Table 1. Phase III studies in the early 1990s

Author	Regimen	*n*	RR (%)	MST (M)
Cullinan[5]	5-FU	51	18	7
	5-FU + ADM	49	27	7
	FAM	51	38	7
Wils[6]	FAM	103	9	7.2
	FAMTX	105	41	10.5
Kelsen[7]	FAMTX	30	33	7
	EAP	30	20	6
Kim[8]	5-FU	94	26	7.5
	FAM	98	25	7
	5-FU + CDDP	103	51	9.2
Cullinan[9]	5-FU	69	–	6.1
	FAMe	53	–	6.1
	FAMe + TZT	79	–	7.7
	FAP	51	–	–
Cocconi[10]	FAM	52	15	5.6
	PELF	85	43	8.1
Webb[11]	ECF	126	46	8.7
	FAMTX	130	21	6.1
Vanhoefer[12]	FAMTX	85	12	6.7
	ELF	79	9	7.2
	5-FU + CDDP	81	20	7.2

RR, response rate; MST, median survival time; FAM, 5-FU; adriamycin (ADM); mitomycin C (MMC); FAMTX, 5-FU, ADM, methotrexate (MTX); EAP, etoposide, ADM, cisplatin (CDD); FAMe, 5-FU, ADM, methyl lomustine (CCNU); FAMe + TZT, 5-FU, ADM, CCNU, triazinate; FAP, 5-FU, ADM, CDDP; PELF, CDDP, epirubicin, leucovorin, 5-FU; ECF, epirubicin, CDDP, 5-FU

based combination chemotherapy, one of which consisted of etoposide plus doxorubicin plus CDDP (EAP)[14] and another of 5-FU plus CDDP (FP).[15] Despite a high response rate and favorable survival, approximately 10% of treatment-related deaths occurred in the EAP study. Consequently, the EAP regimen could not be adopted for future study. Although the dose and treatment schedule of FP in Japan was slightly modified from that of Western trials,[12] its Japanese phase II study recapitulated the response rate and survival.

After these studies, GIOSG/JCOG planned a randomized phase III trial (JCOG9205).[16] At that time, a Western phase III trial comparing 5-FU alone with a three-drug combination regimen consisting of 5-FU, doxorubicin, and MMC (FAM) revealed no survival advantage over 5-FU alone.[5] In JCOG9205, therefore, 5-FU alone was adopted for a control arm, and UFTM, which was popular in Japan on the basis of results from the randomized phase II studies (JCOG8501),[13] and FP, which was commonly used all over the world, were adopted for the investigational arms. As a result, compared to 5-FU alone, FP did not show significantly longer survival despite its higher response rate and longer progression-free survival, associated with more severe toxicities. Furthermore, UFTM resulted in the worst survival and more severe toxicities than 5-FU alone. JCOG9205 concluded that 5-FU alone remained as a control arm for the subsequent phase III study. A Korean trials comparing combination chemotherapy containing 5-FU and CDDP to 5-FU alone also failed to show a survival benefit of combination chemotherapy.[8]

Late 1990s

In the late 1990s, the evaluation criteria for response (Revised Evaluation Criteria in Solid Tumor: RECIST) and toxicities (National Cancer Institute common toxicity criteria: NCI-CTC) were proposed and introduced to Japan. Since then, two new antitumor agents for gastric cancer have been developed in Japan. The phase II study of monotherapy with CPT-11 for gastric cancer resulted in a response rates of 23%, and combination chemotherapy of CPT-11 plus CDDP showed a response rate of 59% and the median survival time of 322 days, associated with grade 4 neutropenia (57%), and grade 3 or 4 diarrhea (20%).[17] S-1 is a new oral fluoropyrimidine, consisting of FT, 5-chloro-2, 4-dihydropyrimidine, and potassium oxonate, which showed a response rate of 45% and a high 2-year survival rate of 17% in a total of 100 patients in its two phase II studies, associated with low incidences (5% or less) of grade 3 or 4 toxicities.[18,19] Subsequently, monotherapy either with paclitaxel[20] or with docetaxel[21] showed a response rate around 20% in their phase II studies. These new drugs were approved in Japan by the results of these phase II studies. Thereafter, combination chemotherapy of S-1 plus CDDP showed a remarkably high response rate, greater than 50%.[22] Furthermore, the combination of S-1 plus CPT-11,[23] paclitaxel,[24] or docetaxel[25] also showed high response rates.

Recent foreign randomized trials

Although no survival benefit of FP over 5-FU alone was confirmed by several phase III trials,[16] FP has been most widely used for unresectable and recurrent gastric cancer all over the world. Table 2 summarizes the results of recent foreign randomized trials, in all of which a control arm contained 5-FU and CDDP.[26–30] Among them, triplet therapy with docetaxel added to FP showed a survival benefit over FP.[26] However, this regimen has not been accepted as a standard chemotherapy worldwide because of its severe hematological toxicities. Capecitabine plus CDDP showed noninferiority to FP,[27] and oxaliplatin showed comparable activities to CDDP.[28] From these studies, continuous infusion of 5-FU and CDDP requiring hydration can be replaced by oral fluoropyrimidine (capecitabine) and oxaliplatin. Thus, chemotherapy with oral fluoropyrimidine plus platinum has become more convenient and is recognized as a standard chemotherapy outside Japan.

JCOG9912

From the promising results of phase II studies of CPT-11 plus CDDP,[17] and monotherapy with S-1,[18,19] GIOSG/JCOG planned a three-arm phase III study to investigate the superiority of CPT-11 plus CDDP and noninferiority of S-1 compared to continuous infusion of 5-FU.[31] The treatment schedules were continuous infusion of 5-FU (800 mg/

Table 2. Recent foreign randomized trials containing 5-FU and CDDP

Author	Regimen	*n*	RR (%)	PFS (M)	MST (M)
Van Cutsem[26]	Doce + CDDP + 5-FU	221	37	5.6	9.2
	CDDP + 5-FU	224	25	3.7	8.6
Kang[27]	Cape + CDDP	139	41	5.6	10.5
	CDDP + 5-FU	137	29	5.0	9.3
Cunningham[28]	ECF	263	41	6.2	9.9
	EOF	245	42	6.5	9.3
	ECX	250	46	6.7	9.9
	EOX	244	48	7.0	11.2
Dank[29]	5-FU/LV + CPT-11	172	32	5.0	9.0
	CDDP + 5-FU	165	26	4.2	8.7
Al-Batran[30]	5-FU/LV + OHP	112	34	5.7	
	5-FU/LV + CDDP	108	25	3.8	

RR, response rate; MST, median survival time; PFS, progression free survival; Doce, Docetaxel; Cape, capecitabine; ECF, epirubicine + cisplatin + 5-FU; EOF, epirubicine + oxaliplatin + 5-FU; ECX, epirubicine + cisplatin + capecitabine; EOX, epirubicine + oxaliplatin + capecitabine; LV, leucovorin; CPT-11, irinotecan; OHP, oxalipatin

Table 3. Results of JCOG9912[31]

Regimen	*n*	RR (%)	PFS (M)	*P*	TTF (M)	*P*	MST (M)	*P*
5-FU	234	9	2.9	–	2.3	–	10.8	
CPT-11 + CDDP	236	38	2.8	<0.001	3.7	0.014	12.3	0.055
S-1	234	28	4.2	0.001	4.0	<0.001	11.4	<0.001*

TTF, time to treatment failure; *P* value, superior to 5-FU; *noninferior

m^2/day) for 5 days repeated every 4 weeks for 5-FU, administration of both CPT-11 (70 mg/m^2) and (CDDP 80 mg/m^2) on day 1, and additional CPT-11 on day 15 repeated every 4 weeks for CPT-11 plus CDDP, and oral administration of S-1 (40 mg/m^2, b.i.d.) for 4 weeks and followed by 2 weeks rest repeated every 6 weeks in S-1. The primary endpoint was overall survival, and secondary endpoints were time to treatment failure, nonhospitalized survival, adverse events, and response rate. Although the eligibility criteria of JCOG9912 were almost similar to other recent phase III studies, the specific points of JCOG9912 were that a measurable lesion according to RECIST was not mandatory and that patients with severe peritoneal metastasis were excluded.

Actually, 704 patients were accrued for 5 years. Final analysis was carried out on February 2007, 1 year after the last patient enrollment. Approximately a quarter of the patients did not have target lesions, and more than 30% of the patients had peritoneal metastasis. As anticipated from the phase II studies, leucopenia and neutropenia were most severe, and grade 3 or 4 hyponatremia, fatigue, anorexia, diarrhea, and nausea were more frequently observed in CPT-11 plus CDDP.

