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Review article

Clinical development of S-1 plus cisplatin therapy as first-line treatment for advanced gastric cancer

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Abstract
We reviewed the clinical development of S-1 and S-1 plus cisplatin (CDDP) therapy for advanced gastric cancer (AGC). S-1 is an active oral fluoropyrimidine in patients with AGC. Phase I/II clinical trials of S-1 plus CDDP for AGC have yielded high response rates and the agents were well tolerated. On the basis of these phase I/II studies, we performed a randomized phase III study comparing S-1 plus CDDP with S-1 alone in patients with AGC. In the S-1 plus CDDP group, S-1 was given orally, twice daily for 3 consecutive weeks, and 60 mg/m^2 CDDP was given intravenously on day 8, followed by a 2-week rest period, within a 5-week cycle. In the S-1 alone group, S-1 was given orally, twice daily for 4 consecutive weeks, followed by 2 weeks of rest, within a 6-week cycle. Median overall survival was significantly longer in the S-1 plus CDDP group (13.0 months) than in the S-1 alone group (11.0 months; $P = 0.04$). Progression-free survival was significantly longer in the S-1 plus CDDP group (median, 6.0 months vs 4.0 months; $P < 0.0001$) and the response rate was also significantly higher (54.0% vs 31.1%; $P = 0.002$). There were more grade 3 or 4 adverse events, including leukopenia, neutropenia, anemia, nausea, and anorexia in the S-1 plus CDDP group, but the events were manageable. No treatment-related deaths were observed. As a result of this study, S-1 plus CDDP therapy has become a standard first-line treatment for AGC in Japan.

Key words S-1 · CDDP · Gastric cancer

Introduction

Gastric cancer is particularly prevalent in East Asia, Eastern Europe, and Central and South America. Worldwide, gastric cancer remains the second cause of death from cancer, with about 700 000 confirmed deaths annually [1, 2]. In Japan, gastric cancer is one of the most frequent causes of death from cancer, despite dramatic advances in diagnosis and therapy [3]. Outcomes are extremely poor among patients with unresectable gastric cancer, with the median survival ranging from 3 to 5 months with the best supportive care [4–6].

Randomized controlled trials of various treatment regimens have produced disappointing results in patients with advanced gastric cancer (AGC), with survival of only 6 to 11 months. Median survival times (MSTs) have gradually improved, but are still less than 1 year [7–13]. Standard treatments remain a matter of debate.

In this context, we evaluated the effectiveness of S-1 plus cisplatin (CDDP) therapy in a randomized phase III study based on the promising activity of several clinical studies of S-1. This review focuses on the clinical development of S-1 and S-1 plus CDDP therapy for AGC.

Drug concept of S-1

S-1 (TS-1; Taiho Pharmaceutical, Tokyo, Japan) is an oral anticancer drug that combines tegafur (FT), a prodrug of 5-fluorouracil (5-FU), with 5-chloro-2, 4-dihydropyridine (CDHP; gimeracil) and potassium oxonate (Oxo; oteracil potassium) in a molar ratio of 1:0.4:1. CDHP reversibly antagonizes the activity of dihydropyrimidine dehydrogenase (DPD), the rate-limiting enzyme for the degradation of 5-FU. CDHP has 180-fold higher DPD inhibitory activity than that of uracil in vitro [14]. High concentrations of 5-FU in serum and tumors are thereby maintained for prolonged periods. Potassium oxonate blocks the phosphorylation of 5-FU in the gastrointestinal tract, reducing gastrointestinal adverse effects, the prime dose-limiting toxicity of 5-FU [15].

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Pharmacokinetics of S-1 in cancer patients

Hirata et al. [16] investigated the pharmacokinetics of 5-FU, intact FT, CDHP, and Oxo, after single or consecutive administration of S-1, at a standard dose of 80 mg/m^2 per day, in patients with advanced cancer (n = 12). The initial dose of S-1 for each patient was determined according to body surface area (BSA) as follows: for BSA less than 1.25 m^2, 80 mg/day; for BSA 1.25 m^2 to 1.5 m^2, 100 mg/day; and for BSA more than 1.5 m^2, 120 mg/day. For single administration, half of the standard dose was administered. For 28-day consecutive administration, the standard dose was given daily in two divided doses after breakfast and dinner. The actual average single dose per BSA was 35.9 mg/m^2 (range, 31.7–39.7 mg/m^2). Pharmacokinetic parameters of plasma 5-FU were as follows: Cmax, 128.5 ± 41.5 ng/ml; Tmax, 3.5 ± 1.7 h; AUC_{0-14}, 723.9 ± 272.7 ng·h/ml; and $T_{1/2}$, 1.9 ± 0.4 h. In the 28-day consecutive regimen, there was no drug accumulation. These data indicated that the pharmacokinetics of orally administered S-1 were comparable to those of continuous infusion of 5-FU.

