

Review

New Chemotherapy Strategies for Gastric Cancer

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Abstract. Gastric cancer chemotherapy has entered a new era with the introduction of new drugs such as S-1, irinotecan (CPT-11), paclitaxel and docetaxel. Recent phase III studies have indicated that S-1 monotherapy, a remnant reference arm from a previous study, was not inferior to 5-FU alone, and that the combination of S-1 with cisplatin and CPT-11 showed higher efficacy than S-1 alone with tolerable side-effects for advanced and recurrent gastric cancer. In the adjuvant setting, S-1 monotherapy prolonged survival following surgery compared with surgery alone after curative extended (D2) lymph-node dissection for stage II/III gastric cancer. However, some issues remain, such as the sequence of several duplet chemotherapies, treatment following cases of S-1 failure, the relative efficacy of doublet and triplet therapies, and the impact of molecular-targeting.

Several new drugs have recently been introduced for the treatment of gastric cancer, including irinotecan (CPT-11), taxanes (docetaxel and paclitaxel) and S-1, that can be used in combination with older, standard drugs, such as cisplatin (CDDP). These drugs have created a new era of chemotherapy for gastric cancer; for instance, S-1 regimens have been reported to have single efficacy rates of 44-49% (1, 2), while S-1 in combination with CDDP showed a 78% efficacy rate (3). S-1 is a novel oral anticancer drug composed of tegafur (FT), 5-chloro-2,4-dihydropyridine (gimeracil CDHP), and oteracil potassium (Oxo) in a molar ratio of 1:0.4:1. This agent was designed to enhance the oral efficacy of FT, a prodrug of 5-fluorouracil (5-FU). CDHP inhibits the activity of dihydropyrimidine dehydrogenase

(DPD), an enzyme that degrades 5-FU, and is about 180-fold more potent than uracil, thereby maintaining prolonged blood and tumour 5-FU concentrations. Oxo is distributed throughout the gastrointestinal tract at high concentrations following oral administration, and prevents phosphorylation (*i.e.*, activation) of 5-FU by inhibiting activity of the enzyme orotate phosphoribosyl transferase (OPRT). Therefore, S-1 improves the tumour-selective toxicity compared to 5-FU alone due to the actions of both CDHP and Oxo (4). Currently, there are several regimens to choose for advanced gastric cancer and in the adjuvant setting following surgery. In the present paper, the new advances in gastric cancer chemotherapy for advanced or recurrent cases of gastric cancer and for the adjuvant setting are reviewed.

Chemotherapy for Unresectable or Recurrent Gastric Cancer

S-1 (JCOG9912). Boku *et al.* reported a randomized phase III study (JCOG9912 trial) that compared 5-FU alone, combined CPT-11 and CDDP (CP) (5), and S-1 alone in advanced gastric cancer under the Gastrointestinal Oncology Study Group/Japan Clinical Oncology Group (6).

Seven hundred and four patients with unresectable or recurrent gastric adenocarcinoma with or without target lesions were randomized to each of the three arms (details in Table I). At final analysis, twelve months after the last patient entered the trial, 601 patients (85%) had died. The overall survival (OS), the primary endpoint was 10.8 months for 5-FU, 12.3 months for CP and 11.4 months for S-1 (Table I). The median time to treatment failure (TTF) and non-hospitalized survival (NHS) were 2.3 and 7.2 months for 5-FU, 3.7 and 9.5 months for CP and 4.0 and 9.2 months for S-1, respectively. In a subset analysis, the response rates (RRs) of 5-FU, CP and S-1 with tumour lesions (n=175, 181, and 175, respectively) were 9%, 38%, and 28%, respectively, with median survival times (MST) of 9.0, 12.1 and 10.5 months, respectively. Hazard ratios (HR)s with respect to 5-FU were 0.78 (95% CI, 0.63-0.98) for CP and 0.85 (0.68-

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Table I. Survival effects in the JCOG9912 Phase III trial.

