-1 followed by curative gastrectomy	Suzuki
P-280	Three cases with effective response to S-1 for inoperable gastric cancer	Urano
P-281	Improvement in the survival of patients with advanced gastric cancer by S-1	Watanabe
P-282	Significance of S-1 for advanced or recurrent gastric cancer	Ohashi
P-283	A clinical study of S-1 in patients with advanced and recurrent gastric cancer	Teruya
P-284	Feasibility and efficacy of S-1 adjuvant chemotherapy for resectable stage IV gastric cancer	Fujitani

CPT-II, Irinotecan; FLEP, 5-FU + leucovorin + etoposide + CDDP; LN, lymph node; GFP, green fluorescent protein; DIC, disseminated intravascular coagulation

patients with advanced or recurrent gastric cancer. Fujitani et al. reported on the safety and efficacy of S-1 for stage IV cancer, and showed the possibility that S-1 contributes to the survival of patients when used in adjuvant chemotherapy for stage IV gastric cancer.

There were two reports of basic studies, both about S-1 in animal models of peritoneal metastasis. Mori demonstrated the usefulness of S-1 for peritoneal dissemination, using an experimental model of peritoneal dissemination of gastric cancer. Mochizuki et al. presented an experimental study in a model of peritoneal dissemination of green fluorescent protein (GFP)-tagged human gastric cancer. They reported that the inhibitory effect of S-1 on peritoneal disseminated metastasis improved as the number of viable cancer cells in the peritoneal cavity decreased, and that S-1 improved survival prognosis if the number of cancer cells was small.

Papers on combination chemotherapy with S-1 included six reports on the results of clinical studies or the results of clinical practice at individual medical centers, and three case reports. Combination chemotherapy involved S-1 + CDDP in seven reports (the majority), S-1 + irinotecan (CPT-11) in one report, and 5-FU + leucovorin + etoposide + CDDP (FLEP) + S-1 in one report.

Summary and future prospects

The S-1-related studies presented at the 74th Japanese Gastric Cancer Congress have been summarized. Several studies showed that S-1 was generally as effective against tumors in the postmarketing surveillance in clinical practice as in phase II studies at the time of its development. Because S-1 is an oral preparation, it can be used on an outpatient basis and should be beneficial from the viewpoint of the patient's quality of life (QOL). These results indicate that S-1 is a key drug that can be used in the first-line treatment of gastric cancer. Some reports suggested the possibility of using S-1 in neoadjuvant chemotherapy and postoperative adjuvant chemotherapy. Thus, it is necessary to verify the usefulness of S-1 in a large-scale prospective randomized trial. The usefulness of S-1 in combination chemotherapy was also suggested by several reports, although only preliminary results have been obtained so far. Further clinical studies must be conducted to establish combination

chemotherapy involving S-1, CDDP, CPT-11, paclitaxel, and docetaxel.

Because S-1 is expected to become the standard drug for the treatment of gastric cancer, it will be necessary to build up evidence by further accumulation of data from clinical trials and clinical practice in the future.

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