Subsequently, Yamada et al. [17] compared the pharmacokinetics of oral S-1 at the standard dose (the median actual dose of S-1 was 71.6 mg/m^2 per day) with those of protracted venous infusion (PVI) of 250 mg/m^2 5-FU within the same AGC patients (n = 10). They found that oral S-1, at the present recommended doses in Japan, produced a higher Cmax (230 ± 69 ng/ml for S-1 vs 93 ± 13 ng/ml for PVI of 5-FU) and a greater AUC (1364 ± 374 ng·h/ml for S-1 vs 728 ± 113 ng·h/ml for PVI of 5-FU) of plasma 5-FU than did PVI of 5-FU, with no elevation of the plasma concentration of α-fluoro-β-alanine, a catabolite of 5-FU that is thought to cause the cardiotoxic and neurotoxic effects of 5-FU by inhibiting the tricarboxylic acid cycle [18–20].

S-1 monotherapy for advanced gastric cancer (AGC)

An early phase II study of S-1 has reported a high response rate of 53.6% in patients with AGC [21]. In two subsequent late phase II registration studies, S-1 demonstrated excellent activity for gastric cancer, with response rates of 49% (25/51) and 40% (20/50), respectively [22, 23]. The median survival times obtained in these studies were 250 days and 207 days, although the treatment regimen was single-agent S-1. As for the safety of the regimen, an incidence of 10%-20% of grade 3 or more adverse reactions, including leukopenia, neutropenia, decreased hemoglobin, and diarrhea was observed. However, the toxicity profile of S-1 was generally mild and there were no severe or unexpected adverse reactions. Based on these results, S-1 was approved for the treatment of gastric cancer by the Ministry of Health, Labour, and Welfare (MHLW) of Japan, in 1999.

Furthermore, the results of Japanese nationwide post-marketing studies in patients with AGC confirmed that the safety and efficacy profiles of S-1 were similar to those seen in the registration study (n = 3801) [24]. For these reasons, S-1 has already been used as a first-line treatment for AGC patients in Japan.

A Japan Clinical Oncology Group (JCOG) study,(the JCOG9205 study) obtained similar MSTs, of about 7 months, with both 5-FU alone and 5-FU plus CDDP in patients with unresectable AGC in a randomized phase III study [10]. Subsequent clinical trials in Japan therefore included 5-FU monotherapy as the reference arm. The JCOG9912 study by Boku et al. [25] was designed to test the hypotheses that S-1 alone was not inferior to 5-FU alone, used as a control, and that irinotecan plus CDDP was superior to 5-FU alone in patients with advanced, unresectable, or recurrent gastric cancer. In their study, although irinotecan plus CDDP was not superior to 5-FU alone, S-1 was not inferior to the 5-FU-alone regimen in terms of survival as the primary endpoint. In the S-1 group and the 5-FU alone group, median survival times were 11.4 months and 10.8 months, progression-free survivals were 4.2 months and 2.9 months, and 28% and 9% of patients responded, respectively. Thus, S-1 monotherapy actually became a new standard treatment option for AGC patients in Japan.

