Standard First-Line Chemotherapy for Metastatic Gastric Cancer in Japan Has Met the Global Standard: Evidence From Recent Phase III Trials

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ABSTRACT

In Japan, standard first-line chemotherapy for metastatic gastric cancer was initially 5-fluorouracil (5-FU) monotherapy. This is based on the Japan Clinical Oncology Group (JCOG) 9205 phase III trial. Based on recent Japanese phase III trials, S1 plus cisplatin combination chemotherapy was established as the standard first-line chemotherapy, and this combination has met the global standard regimen of 5-FU (capecitabine) plus a platinum analog (cisplatin or oxaliplatin). Since the same standard regimen has been established outside Japan, many global trials are currently ongoing in other countries aside from Japan. With the recent development of many molecular targeted agents, global collaboration in clinical trials is necessary for their immediate evaluation. We review the results of recent phase III trials of first-line chemotherapy for metastatic gastric cancer in Japan and other countries.

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Until the mid-1990s, gastric cancer was the most common cause of cancer death worldwide.[1] Although the incidence of gastric cancer has been declining in the past several decades, it is still quite common worldwide and remains the second most common cause of cancer death, with approximately 934,000 new cases and 700,000 deaths recorded in 2002.[1,2] Interestingly, its incidence in East Asia is higher than that in Western countries, representing about 60% of new gastric cancer cases world wide.[3] In Japan, the most common site of cancer is the stomach (18% of all cancer incidences in 2002).[4] In addition, the proportion of early-stage cancer in Japan is higher than that in any other country, and gastric cancer remains the second leading cause of cancer death (15% of all deaths).[4]

Although Western countries have fewer cases of gastric cancer than Eastern countries, most reports of randomized controlled trials of chemotherapy for gastric cancer come from Western countries, because clinical trial methodology was developed in these countries. Recently, however, some reports of phase III trials of first-line chemotherapy for unresectable or recurrent gastric cancer have come from Asian countries, particularly from Japan. Moreover, other phase III trials are under way in Asia as components of global trials. Herein, we review and summarize the results of phase III trials of first-line chemotherapy for metastatic gastric cancer in Japan and other countries.

PHASE III TRIALS OUTSIDE JAPAN

A summary of the six recent phase III trials of first-line chemotherapy for unresectable or recurrent gastric cancer is presented in Table 1.

Docetaxel in Combination With Cisplatin Plus 5-FU

Several studies have shown that docetaxel/cisplatin/5-FU (DCF) produces significantly longer survival than cisplatin/5-FU (CF)[5] as measured by time to progression (median 5.6 vs. 3.7 months; hazard ratio [HR] 1.47, 95% confidence interval [CI] 1.19–1.82), overall survival (median 9.2 vs. 8.6 months; HR 1.29, 95% CI 1.0–1.6), quality of life,[6] and clinical benefit.[7] These studies have clearly demonstrated the beneficial effect of adding docetaxel; however, DCF has not yet been accepted as a global standard regimen against gastric cancer because of its severe hematologic toxicity. To reduce this toxicity, a modified DCF regimen has recently been suggested.[8]

Infusional 5-FU vs. Oral Fluoropyrimidine

In three trials comparing the efficacy of infusional 5-FU with oral fluoropyrimidine, one demonstrated that capecitabine/cisplatin was not inferior to CF in overall survival (median 10.5 vs. 9.3 months; HR 0.85, 95% CI 0.64–1.13) or the incidence or severity of adverse effects.[9] In a REAL-2 trial, capecitabine was compared with 5-FU and oxaliplatin with cisplatin in a 2 × 2 factorial design.[10] The trial randomly assigned patients to receive epirubicin/cisplatin/5-FU (ECF) (standard arm), epirubicin/oxaliplatin/5-FU (EOF), epirubicin/cisplatin/capecitabine (ECX), or epirubicin/oxaliplatin/capecitabine (EOX). Analysis showed a significant improvement in overall survival