Table 3 summarizes the antitumor effects found in JCOG9912. The response rate of CPT-11 plus CDDP was 38%, and those of S-1 and 5-FUci were 28% and 9%, respectively. These toxicities and response rates were anticipated from the results of their phase II studies. The median progression-free survival time of 5-FU was 2.9 months, that of CPT-11 plus CDDP, 4.8 months, and for S-1, 4.2 months. The median time to treatment failure of 5-FU was 2.3 months, CPT-11 plus CDDP was 3.7 months, and S-1 was 4.0 months. As for the reasons for treatment failure, in 5-FU and S-1 more than 85% of the patients stopped treatment as a consequence of disease progression. In CPT-11 plus CDDP, more than 30% of the patients stopped treatment for reasons related to toxicities, and this seems to have caused the short time to treatment failure of this regimen. Both CPT-11 plus CDDP and S-1 showed a longer nonhospitalized survival compared to 5-FU. Because infusion chemotherapy is commonly performed with hospitalization in Japan, it is considered that nonhospitalized survival reflects a patient's benefit from the quality of life point of view.

As for the overall survival, up to 1 year, CPT-11 plus CDDP showed the best survival, whereas S-1 showed the best survival after 1 year. The median survival times (MST) of 5-FU, CPT-11 plus CDDP, and S-1 were 10.8, 12.3, and 11.4 months, respectively. According to the prespecified significance level, only noninferiority of S-1 was shown to be statistically significant. The efficacy of monotherapy with S-1 seemed to be comparable to that of FP reported in other trials. In conclusion, S-1 should be considered for the standard chemotherapy of unresectable or recurrent gastric cancer.

Other Japanese phase III trials

There were two other randomized phase III trials, both of which contained monotherapy with S-1 as a control arm. One verified the superiority of S-1 plus CDDP compared with S-1 alone in overall survival (SPIRITS trial).[32] The subjects were 305 patients without prior chemotherapy.

Table 4. Recent phase III trials in Japan

Trial	Regimens	*n*	RR (%)	PFS (M)	MST (M)
JCOG9912[31]	5-FU	234	9	2.9	10.8
	CPT-11 + CDDP	236	38	4.8	12.3
	S-1	234	28	4.2	11.4
SPIRITS[32]	S-1	150	31	4.0	11.0
	S-1 + CDDP	148	54	6.0	13.0
GC0301/TOP002[33]	S-1	160	27	–	10.5
	S-1 + CPT-11	155	42	–	12.8

Treatment schedule of monotherapy with S-1 was same as in JCOG9912. In the S-1 and CDDP protocols, S-1 was given orally, twice daily for 3 consecutive weeks, and CDDP (60 mg/m^2) was given on day 8 followed by a 2-week rest. Overall survival was significantly longer in the S-1 plus CDDP (MST, 13.0 months) than S-1 (MST, 11.0 months) ($P = 0.04$). Progression-free survival was significantly longer in S-1 plus CDDP (median, 6.0 months vs. 4.0 months; $P < 0.0001$) and the response rate was also significantly higher (54.0% vs. 31.1%; $P = 0.002$).

Another phase III study evaluated the efficacy and safety of S-1 plus CPT-11 comparing with S-1 (GC0301/TOP002).[33] The subjects 326 were chemo-naive patients. The treatment schedule of S-1 plus CPT-11 was S-1 from day 1 to 21 and CPT-11 (80 mg/m^2) on days 1 and 15, repeated every 5 weeks. The response rate of S-1 plus CPT-11 was 41.5% higher than that of S-1, 26.9% ($P = 0.035$). Although the median survival time of S-1 was 10.6 months and that of S-1 plus CPT-11 was 13.0 months, S-1 plus CPT-11 did not show significant superiority ($P = 0.23$).

Current standard chemotherapy and future perspectives

From the results of Japanese phase III trials (Table 4), S-1 plus CDDP can be recognized as a standard chemotherapy for unresectable or recurrent gastric cancer. There seems to be no significant difference between capecitabine and S-1, and between CDDP and oxaliplatin. Thus, Japan and Western countries share the consensus of standard chemotherapy with oral fluoropyrimidine plus platinum. Because feasibility of S-1 differs between Caucasian and Asians, the ongoing global phase III trial (FLAGS trial) comparing S-1 plus CDDP with FP is expected to show that S-1 plus CDDP can be a globally recognized standard regimen. However, strictly speaking, whatever the combination of oral fluoropyrimidine and platinum may be, it does not seem to have brought remarkable progress compared to FP.

At present, some molecular target agents have been investigated for gastric cancer. These agents in the new generation are expected to make revolutionary progress in chemotherapy for unresectable or recurrent gastric cancer. Another progression based on individualization against gastric cancer with heterogeneous biological behavior is also warranted.

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REVIEW ARTICLE

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Chemotherapy for metastatic gastric cancer in Japan

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Abstract Until the 1990s, there were no chemotherapy regimens with old-generation anticancer agents showing a survival benefit over 5-fluorouracil (FU) alone, and standard chemotherapy for metastatic gastric cancer had not been established. In the late 1990s, several new active agents were developed and some phase III trials with these agents were conducted; the new agent S-1 showed noninferiority to 5-FU in these trials. S-1 plus cisplatin is the first doublet chemotherapy to have shown a survival benefit over monotherapy with S-1. It has been demonstrated that capecitabine and oxaliplatin (OHP) can replace 5-FU and cisplatin (CDDP), offering more convenient treatment options. Thus, combination chemotherapy with an oral fluoropyrimidine (S-1 or capecitabine) and platinum (CDDP or OHP) has been recognized as standard chemotherapy for metastatic gastric cancer all over the world. However, it can be said that none of these new combination chemotherapies have shown remarkable progress from 5-FU plus cisplatin regimens. It is expected that triplet chemotherapy with a taxane; the use of molecular targeting agents; and the establishment of treatment strategies including second line chemotherapy, will lead to remarkable progress in personalized medicine in the near future.

Key words gastric cancer · chemotherapy · clinical trial

Introduction

Gastric cancer is the second leading cause of cancer-related death worldwide, accounting for more than 20 deaths per 100000 population annually in East Asia, Eastern Europe, and parts of Central and South America.[1] Gastric cancer is the second most frequent cause of cancer death after lung cancer in Japan (despite the markedly higher curability obtained by early detection and surgical resection than in Western countries), because the prognosis of metastatic (unresectable or recurrent) gastric cancer is miserable. An effective standard chemotherapy should be established.

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In the twentieth century

In the twentieth century several active agents such as 5-fluorouracil (5-FU), cisplatin (CDDP), methotrexate (MTX), doxorubicin (ADM), etoposide, leucovorin (LV), and mitomycin C (MMC) had been developed, and not a few combination chemotherapy regimens showing high response rates were also developed. Randomized trials showed that 5-FU-based chemotherapy resulted in a substantial survival benefit compared to best supportive care[2–4] (Table 1).

Not a few randomized trials comparing chemotherapy regimens were conducted in the 1990s[5–12] (Table 2). While triplet therapy with epirubicin, CDDP, and 5-FU (ECF) showed a survival benefit over another triplet therapy with 5-FU, ADM, and MTX (FAMTX) in Europe,[10] three phase III trials, in the United States, Korea, and Japan, comparing CDDP-based combination chemotherapy regimens did not show a survival benefit over 5-FU alone in spite of the higher response rate and longer progression-free survival in the CDDP-based arms.[8,9,12] In the phase III trial (Japan Clinical Oncology Group [JCOG] 9205) that investigated the survival benefit of 5-FU plus CDDP (FP) and tegafur-uracil plus MMC (UFTM) compared to 5-FU, there were no differences in overall survival, and 5-FU was associated with the least toxicities among the three arms.[12] Thus, there was no consensus about a standard chemotherapy regimen for metastatic gastric cancer, while FP was actually the most common chemotherapy regimen used for metastatic gastric cancer all over the world. The control arms of the next randomized trial were monotherapy with a fluoropyrimidine in Japan, ECF in Europe, and FP in the United States and other areas.