Clinical development of S-1 plus CDDP (SP) therapy

Cisplatin (CDDP) is also a key drug for the chemotherapy of AGC. Combinations of 5-FU and CDDP were shown to be synergistic in preclinical [26–28] and clinical studies [29] of AGC, with acceptable toxicity. Based on these studies and the promising activity of S-1 observed in the late phase II studies, we conducted a phase I/II study of S-1 in combination with CDDP. S-1 was given orally at 40 mg/m^2 b.i.d. for 21 consecutive days followed by a 2-week rest. CDDP was planned to be given intravenously on day 8, at a dose of 60, 70, or 80 mg/m^2 depending on the dose-limiting toxicity (DLT). In the phase I portion, the maximum tolerated dose of CDDP was presumed to be 70 mg/m^2, because 33.3% of patients (2/6) developed DLTs, mainly neutropenia. Therefore, the recommended dose (RD) of CDDP combined with 80 mg/m^2 of S-1 was estimated to be 60 mg/m^2. Plasma pharmacokinetic analysis was performed on samples obtained from 12 patients during the first course of the phase I portion. CDDP did not affect the plasma pharmacokinetics of any S-1 component, which was considered to be safely administered in this combination regimen.

In the phase II portion, the efficacy and safety of the regimen was evaluated in 19 patients, including 6 patients in the RD level in the phase I portion. The median number of cycles administered was four (range, 1–8). The incidences of grade 3 or more hematological and nonhematological toxicities were 15.8% and 26.3%, respectively, but all were manageable. The objective response rate was 74% (14/19; 95% confidence interval [CI], 54.9%-90.6%), and the median survival time was 383 days.

Thus, this regimen was considered to be promising against AGC, with acceptable toxicity.

Randomized phase III study of S-1 plus CDDP therapy for advanced gastric cancer (AGC)

Based on a previous phase I/II study, we conducted a randomized phase III study of S-1 plus CDDP therapy which was compared to S-1 monotherapy (designated as the SPIRITS trial: S-1 Plus CDDP versus S-1 In RCT In the Treatment for Stomach Cancer) [30]. The primary objective of this phase III study was to determine whether the S-1 plus CDDP therapy (group SP) was superior to S-1 monotherapy (group S) in terms of overall survival. In the S-1 plus CDDP group, S-1 was given orally, twice daily for 3 consecutive weeks, and 60 mg/m^2 CDDP was given intravenously on day 8, followed by a 2-week rest period, within a 5-week cycle. In the S-1 alone group, S-1 was given orally, twice daily for 4 consecutive weeks, followed by 2 weeks of rest, within a 6-week cycle. A total of 305 patients were registered at 38 centers in Japan from March 2002 through November 2004 and randomly assigned to the two treatment groups. At study enrollment, there was no significant difference between the treatment groups regarding any single clinical characteristic. No patient had locally advanced disease alone. Histologically, diffuse-type and intestinal-type adenocarcinomas, respectively, were diagnosed in 103 patients (70%) and 45 patients (30%) in group SP, as compared with 89 (59%) and 60 (40%) in group S, indicating a worse outcome to be expected in group SP than in group S [31].

Median follow-up was 2 years and 11 months. Median overall survival as the primary endpoint was significantly longer in group SP than in group S (13.0 months vs 11.0 months; P = 0.04). The hazard ratio (HR) for death was 0.77 (95% CI, 0.61 to 0.98). Median progression-free survival as a secondary endpoint was significantly longer in group SP than in group S (6.0 months vs 4.0 months; $P < 0.0001$). The HR for disease progression was 0.57 (95% CI, 0.44 to 0.73).

Among the 87 patients with target lesions in group SP, 1 had a complete response and 46 had partial responses, for a response rate of 54.0% (95% CI, 43.0% to 64.8%). Of the 106 patients with target lesions in group S, 1 had a complete response and 32 had partial responses, yielding a response rate of 31.1% (95% CI, 22.5 to 40.9). The response rate was significantly higher in group SP (P = 0.002).

The incidences of grade 3 or 4 hematological adverse events in group SP and group S were mainly as follows: leukopenia, 11.5% vs 2.0%; neutropenia, 39.9% vs 10.7%; and anemia, 25.7% vs 4.0%. The incidence of febrile neutropenia was 3.4% in group SP and 1.3% in group S. The incidences of grade 3 or 4 nonhematological adverse events in group SP and group S were mainly as follows: anorexia, 30.4% vs 6.0%; nausea, 11.5% vs 1.3%; vomiting, 4.1% vs 2.0%; fatigue, 4.1% v. 1.3%; and diarrhea, 4.1% vs 3.3%. There were no treatment-related deaths in either group.