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Table 1. Summary of recent phase III trials conducted in countries other than Japan

Author	Treatment	n	RR (%)	Median PFS (months)	*P* value	MST (months)	*P* value
Van Cutsem et al.[5]	5-FU + cisplatin	224	25	3.7*	<.001	8.6	.02
	5-FU + cisplatin + docetaxel	221	37	5.6*		9.2	
Kang et al.[9]	5-FU + cisplatin	156	29	5.0	.003†	9.3	.27
	Capecitabine + cisplatin	160	41	5.6		10.5	
Cunningham et al.[10]	ECF	263	38	6.2	—	9.9	—
	EOF	245	40	6.5	.77	9.3	.69
	ECX	250	41	6.7	.80	9.9	.2
	EOX	244	47	7.0	.07	11.2	.11
Ajani et al.[11]	5-FU + cisplatin	508	31	5.6	.92	7.9	.198
	S-1 + cisplatin	521	29	5.3		8.6	
Al-Batran et al.[12]	5-FU + cisplatin + LV	112	25	3.9*	.077	8.8	NS
	5-FU + L-OHP + LV	106	34	5.8*		10.7	
Dank et al.[13]	5-FU + cisplatin	163	160	4.2	.088	8.7	.53
	Irinotecan + 5-FU + LV	170	155	5.0		9.0	

* Time to progression.
† Not inferior.
Abbreviations: RR = response rate; PFS = progression-free survival; MST = median survival time; 5-FU = 5-fluorouracil; ECF = epirubicin/cisplatin/5-FU; EOF = epirubicin/oxaliplatin/5-FU; ECX = epirubicin/cisplatin/capecitabine; EOX = epirubicin/oxaliplatin/capecitabine; LV = leucovorin; NS = not significant

in both capecitabine-containing arms (median survival time [MST] 10.9 vs. 9.6 months; HR 0.86; 95% CI 0.8–0.99), with both arms showing similar toxicity. These two previous studies suggest that capecitabine can replace 5-FU in gastric cancer therapy.

The recent FLAGS trial compared the overall survival of patients with advanced gastric cancer receiving S-1 (tegafur/gimestat/potassium oxonate)/cisplatin vs. CF.[11] The MST was 8.6 months with S-1/cisplatin and 7.9 months with CF (HR 0.92, 95% CI 0.80–1.05; *P* = NS). S-1/cisplatin caused significantly less neutropenia, thrombocytopenia, leukopenia, febrile neutropenia, hypokalemia, stomatitis, hypophosphatemia, and hypomagnesemia. The study results suggest that S-1 can replace 5-FU for the treatment of patients with advanced gastric cancer.

Cisplatin vs. Oxaliplatin

Two trials recently compared the efficacy of oxaliplatin-based regimens with cisplatin-based regimens. The first study, the REAL-2 trial for advanced esophagogastric cancer, showed similar survival between two oxaliplatin-containing arms and two cisplatin-based arms (MST 10.4 vs. 10.0 months; HR 0.92, 95% CI 0.80–1.10).[10] In particular, oxaliplatin-treated patients experienced significantly less grade 3/4 neutropenia, alopecia, thromboembolism, and renal dysfunction, but significantly more peripheral neuropathy and diarrhea.

The second study was a phase III trial that compared the efficacy of 5-FU/ leucovorin/oxaliplatin (FLO) with 5-FU/leucovorin/cisplatin (FLP) for the treatment of metastatic gastroesophageal adenocarcinoma. Results of this trial showed no significant differences in progression-free survival (median 5.8 vs. 3.9 months; *P* = .077) or overall survival (median 10.7 vs. 8.8 months).[12] In particular, FLO induced significantly less nausea, vomiting, fatigue, renal toxicity, and alopecia than did FLP, but more grade 3/4 sensory neuropathy. Both trials demonstrate that oxaliplatin can replace cisplatin for the treatment of esophageal/gastric cancer.