	n	MST	1-ysr	HR (95% CI)	1-sided p-value
5-FU	234	10.8	44.0%		
CP	236	12.3	52.5%	0.85 (0.70-1.04)	0.055 (superiority)
S-1	234	11.4	47.9%	0.83 (0.68-1.01)	<0.001 (non-inferiority) 0.034 (superiority)

n, number; MST, mean survival time in months; 1-ysr, one-year survival rate; HR, hazard ratio. 5-FU: 5-fluorouracil at 800 mg/m²/d, *ci*, d1-5, *q4w*. CP: irinotecan (CPT-11) at 70 mg/m², *div*, d1&15 and cisplatin (CDDP) at 80 mg/m², *div* d1, *q4w* (Ref. 16). S-1: S-1 at 40 mg/m², *b.i.d.*, d1-28, *q6w*. Treatments continued until disease progression or unacceptable toxicity.

1.06) for S-1. In the subset of cases without tumour lesions, the MSTs for 5-FU, CP and S-1 (n=59, 55, and 59, respectively) were 13.5, 14.4, and 18.1 months, respectively, with HRs of 1.02 (0.68-1.55) for CP and 0.82 (0.55-1.24) for S-1. Thus, S-1 showed significant non-inferiority to 5-FU, while CP failed to show statistically significant superiority to 5-FU for all patients. In terms of adverse effects, no grade 4 neutropenia was encountered in the 5-FU or S-1 groups, compared with 37 cases in the CP group. No cases of grade ≥3 febrile neutropenia or infection with neutropenia were observed in the 5-FU and S-1 groups, while 9 and 8 cases, respectively, were observed in the CP group. Within 6 months of treatment, 13, 33, and 12 cases of anorexia and 0, 9 and 8 cases of diarrhoea were observed in the 5-FU, CP and S-1 groups, respectively. The numbers of treatment-related deaths were 0 for 5-FU, 3 for CP and 1 for S-1. Instances of incomplete treatment were mostly observed in the CP group, and of the patients that withdrew from the study, 36% were due to toxicity, and 39% due to patient refusal.

Therefore, the CP treatment was not superior to 5-FU, and CP-associated toxicity was markedly higher than for the other two arms. S-1 showed non-inferiority to 5-FU with low toxicity and could be considered as the standard regimen for advanced and/or recurrent gastric cancer.

S-1 + cisplatin. Koizumi *et al.* reported results of SPIRITS (the S-1 plus cisPlatin vs. S-1 In RCT In the Treatment of Stomach cancer) trial, a phase III study of S-1 alone (Arm A) versus S-1 + CDDP (Arm B) in the treatment of advanced gastric cancer, conducted as a randomized, controlled, open label, parallel, multicenter study (7). The patients were randomized to one of two treatment arms. The Arm A, treatment consisted of oral S-1 (40 mg/m²) twice daily for 28 days followed by 14 days rest, and Arm B, oral S-1 (40 mg/m²) twice daily for 21 days followed by 14 days rest plus CDDP (60 mg/m²) *i.v.* on day 8.

Patients with unresectable/recurrent advanced gastric cancer, age 20-74, and no prior chemotherapy were

randomized to the two treatment arms. At the end of the trial, the total number of eligible patients was 299, with 150 in Arm A (median age 62.0 years), and 149 in Arm B (median age 61.5 years). At 2 years follow-up after the last patient entered the trial, the MST for Arm A was 335.5 days (95% CI: 292.0-402.0), compared to 396.0 days (95% CI: 342.0-471.0) for Arm B. The OS for Arm B was superior to Arm A (log-rank *p*=0.0366, HR: 0.774, 95% CI: 0.608-0.985), while the RR was 31.1% for Arm A and 54.0% for Arm B. The most common grade 3/4 toxicities for Arms A and B were: leucopenia, 2.0% vs. 11.5%; neutropenia, 10.7% vs. 39.9%; anaemia (decreased Hb), 4.0% vs. 25.7%; nausea, 1.3% vs. 11.5%; and anorexia, 6.0% vs. 30.4%, respectively. No treatment related deaths were observed.