The median initial actual dose of S-1 was 36.1 mg/m^2 b.i.d. (range, 31.7–39.8 mg/m^2) in group SP and 36.0 mg/m^2 b.i.d. (range, 28.8–39.9 mg/m^2) in group S; i.e., the dose was similar in the two groups. The median relative dose intensity was 93.3% for the scheduled cycles of therapy in group SP, as compared with 98.0% in group S. Median time to treatment failure was 4.8 months in group SP and 3.9 months in group S (P = 0.009; HR, 0.699; 95% CI, 0.536–0.912).

In summary, we concluded that the S-1 plus CDDP therapy was superior to S-1 monotherapy, with a favorable toxicity profile.

In recent previous phase III clinical trials of chemotherapy in patients with gastric cancer, the following median survival times have been reported: 9.2 months for docetaxel and CDDP plus 5-FU (DCF) by the V325 Study Group [11], 10.5 months for a combination of capecitabine and CDDP (XP) by Kang et al. [8]; and 9.9 months for a combination of epirubicin, CDDP, and 5-FU (ECF) and 11.2 months for a combination of capecitabine, oxaliplatin, and epirubicin (EOX) in the REAL2 trial [7]. No previously reported well-tolerated chemotherapy regimen in patients with AGC has obtained a median survival time of 1 year or longer (Table 1). We hypothesized that the median survival time of longer than 1 year and the median progression-free survival of 6.0 months was ascribable to synergism between S-1 and CDDP. Furthermore, this is also the first phase III trial to show better results with combination chemotherapy than monotherapy. These results suggest that S-1 plus CDDP may represent just one step in the process of developing a standard treatment for AGC, although we need to consider the fact that therapeutic outcomes in Japan are generally better than those in Western trials.

Most recently, the Chinese SC-101 study revealed that S-1 plus CDDP therapy was superior to 5-FU plus CDDP therapy, with the response rate as the primary

Table 1. Recent randomized phase III studies in advanced gastric cancer

Author	Regimen	*n*	RR (%)	PFS (months)	OS (months)	*P* value (OS)
Koizumi et al. [30] (2008)	S-1	150	31	4.0	11.0	
	S-1 + CDDP	148	54	6.0	13.0	0.04
Jin et al. [32] (2008)	S-1	77	25	—	8.9	
	S-1 + CDDP	74	38	—	14.4	<0.001,[a] 0.038[b]
	5-FU + CDDP	73	19	—	10.3	
Boku et al. [25] (2007)	5-FU	234	9	2.9	10.8	
	CPT-11/CDDP	236	38	4.8	12.3	0.055
	S-1	234	28	4.2	11.4	<0.001[c]
Ohtsu et al. [10] (2003)	5-FU	105	11	1.9	7.1	NS
	UFT + MMC	70	9	2.4	6.0	
	5-FU + CDDP	105	34	3.9	7.3	
Van Cutsem et al. [11] (2006)	CF	224	25	3.7[d]	8.6	
	DCF	221	37	5.6	9.2	0.02
Cunningham et al. [7] (2008)	ECF	263	41	6.2	9.9	NS
	EOF	245	42	6.5	9.3	
	ECX	250	46	6.7	9.9	
	EOX	244	48	7.0	11.2	
Kang et al. [8] (2006)	FP	137	29	5.0	9.3	NS
	XP	139	41	5.6	10.5	

RR, response rate; PFS, progression-free survival; OS, overall survival
[a] vs S-1
[b] vs 5-FU + CDDP
[c] Noninferiority
[d] Time to tumor progression

endpoint [32]. In this study, the overall survival with S-1 plus CDDP therapy was also superior to those of both the 5-FU plus CDDP therapy and the S-1 alone regimen. These data suggests that S-1 plus CDDP therapy may provide a favorable outcome, at least in Asian populations.

At present, a large randomized controlled trial, the First-Line Advanced Gastric Cancer Study (FLAGS) is being conducted in 24 countries to determine whether S-1 plus CDDP is superior to 5-FU plus CDDP. In the FLAGS trial, the enrollment of about 1000 patients has recently been completed, and the results are pending [33].

Conclusion

We believe that our results will establish S-1 plus CDDP as a standard treatment for gastric cancer in Japan, and as such, the SPIRITS study can be considered to be a clinical practice-changing trial. Further studies are warranted to investigate the S-1 plus CDDP regimen as a cytotoxic backbone in combination with novel targeted agents.

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