Int J Clin Oncol (2008) 13:196–200
DOI 10.1007/s10147-008-0784-0

REVIEW ARTICLE

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Chemotherapy for metastatic disease: review from JCOG trials

Received: March 23, 2008

Abstract The Gastrointestinal Oncology Study Group of Japan Clinical Oncology Group (GIOSG/JCOG) has conducted several clinical trials to establish standard chemotherapy for unresectable or recurrent gastric cancer. From the late 1980s to early 1990s, two phase II studies by JCOG evaluated oral fluoropyrimidines, and others introduced Western chemotherapy regimens. Thereafter, the first phase III study (JCOG9205), comparing 5-fluorouracil (5-FU), 5-FU plus cisplatin (CDDP) (FP), and uracil and tegafur (UFT) plus mitomycin (UFTM), could not show a survival benefit of either FP or UFTM over 5-FU alone. In the late 1990s, new active agents such as irinotecan (CPT-11) and S-1 (new oral fluoropyrimidine) showed promising results in their phase II trials. The latest phase III study (JCOG9912), comparing 5-FU, CPT-11 plus CDDP, and S-1, showed significant noninferiority of S-1 to 5-FU in overall survival, associated with a better response rate and progression-free survival and acceptable toxicities, and concluded that S-1 should be considered for the standard chemotherapy of unresectable or recurrent gastric cancer. Simultaneously, another Japanese phase III trial comparing S-1 with S-1 plus CDDP showed a survival benefit of S-1 plus CDDP. At present, S-1 plus CDDP is recognized as standard chemotherapy for unresectable or recurrent gastric cancer, and new treatment with molecular target agents is under development.

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

Introduction

According to global estimates of cancer incidence in 2002, gastric cancer remains one of the major causes of cancer death worldwide.[1] In Japan, despite a remarkably improving survival trend through early detection and curative surgery, gastric cancer is the second most frequent cancer-related cause of death after lung cancer. Especially, unresectable or recurrent gastric cancer shows a poor prognosis. Development of effective standard chemotherapy is an important issue.

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From 1985 to 1992

Several phase III trials demonstrated that a 5-fluorouracil (5-FU)-based regimen provides superior survival in patients with unresectable or recurrent gastric cancer compared with best supportive care.[2–4] Although this survival advantage appears to be remarkable and there were not a few randomized trials using anthracyclin, mitomycin (MMC), 5-FU, methotraxate, and cisplatin (CDDP) for unresectable or recurrent gastric cancer up until the early 1990s (Table 1),[5–12] no global standard regimen was established.

The Gastrointestinal Oncology Study Group of Japan Clinical Oncology Group (GIOSG/JCOG) has conducted several clinical trials to establish standard chemotherapy for unresectable or recurrent gastric cancer. From the late 1980s to the early 1990s, some of them evaluated oral fluoropyrimidines that had originated from Japan. There are quite a few oral fluoropyrimidines available for gastric cancer in Japan. Among them, tegafur (FT) and FT plus uracil (UFT) were the most popular. Because monotherapy with oral fluoropyrimidine did not show high response rates, its combination chemotherapy was investigated. A randomized phase II study (JCOG8501) comparing FT plus MMC (FTM) with UFT plus MMC (UFTM) was carried out.[13] This study demonstrated a higher response rate in UFTM than in FTM, whereas no survival differences were observed between the two arms.

Subsequently, the trials in GIOSG/JCOG investigated the feasibility and reproducibility of Western chemotherapy regimens. There were two phase II studies of a platinum-

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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