The combination treatment of S-1 and CDDP was superior to S-1 alone in terms of the primary end-point of OS without severe side-effects for patients with advanced gastric cancer. This indicated that this regimen could be regarded as a first-line standard treatment for advanced gastric cancer. The commonly used standard regimen of 5-FU + CDDP (5-FU [1,000 mg/m²/day, day 1-5] + CDDP [100 mg/m²/day, day 1]) is currently being compared against the S-1 (50 mg/m²/day, day 1-21) + CDDP (75 mg/m²/day, day 1) regimen in the FLAGS (The First-Line Advanced Gastric Cancer Study) trial worldwide (8), and the results will be reported in 2009.

S-1 + CPT-11. The use of S-1 plus CPT-11 (IRIS) versus S-1 alone as a first line treatment for advanced gastric cancer was tested by a multicenter, randomized phase III trial (GC0301/TOP-002) conducted by Imamura *et al.* (9). Previously untreated patients with advanced gastric cancer were randomized to either Arm A (oral S-1 80 mg/m²/day from day 1 to 28 followed by a 14-day rest), or Arm B (oral S-1 80 mg/m²/day from day 1 to 21 and intravenous irinotecan 80 mg/m² on days 1 and 15 followed by a 14-day rest). Treatments continued unless disease progression occurred. Inclusion criteria included a performance status (PS) (Eastern Cooperative Oncology Group; ECOG) of 0 to 2 and adequate major organ function.

The median age of the 326 patients was 63 years and 97% had PS 0-1, the distribution of intestinal/diffuse/other subtypes was 44%/55%/1% vs. 41%/58%/1%, for Arm A and B, respectively. The RRs were 26.9% for Arm A and 41.5% for Arm B (*p*=0.035) for the 187 evaluable cases (93 in Arm A vs. 94 in Arm B). Out of the 319 toxicity-evaluable patients (161 in Arm A vs. 158 in Arm B), the grade 3 or 4 toxicities encountered in Arms A and B were: neutropenia 9.3% vs. 26.6%; diarrhoea 5.6% vs. 15.8%; anorexia 9.9% vs. 15.8%; nausea 3.7% vs. 7.0% and vomiting 0.6% vs. 2.5%, respectively. Although the MST of Arm A was 318 days (95% CI: 286-395 days) and of Arm B was 389 days (95% CI: 286-395 days), Arm B didn't show statistically significant superiority to Arm A (log-rank test *p*=0.23; HR=0.86).

S-1 + docetaxel. The combination of docetaxel and S-1 has been evaluated in two Phase II studies. In one study, Yoshida *et al.* assessed the efficacy and toxicity of docetaxel and S-1 for patients with advanced or recurrent gastric cancer (10). The patients received intravenous docetaxel 40 mg/m² on day 1 and then S-1 40 mg/m² twice daily for 14 days followed by a 1-week rest. The RR was 56.3% (95% CI, 38%-66%), MST 14.3 months, and median TTP 7.3 months. No grade 4 non-haematological toxicities were reported, and all treatment-related toxicities were resolved. In the second Phase II study (11), treatment consisted of intravenous docetaxel 50 mg/m² on day 1 and then S-1 40 mg/m² twice daily for 14 days, followed by a 2-week rest. The maximum tolerated dose of docetaxel was later determined to be 50 mg/m², and the recommended dose reduced to 40 mg/m². Of the 46 patients who received treatment, the RR and estimated median OS were 46% (95% CI, 31%-61%) and 14.0 months, respectively. The most common grade 3/4 toxicity was neutropenia, which was predictable and manageable. These two Phase II studies indicated that the docetaxel/S-1 regimen resulted in extended survival despite a modest RR, and that toxicities were manageable. A Phase III study (JACCRO GC-03/START trial) is currently underway to compare S-1 alone with S-1 + docetaxel 40 mg/m² in Japanese and Korean patients with advanced or recurrent gastric cancer (12).