At the millennium

Clinical trials with new agents in Japan

In the late 1990s, new agents such as irinotecan (CPT-11), S-1, taxanes (paclitaxel [PTX] and docetaxel [DOC]) were introduced in clinical practice. Among them, CPT-11, S-1 (a new oral fluoropyrimidine, consisting of FT, 5-chloro-2, 4-dihydropyrimidine, and potassium oxonate), and capecitabine were developed in Japan. Monotherapy with many of these new drugs showed response rates of around 20%, whereas two phase II studies of monotherapy with S-1 resulted in a response rate of 45% with a median survival time (MST) of 8 months.[13,14]

In a phase II trial of CPT-11 plus CDDP, the response rate was 59% and the MST was 11 months.[15] A phase I/II trial of combination chemotherapy of S-1 plus CDDP showed outstanding results, with a response rate of 74% and MST of 12 months.[16] Other S-1 based combination chemotherapies also showed response rates of around 50%.[16-18]

With these promising results of combination chemotherapy, four phase III trials containing S-1 were conducted in Japan, and the results of three trials were reported[19-21] (Table 3). In JCOG9912, comparing CPT-11 plus CDDP and S-1 alone to 5-FU alone, although CPT-11 plus CDDP showed the best response rate and progression-free survival (PFS) among the three arms, treatment failure due to toxicities was observed most frequently in this arm. S-1 showed highly significant noninferiority to 5-FU in overall survival,[19] associated with a higher response rate, longer PFS, longer time to treatment failure, and longer nonhospitalized survival. In the SPIRITS trial, comparing S-1 plus CDDP to S-1 alone, S-1 plus CDDP showed a significantly longer survival than S-1 alone, with acceptable toxicities.[20] In the GC0301/TOP002 trial, comparing S-1 plus CPT-11 with S-1 alone, S-1 plus CPT-11 did not show a significantly longer survival than S-1 alone.[21] From these trials, S-1 plus CDDP has been recognized as the standard chemotherapy for metastatic gastric cancer in Japan. Patient enrollment in the international Japan-Korea trial (START trial), comparing S-1 plus DOC to S-1 alone, has been finished.

Clinical trials with new agents in Western countries

DOC, capecitabine, and oxaliplatin (OHP) have been investigated[22-25] in Western countries (Table 4). In a phase III trial comparing triplet chemotherapy with 5-FU, CDDP, and DOC (DCF) to FP, DCF showed a higher response rate, longer PFS, and significantly longer survival than FP.[22] In a phase III trial comparing capecitabine plus CDDP (XP) to FP, the XP regimen showed noninferiority to FP in

Table 1. Randomized trials comparing various regimens to best supportive care (BSC)

Author	Regimen	*n*	RR (%)	MST (months)	*P* value
Murad[2]	FAMTX	30	50%	10	0.001
	BSC	10	–	3	
Glimelius[3]	ELF	10	30%	10	<0.02
	BSC	8	–	4	
Pyrhonen[4]	FEMTX	21	29%	12.3	0.0006
	BSC	20	–	3.1	

RR, response rate; MST, median survival time; FAMTX, 5-FU, ADM, methotrexate (MTX); ELF, etoposide, 5-FU, leucovorin; FEMTX, 5-FU, epirubicin, MTX

Table 2. Randomized trials in the twentieth century

Author	Regimen	*n*	RR (%)	MST (months)	*P* value
Cullinan[5]	5-FU	51	18	7	NS
	5-FU + A	49	27	7	
	FAM	51	38	7	
Wils[6]	FAM	103	9	7.2	0.004
	FAMTX	105	41	10.5	
Kelsen[7]	FAMTX	30	33	7	NS
	EAP	30	20	6	
Kim[8]	5-FU	94	26	7.5	NS
	FAM	98	25	7	
	5-FU + CDDP	103	51	9.2	
Cullinan[9]	5-FU	69	–	6.1	NS
	FAMe	53	–	6.1	
	FAMe + TZT	79	–	7.7	
	FAP	51	–	–	
Webb[10]	ECF	126	46	8.7	0.0005
	FAMTX	130	21	6.1	
Vanhoefer[11]	FAMTX	85	12	6.7	NS
	PELF	79	9	7.2	
	5-FU + CDDP	81	20	7.2	
Ohtsu[12]	5-FU	105	11	7.1	NS
	UF + MMC	70	9	6	
	5-FU + CDDP	105	34	7.3	

FAM, 5-FU, adriamycin (ADM), mitomycin C (MMC); FAMTX, 5-FU, ADM, methotrexate (MTX); EAP, etoposide, ADM, cisplatin (CDDP), FAMe, 5-FU, ADM, methyl lomustine (CCNU); FAMe + TZT, 5-FU, ADM, CCNU, triazinate; FAP, 5-FU, ADM, CDDP; PELF, CDDP, epirubicin, leucovorin, 5-FU; ECF, epirubicin, CDDP, 5-FU; NS, not significant

Table 3. Recent phase III trials in Japan

Trial	Regimen	*n*	RR (%)	PFS (months)	TTF (months)	MST (months)
JCOG9912[19]	5-FU	234	9	2.9	2.3	10.8
	CPT-11 + CDDP	236	38	4.8	3.7	12.3
	S-1	234	28	4.2	4.0	11.4
SPIRITS[20]	S-1	150	31	4.0	3.9	11.0
	S-1 + CDDP	148	54	6.0	4.8	13.0
GC0301/TOP002[21]	S-1	160	27	–	3.6	10.5
	S-1 + CPT-11	155	42	–	4.5	12.8

PFS, progression-free survival; TTF, time to treatment failure

Table 4. Recent global phase III trials

Author	Regimen	*n*	RR (%)	PFS (months)	MST (months)
Kang[23]	Cape + CDDP	139	41	5.6	10.5
	5-FU + CDDP	137	29	5.0	9.3
Van Cutsem[22]	5-FU + CDDP	224	25	3.7	8.6
	DOC + 5-FU + CDDP	221	37	5.6	9.2
Cunningham[24]	ECF	263	41	6.2	9.9
	EOF	245	42	6.5	9.3
	ECX	250	46	6.7	9.9
	EOX	244	48	7.0	11.2
Al-Batran[25]	5-FU/LV + CDDP	108	25	3.8	8.8
	5-FU/LV + OHP	112	34	5.7	10.7

Cape, capecitabine; DOC,, docetaxel; ECF, epirubicin + cisplatin (CDDP) + 5-FU; EOF, epirubicin + oxaliplatin (OHP) + 5-FU; ECX, epirubicin + CDDP + capecitabine; EOX, epirubicin + OHP + capecitabine; LV, leucovorin;

overall survival.[23] In the REAL-2 trial (capecitabine vs 5-FU, OHP vs CDDP [2 × 2 design] combined with epirubicin), it was concluded that 5-FU and CDDP could be replaced by capecitabine and OHP, respectively.[24]

Future directions

Triplet chemotherapy

A triplet DCF regimen based on a triweekly schedule of DOC first showed a survival benefit compared to FP. However, because the incidence of febrile neutropenia was around 30%,[22] the DCF regimen has not been accepted as standard chemotherapy all over the world. Recently, biweekly or weekly schedules of DOC have been investigated, and these schedules have succeeded in reducing hematological toxicities. Modified triplet taxane-containing chemotherapy based on an oral fluoropyrimidine and platinum should be investigated in phase III trials.

Molecular targeting agents

For colorectal cancer, molecular targeting agents such as bevacizumab, cetuximab, and panituzumab have been introduced to clinical practice. Similarly, for metastatic gastric cancer, two phase II trials, one with bevacizumab,[26] the other with cetuximab,[27] based on combination chemotherapy with cytotoxic agents showed very promising PFS, of around 8 months. Patient accrual to two global phase III trials, the ToGA trial (capecitabine or 5-FU + CDDP ± herceptin for Her-2-positive gastric cancer) and the AVAGAST trial (capecitabine or 5-FU + CDDP ± bevacizumab) will be finished soon. The results of these trials are expected to come in about 2 years. Moreover, many other molecular targeting agents, such as RAD001,[28] sunitinib,[29] lapatinib, and nimotuzumab are under investigation.