Irinotecan vs. Cisplatin

In a recent randomized phase III trial, irinotecan/5-FU/leucovorin (IF) was demonstrated to produce a superior, though non-significant, time to progression (median 5.0 in IF vs. 4.2 months in CF; HR 1.23, 95% CI 0.97–1.57) and overall survival (median 9.0 in IF vs. 8.7 months in CF; HR 1.08, 95% CI 0.86–1.35) compared with CF in chemotherapy-naïve patients with advanced adenocarcinoma of the stomach or esophagogastric junction.[13] CF caused more neutropenia, thrombocytopenia, and stomatitis, but not diarrhea. The results of the trial indicate the feasibility of using irinotecan in combination therapy for gastric or esophagogastric adenocarcinoma.

Summary

The combination of 5-FU (capecitabine) and a platinum analog (cisplatin or oxaliplatin) currently remains the most widely accepted first-line regimen for patients with unresectable or recurrent gastric cancer outside Japan.

PHASE III TRIALS IN JAPAN

A summary of the findings of four Japanese phase III trials of first-line chemotherapy for unresectable or recurrent gastric cancer is shown in Table 2.

JCOG9205 Trial (5-FU vs. UFT/MMC vs. Cisplatin/5-FU)

In the early 1990s, the Gastrointestinal Oncology Study Group of the Japan Clinical Oncology Group (GIOSG/JCOG) conducted the JCOG9205 trial,[14] the first large-scale phase III trial for patients with unresectable, advanced gastric cancer in Japan. The reference arm was 5-FU alone, and the test arms were CF and uracil/tegafur/mitomycin-C (UFTM). An interim analysis revealed that UFTM was associated with significantly poorer survival and higher incidences of hematologic toxicity

vs. 5-FU alone; thus, the UFTM arm was terminated. The trial showed that CF did not produce significantly longer survival than 5-FU alone (MST 7.3 vs. 7.1 months; $P = .34$). Moreover, CF induced significantly higher toxicity than 5-FU alone, leading to 5-FU alone being selected as the standard therapy in Japan, unlike in other countries where CF is the standard treatment for metastatic gastric cancer.

JCOG9912 Trial (5-FU vs. Irinotecan/Cisplatin vs. S-1)

S-1 is an oral fluoropyrimidine treatment that combines tegafur with two modulators of 5-FU metabolism. 5-Chloro-2,4-dihydroxypyridine is a reversible inhibitor of dihydropyrimidine dehydrogenase (DPD) and is added to enhance the anticancer activity of 5-FU by increasing its half-life. S-1 at the currently recommended dose has been shown to produce a higher maximum plasma 5-FU concentration and a greater area under the time vs. concentration curve (AUC) than protracted intravenous infusion of 5-FU, with no elevation in plasma F-β-alanine concentration, the main metabolite of 5-FU.[15] Potassium oxonate is combined to reduce the diarrheal toxicity of tegafur. Two phase II trials reported a response rate of 45% and a 2-year survival rate of 17% among a total of 100 patients, with the incidence rate of grade 3/4 toxicities less than 5%.[16,17]

In another phase II trial, irinotecan/cisplatin (IC) showed a high response rate of 59% and a long MST of 322 days.[18] Although the incidences of grade 4 neutropenia (57%) and grade 3/4 diarrhea (20%) were high, no treatment-induced deaths occurred.

On the basis of these promising results, GIOSG/JCOG initiated the JCOG9912 phase III trial using 5-FU alone as the standard regimen and IC and S-1 alone as the test arms. The trial compared overall survival among treatments and demonstrated the clinical benefit of S-1 and its noninferiority to 5-FU (MST 10.8 vs. 11.4 months; HR 0.83, 95% CI 0.68–1.01) but not its superiority to 5-FU (HR 0.85, 95% CI 0.70–1.04). The incidence of grade 3/4 toxicities was highest in the IC arm and, except for diarrhea, similar between S-1 and 5-FU.[19] After completion of the JCOG9912 trial, S-1 was adopted as the standard treatment for metastatic gastric cancer in Japan.