Adjuvant Chemotherapy for Advanced Gastric Cancer

INT-0116. Macdonald *et al.* investigated the effect of administering adjuvant chemoradiotherapy following surgery on the survival of patient (13). A total of 556 patients with resected adenocarcinoma of the stomach or gastroesophageal junction were randomized to receive surgery plus postoperative chemoradiotherapy or surgery alone. Adjuvant therapy consisted of 5-FU and leucovorin, followed by 4,500 cGy of radiation. The median OS in the surgery-alone group was 27 months, compared to 36 months in the adjuvant chemoradiotherapy group, with an HR for death of 1.35 ($p=0.005$) for the surgery-alone arm. The study concluded that adjuvant chemoradiotherapy was indicated for all patients at high risk for recurrence of adenocarcinoma of the stomach or gastroesophageal junction who have undergone curative resection. While this regimen is now recommended by the National Comprehensive Cancer Network (NCCN) guidelines, the Japanese Gastric Cancer Association has not recommended such adjuvant therapies as standard treatment due to the low rate of lymph node dissection performed by Macdonald *et al.*

MAGIC. Cunningham *et al.* conducted the MAGIC (the MRC Adjuvant Gastric Infusional Chemotherapy) trial (ISRCTN 93793971) to determine whether epirubicin,

CDDP, and infusional 5-FU (ECF) conferred a survival advantage to operable gastric cancer patients (14). A total of 503 patients with operable adenocarcinoma of the stomach, esophagogastric junction, or lower esophagus were randomized to receive either perioperative chemotherapy ($n=250$) or surgery alone ($n=253$). Survival HR was 0.75 ($p=0.009$) and progression-free survival HR 0.66 ($p=0.001$) for patients in the perioperative chemotherapy group. While this study suggested that perioperative chemotherapy was beneficial, the mortality rate was 6% in both arms, and within the perioperative chemotherapy arm only 55% of the patients initiated chemotherapy and only 42% completed it.

ACTS-GC. Sakuramoto *et al.* evaluated single-agent S-1 as an adjuvant chemotherapy for Japanese patients with stage II/III (Japanese Classification of Gastric Carcinoma) gastric cancer following curative extended (D2) lymph-node dissection (ACTS-GC trial; the Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer) (15). Eligibility criteria included R0 resection, pathological stage II/III, age 20-80 years, no prior adjuvant treatment and adequate organ function. The 1,059 patients were randomly assigned to receive surgery plus S-1 or surgery alone and no significant differences in baseline characteristics were observed between the two groups. S-1 at 80 mg/m²/day was administered for 4 weeks followed by a 2-week rest beginning within 45 days of surgery and ending 1 year after surgery.

When the first interim analysis was conducted one year after completion of enrollment, the HR of death for S-1 with respect to surgery alone was 0.57 (95% CI, 0.40-0.81; $p=0.0016$). Based on these results, the data and safety monitoring committee recommended halting this trial. At this point, the 3-year OS was 80.1% for S-1 patients compared with 70.1% for patients who received surgery alone, and the HR of death for S-1 was 0.68 (95% CI, 0.52-0.87; $p=0.003$). A total of 65.8% patients completed S-1 therapy. The results of this trial demonstrated that adjuvant chemotherapy with S-1 for stage II/III gastric cancer was feasible and effective and suggested that adjuvant S-1 should be adopted as the standard treatment following curative D2 gastric dissection.

Discussion

The Phase II results of several regimens have been reported in the Japanese Guideline for Treatment of Gastric Cancer (16), giving response rates and survival periods as shown in Figure 1. Response rates ranged from 41% to 78% by S-1 plus CDDP and survival times ranged from 7 to 12.6 months, which were markedly higher than the survival time of 3.6 months observed for best supportive care. Based on these results, the Guideline concluded that "cancer chemotherapy is recommended for advanced and recurrent gastric cancer, however the standard treatment is not