Personalization

Gastric cancer shows heterogeneous behavior such as peritoneal metastasis and hematological metastasis. In a subset analysis of the JCOG9912 and SPIRITS trials, CPT-11 plus CDDP and S-1 plus CDDP showed some difference in chemotherapy effects according to the presence or absence of target lesions defined by the Response Evaluation Criteria In Solid Tumors (RECIST).[19,20] The peritoneum is a common metastatic site, and the prognosis of patients with severe peritoneal metastasis is considered to be poor because such metastasis causes various kinds of complications such as ascites, bowel obstruction, and hydronephrosis. These patients usually do not have target lesions according to RECIST. For these reasons, patients with severe peritoneal metastasis are generally excluded from clinical trials. The Gastrointestinal Oncology Study Group of the JCOG has decided to employ different treatment strategies according to the presence or absence of severe peritoneal metastasis, and has initiated two randomized trials focusing on peritoneal metastasis. It is expected that an optimal chemotherapy regimen will be selected by the tumor behavior. On the other hand, if the ToGA trial succeeds in showing a survival benefit of herceptin for Her-2-positive patients,[30] the first-line chemotherapy should be selected by the Her-2 status, as is done for breast cancer. Thus, the idea of personalized treatment will become a reality in the future.

After failure of first-line chemotherapy

For colorectal cancer, the three drugs – 5-FU, CPT-11, and OHP – should all be used during the whole treatment course.[31] In Japanese phase III trials, survival after the failure of first-line chemotherapy was longer than that in Western trials.[19-21] It is considered that the high proportions of patients in these trials who received subsequent chemotherapy after the first-line chemotherapy may have contributed to the long survival. While combination chemotherapy with a fluoropyrimidine plus platinum is recognized as the standard of care now, CPT-11 and taxanes are the candidates in the second-line setting. However, it has been reported that either CPT-11 or taxanes in the second-line setting resulted in response rates of around 20%[32,33] and approximately half of the patients showed progressive disease. Among the molecular targeting agents, clinical trials of PTX plus lapatinib and CPT-11 plus nimotuzumab have targeted the second-line setting.

It is expected that effective second-line chemotherapy will be developed.

Conclusion

There have been many phase III clinical trials in Japan and all over the world since the late 1990s. Finally, the era of monotherapy with a fluoropyrimidine has finished. Combination chemotherapy with an oral fluoropyrimidine (S-1 or capecitabine) and platinum (CDDP or OHP) has been recognized as standard chemotherapy for metastatic gastric cancer all over the world. However, unfortunately, in chemotherapy for metastatic gastric cancer, none of the new combination chemotherapies have shown remarkable progress from FP, while chemotherapy for colorectal cancer has shown remarkable progress during the past decade. Molecular targeting agents and new treatment strategies for metastatic gastric cancer should be investigated consistently.

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Review article

JCOG trials of systemic chemotherapy for unresectable or recurrent gastric cancer

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Abstract

From the late 1980s to the early 1990s, the Gastrointestinal Oncology Study Group of the Japan Clinical Oncology Group (GIOSG/JCOG) conducted several phase II studies, some of which evaluated oral fluoropyrimidines and others of which introduced Western regimens to Japanese patients. Thereafter, in the phase III study JOCG9205 comparing 5-fluorouracil (5-FU), 5-FU plus cisplatin (CDDP) (FP), and uracil and tegafur (UFT) plus mitomycin (UFTM), neither FP nor UFTM showed a survival benefit over 5-FU alone. Whereas irinotecan (CPT-11) and S-1 (new oral fluoropyrimidine) were developed with promising action against gastric cancer in the late 1990s, these agents cannot be used for patients with impaired oral intake and bowel passage caused by severe peritoneal metastasis. Sequential methotrexate (MTX) and 5-FU (MF) therapy showed substantial action against peritoneal metastasis. Thus, GIOSG/JCOG followed different treatment strategies according to the presence or absence of severe peritoneal metastasis. The phase III study JCOG9912, comparing 5-FU, CPT-11 plus CDDP, and S-1, showed a highly significant noninferiority of S-1 to 5-FU in overall survival associated with acceptable toxicities and concluded that S-1 should be considered for the standard chemotherapy for gastric cancer without severe peritoneal metastasis. For patients with severe peritoneal metastasis, the phase III study JCOG0106 compares MF to 5-FU. In that study, patient enrollment has been completed and a final analysis is planned at the end of 2008. The randomized phase II study JCOG0407 compares the best available 5-FU with weekly paclitaxel after failure in first-line chemotherapy containing 5-FU.

Key words Gastric cancer · JCOG · Fluoropyrimidine · Cisplatin · Irinotecan

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Introduction

Gastric cancer is the second leading cause of cancer-related death worldwide, accounting for more than 20 deaths per 100000 population annually in East Asia, Eastern Europe, and parts of Central and South America [1]. Gastric cancer is also the second most frequent cause of cancer death after lung cancer in Japan (despite the markedly higher curability obtained by early detection and surgery than in Western countries), because unresectable or recurrent gastric cancer shows a poor prognosis. The development of effective standard chemotherapy is warranted.

For unresectable or recurrent gastric cancer, several phase III trials have demonstrated that a 5-fluorouracil (5-FU)-based regimen provides a survival benefit to these patients over best supportive care [2–4]. Although quite a few randomized trials [5–12], using anthracyclin, mitomycin C (MMC), 5-FU, methotrexate (MTX), and cisplatin (CDDP), were carried out before the early 1990s, none of the chemotherapy regimens showed a survival benefit over 5-FU alone, and no worldwide consensus about a standard regimen has been obtained. For two decades, the Gastrointestinal Oncology Study Group of the Japan Clinical Oncology Group (GIOSG/JCOG) has conducted several clinical trials to establish standard chemotherapy (Table 1).

GIOSG/JCOG trials from establishment to JCOG 9205 [16]

From the late 1980s to the early 1990s, all of the GIOSG/JCOG trials were phase II studies. During this period some oral fluoropyrimidines were developed in Japan, among which tegafur (FT) and FT plus uracil (UFT) were the most popular. Because the response rates of monotherapy with fluoropyrimidines were not satisfactory, combination chemotherapy with these agents was

Table 1. GIOSG/JCOG clinical trials for gastric cancer

Study number	Phase	Study
8501 [13]	rII	A cooperative randomized study of tegafur plus mitomycin C in the treatment of advanced gastric cancer
8903 [14]	II	A phase II study of EAP (etoposide, adriamycin, and cisplatin) in patients with advanced gastric cancer
9001 [15]	II	Phase II study of protracted infusional 5-fluorouracil combined with cisplatin for advanced gastric cancer
9205 [16]	III	Randomized phase III trial of fluorouracil alone versus fluorouracil plus cisplatin versus uracil and tegafur plus mitomycin C in patients with unresectable advanced gastric cancer
9207 [28]	II	A phase II study of sequential methotrexate and 5-fluorouracil chemotherapy in patients with previously treated gastric cancer
9410 [29]	II	A phase II study of doxifluridine in elderly patients with advanced gastric cancer
9603 [23]	II	A phase II study of sequential methotrexate and 5-fluorouracil for advanced gastric cancer with malignant ascites
9912 [20]	III	Randomized phase III study of 5-fluorouracil (5-FU) alone versus combination of irinotecan and cisplatin (CP) versus S-1 alone in advanced gastric cancer
0106	III	Randomized phase III study of 5-FU continuous infusion (5-FUci) versus MTX + 5-FU sequential therapy (MF) in gastric cancer with peritoneal metastasis
0407	rII	Randomized phase II study of best available 5-FU versus low-dose paclitaxel in gastric cancer with peritoneal metastasis refractory to 5-FU containing regimens

investigated. In a randomized phase II study (JCOG 8501) comparing FT plus MMC (FTM) with UFT plus MMC (UFTM) [13], UFTM showed a higher response rate than FTM. It was concluded that UFTM would be a candidate for a test arm in a future phase III trial.

Subsequently, the GIOSG/JCOG introduced Western chemotherapy regimens such as etoposide plus doxorubicin plus CDDP (EAP) [14] and 5-FU plus CDDP (FP) [15]. Although a high response rate and a 5-year survival of 10% were obtained in the EAP trial, treatment-related deaths occurred in 10% of the patients. While the dose and schedule of FP in Japan were slightly modified from those in Western trials [12], the FP trial [15] showed a response rate and survival similar to those of Western trials. Therefore, the FP regimen was selected for a future phase III trial.