SPIRITS Trial (S-1 vs. S-1/Cisplatin)

In a phase I/II study of S-1 combined with cisplatin in patients with advanced gastric cancer, S-1/cisplatin has been shown to have a promising effect, with a high response rate of 76%, a median overall survival of 383 days, and tolerable toxicity.[20] Based on these phase I/II data, a phase III SPIRITS trial[21] was conducted to compare overall survival between patients treated with S-1/cisplatin and S-1 alone as first-line treatment for advanced gastric cancer. Results demonstrated the significant superiority of S-1/cisplatin to S-1 (MST 13.0 vs. 11.0 months; HR 0.77, 95% CI 0.61–0.91). Although the incidence of grade 3/4 adverse events was higher in the S-1/cisplatin arm, toxicities were within the acceptable range. The results of this trial are important for two reasons. First, this was the first trial to demonstrate a significant improvement in overall survival with combination S-1/cisplatin therapy vs. S-1 monotherapy, as well as a significant survival advantage with cisplatin. Second, the Japanese standard treatment for advanced gastric cancer was modified to S-1/cisplatin, as in other countries.

GC0301/TOP002 Trial (S-1 vs. S-1/Irinotecan)

In the GC0301/TOP002 trial, which compared the efficacy of S-1/irinotecan vs. S-1 as first-line treatment for advanced gastric cancer, S-1/irinotecan did not prove significantly superior to S-1 (MST 12.8 vs. 10.5 months; HR 0.86, 95% CI 0.66–1.11).[22] Moreover, though the incidence of grade 3/4 toxicities associated with S-1/irinotecan was comparable to that of S-1, the incidence of diarrhea induced by S-1/irinotecan was higher (16% vs. 6%).

Table 2. Summary of phase III trials conducted in Japan

Study	Treatment	n	RR (%)	Median PFS (months)	*P* value	MST (months)	*P* value
JCOG9205[14]	5-FU	106	11	1.9	—	7.1	—
	5-FU + cisplatin	104	34	3.9	<0.001	7.3	.34
	UFT + MMC	70	9	2.4	—	6.0	.11
JCOG9912[19]	5-FU	234	9	2.9	—	10.8	—
	Irinotecan + cisplatin	236	38	4.8	<0.001	12.3	.055
	S-1	234	28	4.2	0.001	11.4	<.001†
SPIRITS[21]	S-1	150	31	4.0	<0.001	11.0	.04
	S-1 + cisplatin	148	54	6.0		13.0	
GC0301/TOP002[22]	S-1	160	160	3.6*	0.16	10.5	.23
	S-1 + irinotecan	155	155	4.5*		12.8	

* Time to progression.
† Not inferior.
Abbreviations: RR = response rate; PFS = progression-free survival; MST = median survival time; UFT = uracil/tegafur; MMC = mitomycin-C

Summary

On the basis of the findings of these four phase III trials, S-1/cisplatin has been adopted as the standard first-line chemotherapy for unresectable or recurrent gastric cancer in Japan.

S-1/CISPLATIN DOSE DIFFERENCES BETWEEN ASIAN AND WESTERN POPULATIONS

We described earlier how S-1/cisplatin combination chemotherapy was adopted as the standard regimen for metastatic gastric

cancer in Japan. S-1 in particular was developed mainly in Japan and, thus, most clinical trial data have been generated in Japan. Based on promising data from Japan, the efficacy of S-1/cisplatin has been evaluated in Korea, China, and Western countries (Table 3).