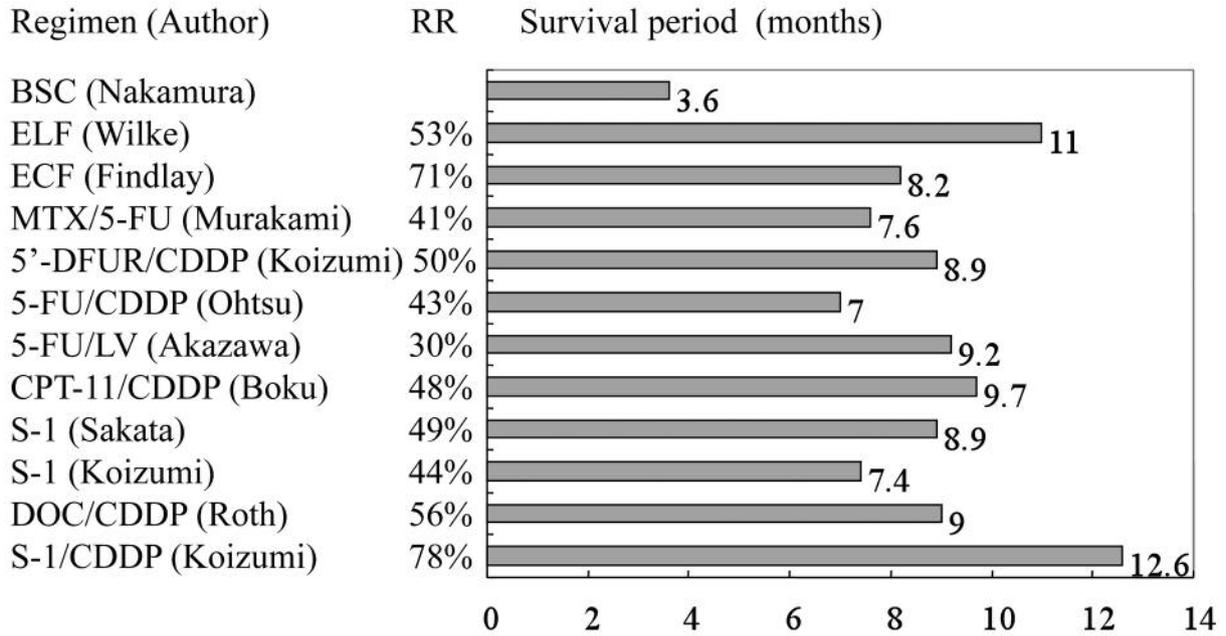


Figure 1. Response rates and survival periods in Phase II studies on advanced/recurrent gastric cancer [from Guideline of Treatment on Gastric Cancer (Ref. 16)]. Abbreviations: RR, response rate; BSC, best supportive care; ELF, epirubicin, leucovorin, and 5-FU; ECF, epirubicin, cisplatin, and 5-FU; MTX/5-FU, methotrexate and 5-FU; 5'-DFUR/CDDP, doxifluridine and cisplatin; 5-FU/CDDP, 5-FU and cisplatin; 5-FU/LV, 5-FU and leucovorin; CPT-11/CDDP, irinotecan and cisplatin; DOC/CDDP, taxotere and cisplatin; S-1/CDDP, S-1 and cisplatin.