When the GIOSG/JCOG was planning a randomized phase III trial (JCOG 9205) [16], it was reported that, in a Western phase III trial [9], combination chemotherapy consisting of 5-FU, doxorubicin, and MMC (FAM) did not show a survival benefit over 5-FU alone Therefore, the GIOSG/JCOG decided to adopt 5-FU alone for the control arm in that trial, which was conducted as a three-arm phase III trial comparing FP and UFTM with 5-FU alone. FP did not show significantly longer survival despite its higher response rate and longer progression-free survival; this was associated with more severe toxicities than 5-FU alone. Furthermore, UFTM resulted in the worst survival among the three treatment arms and showed more severe toxicities than 5-FU alone. JCOG 9205 concluded that 5-FU alone would remain as the control arm for a subsequent phase III study. Although no survival benefit of combination chemotherapy containing 5-FU and CDDP over 5-FU alone has been confirmed in several phase III trials [8, 9, 12], the FP regimen has been the one most widely used for unresectable and recurrent gastric cancer all over the world.

JCOG 9912

In the late 1990s, some new antitumor agents were developed for gastric cancer in Japan. Combination chemotherapy of irinotecan (CPT-11) plus CDDP showed a response rate of 59% and a median survival time of 322 days, associated with grade 4 neutropenia (57%), and grade 3 or 4 diarrhea (20%) [17]. S-1, a new oral fluoropyrimidine, consisting of FT, 5-chloro-2, 4-dihydropyrimidine, and potassium oxonate, showed a response rate of 45% and a high 2-year survival rate of 17% in a total of 100 patients in two phase II studies, associated with low incidences of grade 3 or 4 toxicities[18, 19]. These results seemed very promising, and both a combination of CPT-11 plus CDDP and monotherapy with S-1 were adopted for test arms. The GIOSG/JCOG then planned a three-arm phase III study (JCOG 9912) to investigate the superiority of CPT-11 plus CDDP and the non-inferiority of S-1 compared to continuous infusion of 5-FU [20] (Fig. 1). The primary endpoint was overall survival, and secondary endpoints were time to treatment failure, non-hospitalized survival, adverse events, and response rate.

While the eligibility criteria of JCOG 9912 were similar to those of other recent phase III studies, the specific points of JCOG 9912 were that the presence of measurable lesions according to Response Evaluation Criteria in Solid Tumors (RECIST) was not mandatory and that patients with severe peritoneal metastasis were

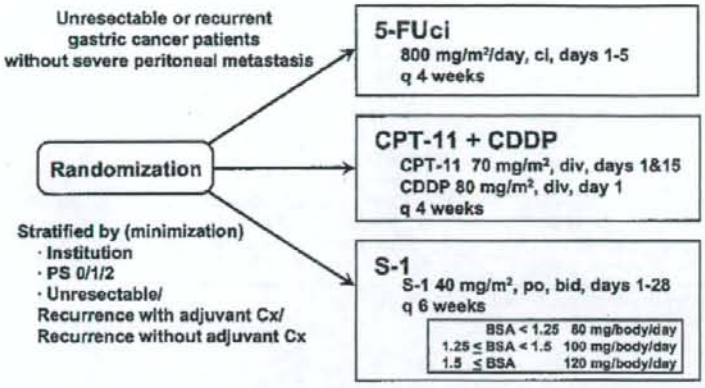

Fig. 1. Schema of JCOG 9912 [20]. *5-FU*, 5 fluorouracil; *ci*, continuous infusion; *CPT-11* irinotecan; *CDDP*, cisplatin; *div*, *PS*, performance status; *Cx*, chemotherapy; *BSA*, body surface area

Table 2. Incidence (%) of grade 3 or greater adverse events in JCOG 9912 [20]

Regimen	5-FU ($n = 234$)	CPT-11 + CDDP ($n = 236$)	S-1 ($n = 234$)
Leukocytes	0	41.5	0.9
Neutrophils	1.3	65.0	5.6
Hemoglobin	15.5	39.3	12.8
Febrile neutropenia	0	9.4	0
Infection with grade 3 or 4 neutropenia	0	7.7	0.4
Infection without neutropenia	3.9	3.8	5.6
AST	4.7	2.6	4.7
ALT	3.4	2.6	3.4
Bilirubin	3.0	1.3	4.3
Creatinine	0	2.1	0.9
Hyponatremia	6.5	22.6	5.2
Fatigue	1.7	10.3	5.1
Anorexia	12.5	32.9	12.4
Diarrhea	0.4	9.0	7.7
Nausea	6.9	20.5	5.6
Stomatitis	3.0	0	1.7
Treatment-related death[a]	0	1.3	0.4

[a] Judged by the independent data and safety monitoring committee of JCOG

excluded. The treatment schedules were: continuous infusion of 5-FU (800 mg/m^2 per day) for 5 days, repeated every 4 weeks, in the 5-FU arm; administration of both CPT-11 (70 mg/m^2) and (CDDP 80 mg/m^2) on day 1 and additional CPT-11 on day 15, repeated every 4 weeks, in the CPT-11 plus CDDP arm; and oral administration of S-1 (40 mg/m^2, b.i.d.) for 4 weeks, followed by 2 weeks' rest, repeated every 6 weeks, in the S-1 arm. Actually, 704 patients were accrued for 5 years. Final analysis was carried out in February 2007, 1 year after the last patient enrollment.

Table 2 summarizes the toxicities in JCOG 9912. Leucopenia and neutropenia were the most severe toxicities, and grade 3 or 4 hyponatremia, fatigue, anorexia, diarrhea, and nausea were most frequently observed in the CPT-11 plus CDDP arm. Only diarrhea was more severe in the S-1 arm than in the 5-FU arm, while there were no remarkable differences in the incidences of other toxicities between the S-1 arm and the 5-FU arm. It was considered that monotherapy with S-1 was feasible.

Table 3 summarizes the results for the efficacy of JCOG 9912. The response rate of the CPT-11 plus CDDP arm was 38%, and those of the S-1 and 5-FU arms were 28% and 9%. The median progression-free survival time of the 5-FU arm was 2.9 months; that of the CPT-11 plus CDDP arm, 4.8 months; and that of the S-1 arm, 4.2 months. Thus, it can be said that the antitumor effect of CPT-11 plus CDDP was the best among the three treatment arms. The median time to treatment failure of the 5-FU arm was 2.3 months; CPT-11 plus CDDP arm, 3.7 months; and the S-1 arm, 4.0 months. As for the reasons for treatment failure, more than 85% of the patients stopped treatment due

Table 3. Efficacy in JCOG 9912 [20]

Regimen	5-FU ($n = 234$)	CPT-11 + CDDP ($n = 236$)	S-1 ($n = 234$)
Response rate by RECIST (%)	9 (15/175)	38 (68/181)	28 (49/175)
PFS (months)	2.9	4.8	4.2
	—	$P < 0.001$*	$P = 0.001$*
TTF (months)	2.3	3.7	4.0
	—	$P = 0.014$*	$P < 0.001$*
MST (months)	10.8	12.3	11.4
	—	$P = 0.055$*	$P = 0.034$*
			$P < 0.001$**

P compared with 5-FU: **P* value for superiority; ***P* value for non-inferiority
PFS, progression-free survival; TTF, time to treatment failure

Table 4. Recent phase III trials in Japan

Trial	Regimen	*n*	RR (%)	PFS (months)	MST (months)
JCOG 9912 [20]	5-FU	234	9	2.9	10.8
	CPT-11+CDDP	236	38	4.8	12.3
	S-1	234	28	4.2	11.4
SPIRITS [21]	S-1	150	31	4.0	11.0
	S-1 + CDDP	148	54	6.0	13.0
GC 0301/TOP 002 [22]	S-1	160	27	—	10.5
	S-1 + CPT-11	155	42	—	12.8

to disease progression in the 5-FU arm and S-1 arm, while more than 30% of the patients stopped treatment for reasons related to toxicities in the CPT-11 plus CDDP arm. Substantial toxicities seemed to shorten the time to treatment failure in the CPT-11 plus CDDP arm.

As for the overall survival, the CPT-11 plus CDDP arm showed the best survival until 1 year, and the median survival times (MSTs) of the 5-FU, CPT-11 plus CDDP, and S-1 arms were 10.8, 12.3, and 11.4 months, while the S-1 arm showed the best survival after 1 year. As a whole, the hazard ratio to 5-FU of CPT-11 plus CDDP was 0.85 (95% confidence interval [CI], 0.70–1.04; $P = 0.055$) and that of S-1 was 0.83 (95% CI, 0.68–1.01; $P = 0.034$ for superiority, $P < 0.001$ for non-inferiority). Because the significance level for superiority after confirming the non-inferiority of S-1 was pre-specified to be 0.025, it was concluded that only the non-inferiority of S-1 was shown to be statistically significant, while there was no consensus about the significance level, 0.025 or 0.05, for superiority after confirming non-inferiority.