A FLAGS trial reported at the 2009 Annual Meeting of the American Society of Clinical Oncology (ASCO) demonstrated noninferiority of S-1/cisplatin compared to 5-FU/cisplatin, with lower toxicities in an S-1/cisplatin group,[23] which further supports the potential role of S-1/cisplatin as first-line chemotherapy for advanced gastric cancer. These findings underscore the potential of the S-1/cisplatin combination regimen to emerge as standard chemotherapy for gastric cancer in other countries, provided one is mindful of the fact that the tolerability of S-1 varies across different ethnic populations. In line with the promising efficacy of this regimen, we further describe below the administration schedules and doses of S-1/cisplatin in Eastern and Western populations.

Table 3. Dose and administration schedule of S-1 plus cisplatin

Author	Country	N	S-1	Cisplatin
Koizumi et al.[21]	Japan	148	80 mg/m^2 on days 1–21 (q 5W)	60 mg/m^2 day 8
Jin et al.[24]	China	74	80 mg/m^2 on days 1–21 (q 5W)	60 mg/m^2 day 8
Lee et al.[25]	Korea	43	80 mg/m^2 on days 1–14 (q 3W)	60 mg/m^2 day 1
Ajani et al.[11]	Mainly Western countries	521	50 mg/m^2 on days 1–21 (q 4W)	60 mg/m^2 day 1

Asian Countries

In a SPIRITS trial conducted in Japan, S-1 was administered for 3 weeks (80 mg/m^2/day) followed by a 2-week rest, with cisplatin (60 mg/m^2) administered on day 8. This regimen produced significantly longer overall survival than S-1 alone.[21]

In China, a randomized phase II trial following the same administration schedule and dose as those in the Japanese SPIRITS trial compared the efficacy of S-1 alone, S-1/cisplatin, and CF.[24] The response rates and MSTs (months) were 25% and 8.8 ($P <$ .001) with S-1, 38% and 14.2 with S-1/cisplatin, and 19% and 10.2 ($P = .038$) with CF.

The incidence of toxicities in the S-1/cisplatin arm was similar to that in the CF arm, but grade 3/4 toxicities were more common in the S-1/cisplatin arm (6.6% vs. 0%). On the basis of these results, S-1/cisplatin is currently considered one of the standard regimens against gastric cancer in China.

In a phase I/II trial[25] in metastatic or recurrent gastric cancer in Korea, S-1 was administered for 2 weeks (80 mg/m^2/day) followed by a 1-week rest, with cisplatin (60 mg/m^2) administered on day 1. The rationale of this regimen was to increase the dose intensity of cisplatin (Korean trial, 20 mg/m^2/week; Japanese and Chinese trials, 13.3 mg/m^2/week). A response rate of 48%, a median progression-free survival of 5.3 months (95% CI 4.6–6.0), and a median overall survival of 10.0 months (95% CI 5.1–14.8) were observed. Although the incidence of grade 3/4 toxicities was similar to that in the SPIRITS trial, 59% of the patients required dose reduction and treatment delay was longer, indicating the need for further refinement of drug administration schedule and doses.

Western Countries

In a phase I study of the efficacy of S-1 plus cisplatin in patients with advanced gastric carcinoma, S-1 was administered at 50 mg/m^2/day on days 1 to 21, and cisplatin intravenously at 75 mg/m^2 on day 1 on a 28-day cycle.[26] This S-1 dose is lower than the 80 mg/m^2/day dose used in Asian countries; the required lower dose is thought to be linked to polymorphic differences in the *CYP2A6* gene, as suggested by Ajani et al.[26] On the other hand, Comets et al speculated that the difference is due to the lower body surface area (on which dosing is based) of Japanese patients vs. American patients,[27] but no specific reason was provided.

DISCUSSION

Based on current phase III trials, the combination of 5-FU (including oral fluoropyrimidines S-1 or capecitabine) with a platinum analog (cisplatin or oxaliplatin) is the most widely accepted first-line chemotherapy regimen for metastatic gastric cancer in Japan and other countries.