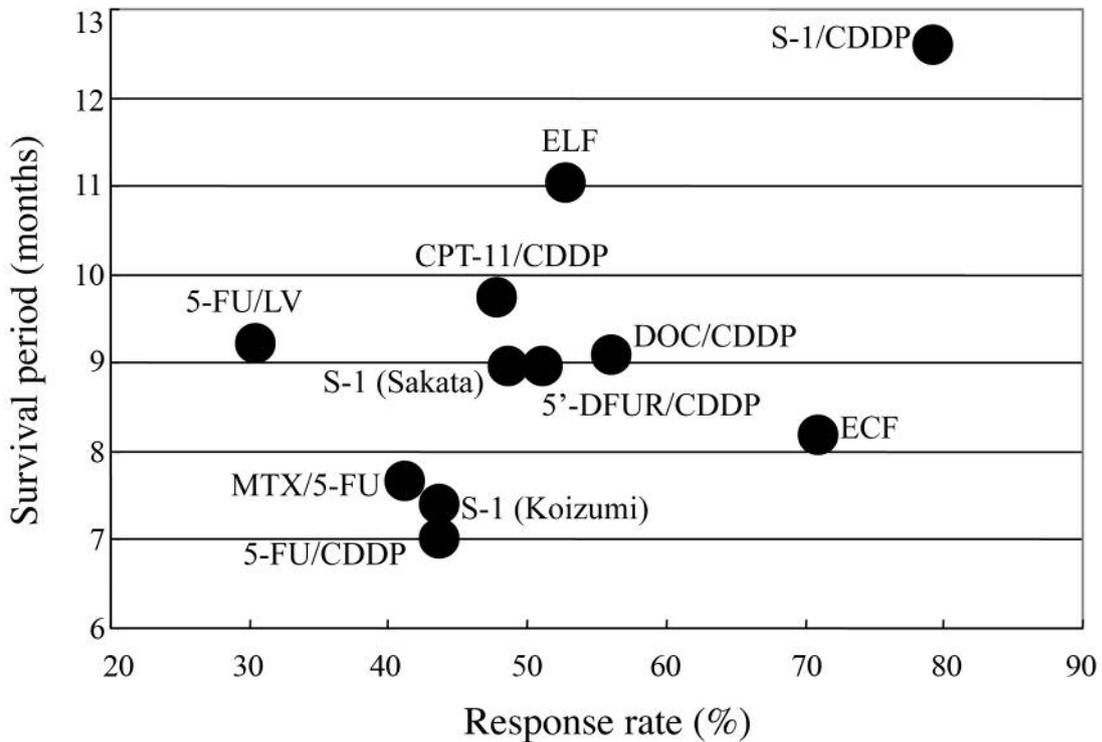


Figure 2. Correlation between response rate and survival period in Phase II studies on advanced/recurrent gastric cancer. No statistically significant correlation was observed between these two variables, although higher response rate tended to exhibit longer survival, for example S-1 + CDDP. $r=0.55$ and $p=0.077$.

established at this time". Indeed, when the response rates of the Phase II results were compared with their respective survival periods (Figure 2), no statistically significant correlation was observed between the two variables, with an r value of 0.55 ($p=0.077$), although higher response rates did tend to correlate with longer survival (for example S-1 + CDDP).

The JCOG9912 of S-1 was based upon the results of the JCOG9205 trial that compared 5-FU alone with 5-FU plus CDDP (FP) and with uracil and tegafur plus mitomycin (UFTM) (17). In the JCOG9205 trial, neither investigational regimen, FP (MST 7.3 months) nor UFTM (MST 6.0 months), showed a significant survival advantage over 5-FU alone (MST 7.1 months). Thus, 5-FU-alone was used as the reference arm in the JCOG9912 trial. The MST of 5-FU-alone increased from 7.1 months (JCOG9205) to 9.0 months (JCOG9912) between the two JCOG trials, while the RR values were stable at 11% and 9% for each trial. Since additional therapy after treatment-failure was not ruled out in the JCOG9912 trial, the similar RR but prolonged MST may have been due to the effects of second and third line chemotherapies, including CDDP, CPT-11 and taxanes.

The S-1 + CDDP and S-1 + CPT-11 regimens showed higher RR values than 5-FU alone in JCOG trials, and the MST of the S-1 + CDDP regimen was greater than that of S-1 alone. However, the use of S-1 combination regimens may be problematic based on the results of the ACTS-GC study that examined S-1 adjuvant chemotherapy following extended lymph-node (D2) dissection of stage II/III gastric cancer. If a recurrence occurs during S-1 administration, it can be assumed that the patient has either inherent or acquired resistance to S-1, rendering further S-1 administration ineffective. In such patients, combination therapy with CPT-11 70 mg/m² on days 1 and 15 and CDDP 80 mg/m² on day 1, repeated every 4 weeks, may be effective. For example, Boku *et al.* treated 44 patients with non-resectable advanced or recurrent gastric cancer with this regimen, and reported an RR of 48%, including 1 complete response (2%) (6). As combinations of S-1 with CDDP, CPT-11 and docetaxel remain to be confirmed by Phase III studies, the best sequence to use in these regimens following instances of late recurrence after S-1 adjuvant therapy is yet to be established. While the commonly used standard 5-FU + CDDP regimen will be compared to S-1 + CDDP in the FLAGS trial (8), doublet combinations should also be compared to triplet regimens such as docetaxel, CDDP and 5-FU (DCF) (18). Furthermore, recently introduced molecular-targeted therapies, including monoclonal antibodies and tyrosine kinase receptor inhibitors, are excellent candidates for combining with conventional antitumor agents, an approach already shown to be successful in colorectal cancer.

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