Because infusion chemotherapy is commonly performed with hospitalization in Japan, it is considered that the non-hospitalized survival reflects a patient's benefit from the quality-of-life point of view. Both the CPT-11 plus CDDP and S-1 arms showed longer non-hospitalized survival compared to the 5-FU arm.

S-1 showed a higher response rate, longer progression-free survival, and longer non-hospitalized survival than 5-FU, associated with feasible toxicities. It can be said that S-1 may be superior to 5-FU in practice. In conclusion, S-1 should be considered as standard chemotherapy for unresectable or recurrent gastric cancer.

Other phase III trials

There have been two other randomized phase III trials with S-1 as a control arm. One investigated the superiority of S-1 plus CDDP compared with S-1 alone in regard to overall survival S-1 plus cisplatin vs S-1 in RCT in the treatment for stomach cancer (SPIRITS trial) [21]. Overall survival was significantly longer in the S-1 plus CDDP arm (MST, 13.0 months) than in the S-1 arm (MST, 11.0 months; $P = 0.04$). The other phase III trial compared the combination of S-1 plus CPT-11 with S-1 (GC 0301/TOP 002) [22]. Although the MST of the S-1 arm was 10.5 months and that of the S-1 plus CPT-11 arm was 12.8 months, S-1 plus CPT-11 did not show significant superiority ($P = 0.23$). The treatment results for the S-1 arm, in terms of response rates and overall survival, were very similar in the three phase III trials (Table 4). Generally, it is recognized that S-1 plus CDDP is the standard treatment for unresectable or recurrent gastric cancer in Japan. Of note, there are two global trials investigating the non-inferiority of oxaliplatin and/or oral pyrimidine (capecitabine) compared to CDDP and continuous infusion of 5-FU; both of these

trials have met their primary endpoints. It can be said that Japan and Western countries share a consensus on standard chemotherapy with oral fluoropyrimidine plus platinum for advanced gastric cancer.

However, strictly speaking, none of the combination chemotherapies with oral fluoropyrimidine and platinum have shown superiority to FP, while S-1 monotherapy showed a response rate and progression-free survival similar to those of FP in the JCOG 9205 trial [16] as results of first-line chemotherapy. Of note, because the final analysis of JCOG 9912 [20] was performed just 1 year after the last patient enrollment, approximately 15% of the patients were censored in the survival curves after 1 year. Therefore, the long-term results of JCOG 9912 have not been obtained yet. While there was a remarkable difference in long-term survival between the arms in the SPIRITS trial (2-year survival rate: S-1, 15.3%; S-1 + CDDP, 23.6%), the 2-year survival rate of the S-1 arm in JCOG 9912 is speculated to be more than 20% from the survival curve at the final analysis. Therefore, it might be considered that it has not yet been clarified which is the better treatment strategy, i.e., whether monotherapy with S-1 followed by subsequent chemotherapy, or intensive combination chemotherapy such as S-1 plus CDDP as the first-line treatment will have a greater impact on long-term survival. The superiority of S-1 plus CDDP combination chemotherapy to FP is now under investigation by the First-Line Advanced Gastric Cancer Study (FLAGS) trial to confirm whether S-1 plus CDDP can be a standard chemotherapy all over the world.

JCOG 0106

The peritoneum, as well as liver and lymph nodes, is a major common metastatic site. The incidence of peritoneal metastasis in patients with unresectable or recurrent gastric cancer is higher than 50%. The prognosis of patients with severe peritoneal metastasis is considered to be poor, because it causes various kinds of complications such as ascites, bowel obstruction, and hydronephrosis, causing deterioration of the patient's general condition; also, these patients usually do not have target lesions according to RECIST. For these reasons, patients with severe peritoneal metastasis are generally excluded from clinical trials. Moreover, new drugs such as CPT-11 and S-1 cannot be used for these patients; the impaired bowel passage caused by severe peritoneal metastasis causes severe CPT-11 toxicities through the reabsorption of its active metabolite SN-38, and the impairment also prevents the oral administration of S-1. These patients were also excluded from the recent Japanese phase III trials. Therefore, evidence from clinical trials cannot be applied to these patients, and it is considered that a standard chemotherapy for gastric cancer patients with severe peritoneal metastasis has not been established.

The GIOSG/JCOG has decided to use different treatment strategies according to the presence or absence of severe peritoneal metastasis, and planned a phase III trial (JCOG 0106) targeting patients with severe peritoneal metastasis (Fig. 2). In this trial, 5-FU alone was adopted as the control arm, from the results of JCOG 9205, because it was the least toxic and could be applied safely to patients with severe peritoneal metastasis. Sequential therapy of 5-FU and MTX with leucovorin rescue (MTX/5-FU) was adopted as the test arm in this trial, based on the results of a phase II study of this regimen (JCOG 9603 [23]), targeting severe peritoneal metastasis; massive ascites was markedly decreased in 13 out of 37 patients (35%). The MTX/5-FU regimen is based on biochemical modulation; it is reported that an increase of phosphoribosyl pyrophosphate in cancer cells through the inhibition of purine synthesis by MTX enhances the effects of 5-FU. The major toxicities with this sequential therapy in the JCOG 9603 trial were leucopenia, anemia,

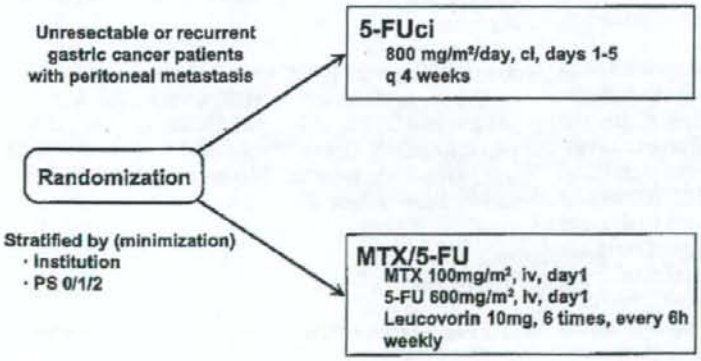

Fig. 2. Schema of JCOG 0106. *MTX*, methotrexate

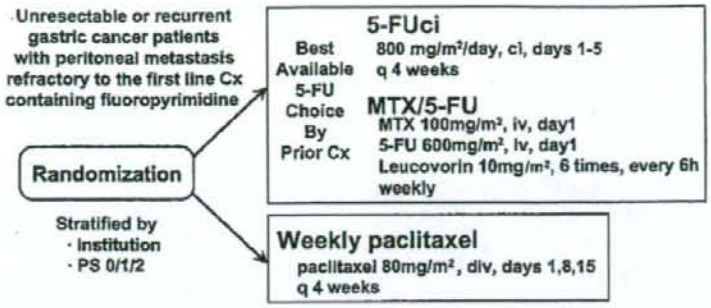

Fig. 3. Schema of JCOG 0407

thrombocytopenia, diarrhea, and renal dysfunction. A total of 237 patients were randomized to either the 5-FU arm or the MTX/5-FU arm between October 2002 and April 2007, and the final analysis is planned for the autumn of 2008.

JCOG 0407

The survival benefit of second-line chemotherapy for unresectable or recurrent gastric cancer has not been confirmed by randomized phase III trials. In a comparison of the overall survival of patients receiving 5-FU as first-line treatment between the JCOG 9205 trial [16] and the JCOG 9912 trial [20], the MST in the JCOG 9912 trial was markedly longer than that in the JCOG 9205 trial. Between the time of the JCOG 9205 trial and the JCOG 9912 trial, new drugs such as CPT-11, paclitaxel [24], and docetaxel [25] were approved in Japan, and they were widely used as second-line treatment in clinical practice [26, 27]. While around half of the patients in the JCOG 9205 trial received second-line chemotherapy, more than 70% of the patients in the JCOG 9912 trial received this treatment. It is considered that second-line chemotherapy may contribute to prolongation of survival. At present, several randomized phase III trials of second-line treatment after the failure of first-line treatment with fluoropyrimidine and/or platinum are underway in Japan.