Among oral fluoropyrimidines, capecitabine is the most widely used agent, except in Japan. Evidence also shows that S-1 is used outside Japan, making it a potential standard oral fluoropyrimidine similar to capecitabine. Moreover, S-1 has been shown more effective in patients with a diffuse type of histology than in those with an intestinal type, as revealed in a subset analysis of the FLAGS trial reported at the 2009 ASCO Annual Meeting.[23] Further investigation of S-1 targeted for the diffuse type is warranted.

When it comes to platinum analogs, cisplatin induces more toxicity than oxaliplatin, except for neurotoxicity. Moreover, cisplatin requires adequate hydration in patients with renal damage. Therefore, oxaliplatin will be more widely used than cisplatin. A Japanese phase II study of S-1/oxaliplatin,[28] also reported at ASCO 2009, showed an overall response rate of 58.8% and a median progression-free survival of 6.5 months with mild toxicity. Based on these results, a phase III trial comparing S1/cisplatin with S1/oxaliplatin is currently being planned.

Although some phase III trials have attempted to show the therapeutic benefits of irinotecan-containing regimens, no clear evidence has yet been shown. From the results of previous data, use in first-line chemotherapy is not recommended. However, translational research using endoscopic biopsy specimens in the JCOG9912 trial has indicated that cisplatin/irinotecan is more effective than S-1 for patients with low DPD or thymidylate synthase (TS) mRNA expression levels in tumor tissue.[29] A phase III trial using DPD or TS as predictive biomarkers for irinotecan/cisplatin efficacy

is warranted.

The therapeutic benefit of combining docetaxel with FP has been shown in one phase III trial. However, the DCF regimen is not accepted as first-line chemotherapy, due to its high toxicity. Even though a START trial comparing docetaxel/S-1 with S-1 alone is currently ongoing in Japan and Korea,[30] we currently recommend docetaxel only after failure of first-line chemotherapy.

Many types of molecular targeted agents have recently been developed for various cancers. Trastuzumab, an anti-human epidermal growth factor receptor 2 (HER2) monoclonal antibody, is the first molecular targeted agent showing therapeutic benefit in a phase III trial (ToGA trial) for metastatic gastric cancer,[31] in which infusional 5-FU or capecitabine plus cisplatin was compared with and without trastuzumab. The response rate was significantly higher with trastuzumab (47% vs. 35%). At a median follow-up of 17.1 months, median overall survival was significantly better with trastuzumab (MST 13.8 vs. 11.1 months; HR 0.74, 95% CI 0.60–0.91, $P = .0046$). Based on the ToGA trial, standard therapy for HER-2 positive metastatic gastric cancer patients will be changed, in which trastuzumab is added with 5-FU (including oral fluoropyrimidines S-1 or capecitabine) plus a platinum analog (cisplatin or oxaliplatin).

Bevacizumab, cetuximab, panitumumab, and lapatinib are also currently being evaluated in global phase III trials. Other molecular targeting agents, such as RAD001, sorafenib, and cediranib, are currently being investigated in early phase clinical trials. It is anticipated that many new, active molecular targeted agents will become available in the near future, as these trials are completed.

Since gastric cancers are of heterogeneous origins possessing many unique characteristics, identifying one standard regimen for all forms is not considered realistic. However, only a few active agents specifically active against gastric cancer have recently been confirmed. In-depth understanding of the biology of gastric cancer through high-level research and identification of efficacious new agents through clinical trials will eventually make it possible to develop tailored treatments for gastric cancer.

In conclusion, based on current phase III trials, it has become clear that the standard chemotherapy for metastatic gastric cancer in Japan is essentially the same as that in other countries. With the recent discovery of many novel molecular targeted agents, further global collaboration in the conduct of clinical trials with a focus on biologic research is necessary to facilitate the timely evaluation of these agents in gastric cancer.

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Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.