Although not a few patients are complicated with severe peritoneal metastasis after the failure of first-line chemotherapy, second-line chemotherapy is limited because of the patients' poor condition. Because a standard second-line chemotherapy for severe peritoneal metastasis has not been established, it is difficult to decide on the control arm for a randomized trial. From our experience in clinical practice, we believe there are two candidates for treatment arms in such clinical trials. One is the "best available fluoropyrimidine", which is based on a mechanism of cytotoxicity that is different from that of 5-FU; this is achieved through the use of different administration methods from the initial therapy; such as continuous infusion (oral agent) and bolus infusion, with and without biochemical modulation by leucovorin or MTX. The other candidate treatment arm is the weekly administration of paclitaxel, which showed a response rate of around 20%, with fewer toxicities than for tri-weekly administration, even as second-line treatment; also with weekly treatment, a high concentration was maintained in ascites. Thus, the GIOSG/JCOG has started a randomized phase II trial (Fig. 3) in patients with severe peritoneal metastasis, comparing best available 5-FU with weekly administration of paclitaxel as second-line chemotherapy after the failure of first-line chemotherapy containing fluoropyrimidine, and patient accrual is under way.

Conclusion

In this article, GIOSG/JCOG clinical trials have been reviewed. There have been many phase III clinical trials in Japan and all over the world. The progress of chemotherapy for unresectable and recurrent gastric has been remarkable since the late 1990s, and standard chemotherapy has been established. In the near future, revolutionary progress can be expected through the development of new drugs, including molecular targeting agents.

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Irinotecan Plus Cisplatin Therapy and S-1 Plus Cisplatin Therapy for Advanced or Recurrent Gastric Cancer in a Single Institution

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Background: From the results of the JCOG9912 and SPIRITS trials, S-1 plus cisplatin (CDDP) therapy (SP) has been recognized as the standard chemotherapy for advanced gastric cancer in Japan. However, in their subsets of patients with the target lesion, irinotecan (CPT-11) plus CDDP therapy (IP) resulted in longer survival than 5-fluorouracil alone while SP exhibited a survival similar to S-1 alone. The objective of this study was to clarify the safety and efficacy of these two regimens.
Methods: Forty-four patients were treated with IP and 32 with SP between September 2002 and July 2006 at Shizuoka Cancer Center. In IP, 70 mg/m^2 CPT-11 was administered on Days 1 and 15, 80 mg/m^2 CDDP on Day 1, repeated every 4 weeks. In SP, 40–60 mg S-1 depending on the patient's body surface area was given orally twice daily for 21 days and 60 mg/m^2 CDDP intravenously on Day 8, repeated every 5 weeks.
Results: The response rate, progression-free survival and median survival were 47% (17 of 36), 170 and 444 days in IP, and 80% (21 of 26), 235 and 469 days in SP. In patients with target lesions, those were 47%, 170 and 431 days in IP, and 80%, 235 and 442 days in SP. The incidence of Grade 3 or 4 toxicity was similar in both groups, but patient refusal of treatment was more frequent for IP than for SP.
Conclusions: Our results demonstrate a better efficacy and feasibility of SP than IP for advanced gastric cancer patients, with or without a target lesion.

Key words: gastric cancer – irinotecan – cisplatin – S-1

INTRODUCTION

Gastric cancer is one of the most frequently occurring malignancies in the world (1). Despite early detection and curative resections, gastric cancer remains the second most common cause of cancer-related death in Japan. For patients with unresectable or recurrent gastric cancer, the main therapeutic option is palliative chemotherapy. 5-fluorouracil (5-FU)-based chemotherapy is widely used for advanced gastric cancer and has been shown to have a survival benefit compared with the best supportive care (2). However, there has been no world-wide consensus about a standard chemotherapy regimen.

Recently, two Phase III studies were reported from Japan (3,4). One was the JCOG9912 trial, which revealed that S-1 alone demonstrated non-inferiority to 5-FU alone and that irinotecan (CPT-11) plus cisplatin (CDDP) therapy failed to demonstrate superiority to 5-FU alone for overall survival. The trial concluded that S-1 alone should be considered for standard chemotherapy of advanced gastric cancer. Another trial was the SPIRITS, which investigated the superiority of S-1 plus CDDP to S-1 alone. The trial found that S-1 plus CDDP was significantly superior to S-1 alone ($P = 0.037$) for overall survival. Generally, S-1 plus CDDP has been recognized as the standard chemotherapy for advanced or recurrent gastric cancer in Japan.

However, in the subset analysis of patients having the target lesion for JCOG9912, the response rates of 5-FU, CPT-11 plus CDDP and S-1 were 9, 38 and 28%, respectively, and their median survival times (MST) were 9.0, 12.1 and 10.5 months (3). These results suggest that therapy with CPT-11 plus CDDP might be more effective than S-1 or 5-FU alone for patients with the target lesions. On the other

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hand, in the subset analysis of patients having the target lesion of the SPIRITS trial, the hazard ratio of S-1 plus CDDP to S-1 alone was higher than 1.0 (4). These results posed a question of which regimen, CPT-11 plus CDDP or S-1 plus CDDP, are more suitable for patients with the target lesions. There was no direct comparison between CPT-11 plus CDDP and S-1 plus CDDP for advanced gastric cancer. The objective of this study was to clarify the safety and efficacy of these two regimens.

PATIENTS AND METHODS

Patients

The subjects in this study were 76 patients treated between September 2002 and July 2006 at the Shizuoka Cancer Center. Among them, 44 patients were treated with CPT-11 plus CDDP (IP group), and 32 patients were treated with S-1 plus CDDP (SP group). The subjects were recruited according to the following selection criteria: histologically proven gastric adenocarcinoma; Eastern Cooperative Oncology Group (ECOG) performance status 0–2; age 20–75 years; no prior chemotherapy or radiation therapy; adequate bone marrow (WBC count $\geq$3000/μl and $\leq$12 000, platelet count $\geq$100 000/μl), liver (serum bilirubin level $\leq$1.5 mg/dl and serum transaminase level $\leq$99 IU/l), and renal function (serum creatinine level$\leq$1.5 mg/dl); no other active malignancy; sufficient oral intake; and the provision of written informed consent. These criteria are almost the same as those of the JCOG9912 and SPIRITS trials. The reasons for exclusion were adenocarcinoma with neuroendocrine carcinoma components in six, brain metastasis in one, and severe liver dysfunction in one from the IP group, and ages older than 75 years in two, performance status 3 in two, adenocarcinoma with neuroendocrine carcinoma components in two, brain metastasis in one, combination with radiotherapy in one, another active malignancy in four, severe liver dysfunction in four, massive pleural effusion and/or ascites in five, dyspnea due to lymphangitis carcinomatosa in two, insufficient oral intake in five, heart failure in one and an old cerebral infarction in one from the SP group. Thus, the subjects of this retrospective study were 44 patients in the IP group and 32 in the SP group.

Treatment Schedule

In the IP group, CPT-11 (70 mg/m^2) was administered by intravenous infusion for 90 min, and after a 2 h interval, CDDP (80 mg/m^2) was administered over 2 h with adequate hydration on Day 1. The same dose of CPT-11 was administered on Day 15. This treatment was repeated every 4 weeks. In the SP group, S-1 was orally administered at a dose not exceeding 40 mg/m^2 based on the patient's body surface area (BSA): BSA $<$1.25 m^2, 40 mg; 1.25 m^2 $\leq$ BSA $<$ 1.5 m^2, 50 mg; and BSA $\geq$ 1.5 m^2, 60 mg. S-1 was administered twice daily for 21 consecutive days and CDDP (60 mg/m^2) was administered intravenously with adequate hydration on Day 8. This treatment was repeated every 5 weeks. Both treatments were repeated until disease progression, unacceptable toxicity or patient refusal.

Evaluation

Laboratory data and patients' conditions were assessed at least every 2 weeks and prior to infusion of anti-tumor agents. The response and toxicities were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) and Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. The target lesion was defined as a measurable lesion 1 cm or larger in diameter detected by CT scan with 5 mm slice. Patients were assessed for response every 1 to 2 months as a rule in both treatment groups. The disease progression was evaluated according to RECIST. The survival time was calculated from the date of chemotherapy initiation to the date of all-cause death or the latest follow-up with the Kaplan–Meier method. Progression-free survival (PFS) was calculated from the start of chemotherapy to the first day of disease progression. If chemotherapy was discontinued for any reason other than progressive disease, PFS was counted to the day of disease progression during the subsequent therapy.

RESULTS

Patient Characteristics

Characteristics of the subjects are listed in Table 1. The median age was 63 and 60 years in the IP and SP group, respectively. For the IP and SP groups, 42 (95%) and 31 (97%) patients had a performance status of 0–1, 21 (48%) and 15 (47%) had an intestinal type of adenocarcinoma, and 22 (52%) and 22 (69%) had multiple metastatic sites, respectively. Thirty-six patients (82%) in the IP group and 26 (81%) in the SP group had target lesions. In the subset with target lesions, the median age was 63 and 60 years, 34 (94%) and 26 (100%) had a performance status of 0–1, 19 (56%) and 14 (54%) had an intestinal type of adenocarcinoma and 21 (58%) and 20 (77%) had multiple metastatic sites, respectively.

Treatment Results

Table 2 summarizes the results of treatment. The total number of treatment courses was 226 in the IP group and 172 in the SP group. The median number of treatment courses was 4.5 (range, 1–14 courses) in the IP group and 5.5 (range, 1–10 courses) in the SP group. In the IP group, the dose intensity of CPT-11 was 29.6 mg/m^2 per week and the intensity of CDDP was 18.1 mg/m^2 per week, which corresponded to 85 and 91% of the planned doses, respectively. In the SP group, the dose intensity of S-1 was 309 mg/m^2 per week and the intensity of CDDP was 11.1 mg/m^2 per

Table 1. Patient characteristics

	All		TL(+)[a]	
	IP ($n=44$)	SP ($n=32$)	IP ($n=36$)	SP ($n=26$)
Age, years				
Median (range)	63 (34–75)	60 (19–75)	63 (34–75)	60 (19–75)
Sex				
Male	37	19	32	16
Female	7	13	4	10
Performance status				
0	27	15	24	13
1	15	16	10	13
2	2	1	2	0
Prior surgery				
Present	18	8	12	7
Absent	26	24	24	19
Macroscopic type				
Type 2	16	9	13	9
Type 3	20	14	17	12
Type 4	5	8	4	4
Unknown	3	1	2	1
Histology				
Intestinal	21	15	19	14
Diffuse	20	17	16	12
Unknown	1	0	1	0
Number of metastatic organs				
1	22	10	15	6
2	15	16	14	14
3	7	6	7	6
Metastatic site				
Lymph node	19	25	17	23
Liver	31	15	31	15
Peritoneum	10	13	5	8
Others	13	6	11	5
Target lesion				
Present	36	26	36	26
Absent	8	6	0	0

IP, irinotecan plus cisplatin; SP, S-1 plus cisplatin.
[a]Patients with the target lesion.

week, which corresponded to 92 and 93% of the planned doses, respectively.

The reasons for treatment failure in the IP group were disease progression in 34 patients (77%), unacceptable toxicity in one (2%), patient refusal related to toxicity in seven (16%) and surgery in two (5%). The reasons for treatment discontinuation in the SP group were disease progression in 29 patients (91%), severe toxicity in one (3%) and patient refusal related to toxicity in two (6%). The incidence of a patient's refusal related to toxicity seemed to be higher in IP than in SP.

Table 2. Treatment results

	IP ($n=44$)	SP ($n=32$)
Treatment course		
Total	226	172
Median(range)	4.5 (1–14)	5.5 (1–10)
Dose intensity (mg/m^2/week)	CPT-11: 29.6	S-1: 309
	CDDP: 18.1	CDDP: 11.1
Relative dose intensity	CPT-11: 85%	S-1: 92%
	CDDP: 91%	CDDP: 93%
Reasons for treatment failure		
Disease progression	34 (77%)	29 (91%)
Toxicity	1 (2%)	1 (3%)
Refusal related to toxicity	7 (16%)	2 (6%)
Operation	2 (5%)	0 (0%)

CDDP, cisplatin.

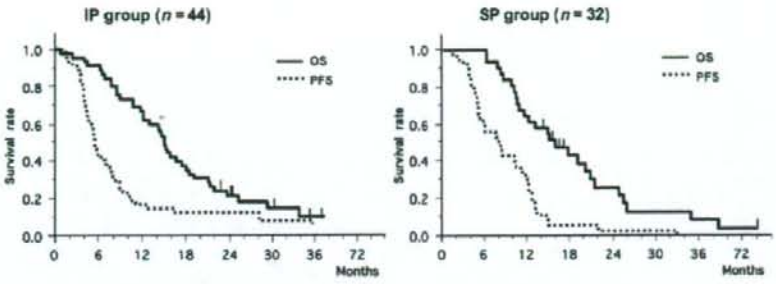
Response and Survival

Thirty-six patients (82%) in the IP group and 26 (81%) in the SP group with target lesions were assessed for their response. The response rates (RRs) were 47% [17 of 36, 95% confidence interval (CI) 30.9–63.5] and 80% (21 of 26, 95% CI 65.6–95.9) in the IP and SP groups, respectively (Table 3). Figure 1 shows the overall survival (OS) and PFS curves of both groups. The MST and PFS of the IP group were 444 and 170 days, and those of the SP group were 469 and 235 days, respectively. Figure 2 shows the OS and PFS of the subset of patients with the target lesion. The MST and PFS of the IP group were 431 and 170 days, respectively, and for the SP group they were 442 and 235 days, respectively. Between the IP and SP groups, there were no obvious differences in the pattern of progressive disease. From these results, while the OS was comparable in both groups, the RR and PFS seemed to be longer in the SP group compared with the IP group, when observing either all patients or the subset with target lesions.

Table 3. Response rate

	n	CR	PR	SD	PD	NE	RR	95% CI
IP	36	0	17	13	4	2	47%	30.9–63.5%
SP	26	1	20	3	1	1	80%	65.6–95.9%

RR, response rate; 95%CI, 95% confidence interval; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable.



		MST	PFS
Group IP	n = 44	444 days	170 days
Group SP	n = 32	469 days	235 days

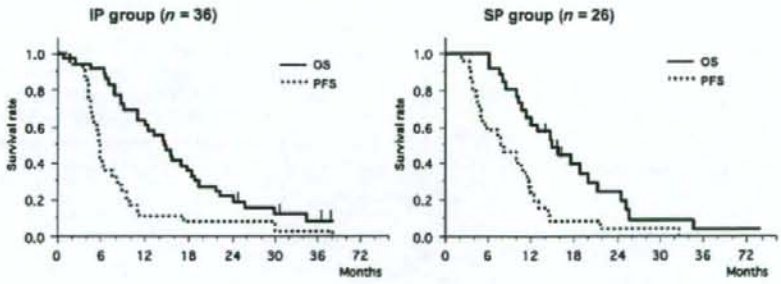
Figure 1. Overall survival curve and progression-free survival (PFS) curve. The median survival time (MST) and PFS were 444 and 170 days in the group receiving irinotecan plus cisplatin (IP) and 469 and 235 days in the group receiving S-1 plus cisplatin (SP), respectively. OS, overall survival.

Adverse Reactions

The adverse events observed in both groups are listed in Table 4. In the IP group, Grade 3 or 4 neutropenia was observed in 15 patients (36%), anemia in 19 (39%), and Grade 3 febrile neutropenia was observed in two (5%). In the SP group, Grade 3 or 4 neutropenia was observed in nine patients (28%), anemia in 10 (31%), thrombocytopenia in four (13%), and Grade 3 febrile neutropenia was observed in two (6%). In both groups, the incidence of either Grade 3 or 4 non-hematological toxicity was $<12\%$. The common non-hematological toxicities in the IP group were anorexia (11%), fatigue (7%) and diarrhea (5%); those in the SP group were anorexia (9%) and nausea (6%). No treatment-related deaths occurred in either group. While the toxicity profiles were different between the groups, there seemed to be no remarkable difference in the incidence of severe toxicity.

Subsequent Chemotherapy

Table 5 shows the second-line chemotherapy for both groups. In the IP group, 38 patients (86%) received second-line chemotherapy after failure of the IP regimen. Twenty-one patients (58%) were treated with S-1 alone and nine patients (25%) were treated with weekly paclitaxel. In the SP group, 26 patients (90%) received second-line chemotherapy, 16 (62%) were administered a CPT-11-based regimen (10, CPT-11 plus mitomycin C; 3, CPT-11 alone; 3, FOLFIRI) and seven (27%) received weekly paclitaxel. Therefore, more than half of the patients were treated by a crossover treatment strategy between S-1 and CPT-11.



		MST	PFS
Group IP	n = 36	431 days	170 days
Group SP	n = 26	442 days	235 days

Figure 2. In patients with target lesions, the MST and PFS were 431 and 170 days in the group receiving IP and 442 and 235 days in the group receiving SP, respectively.