Table 1 Patient characteristics ($n = 45$)

Age (years)	
Median	64
Range	36–75
Gender	
Male	33
Female	12
ECOG performance status	
0	24
1	21
2	0
Borrmann macroscopic type of primary cancer	
0	1
1	1
2	17
3	18
4	5
Unknown	3
Histological type	
Intestinal	25
Diffuse	18
Unclassified	2
Prior chemotherapy	
5-FU alone	18
S-1 alone	15
S-1 + CDDP	6
MTX + 5-FU	2
Others	4

ECOG Eastern Cooperative Oncology Group, *5-FU* 5-fluorouracil, *CDDP* cisplatin, *MTX* methotrexate

Table 2 Evaluation of response ($n = 45$)

Tumor response	Patients	
	n	% (95% CI)
Complete response	0	0
Partial response	13	28.9 (15.6–42.1)
Stable disease	17	37.7 (23.6–51.9)
Progressive disease	14	31.1 (17.6–44.6)
Not evaluated	1	4.4 (0–6.5)
Survival	Months (95% CI)	
PFS	4.1 M (2.5–5.7)	
OS	10.1 M (7.3–12.6)	

CI confidence interval, *PFS* progression-free survival, *OS* overall survival

MMC/CPT-11 combination as second-line chemotherapy could not be definitively concluded as efficacious for further investigation.

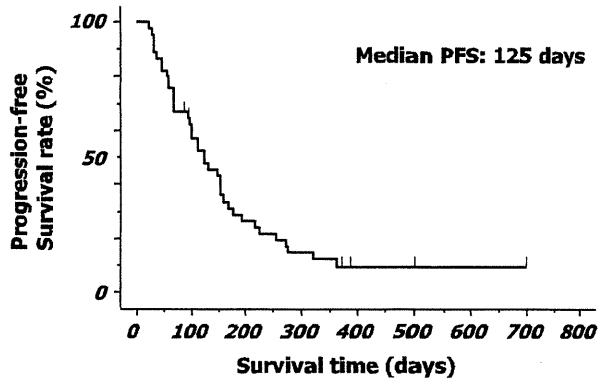

Fig. 1 Kaplan–Meier estimates of progression-free survival (*PFS*) rates

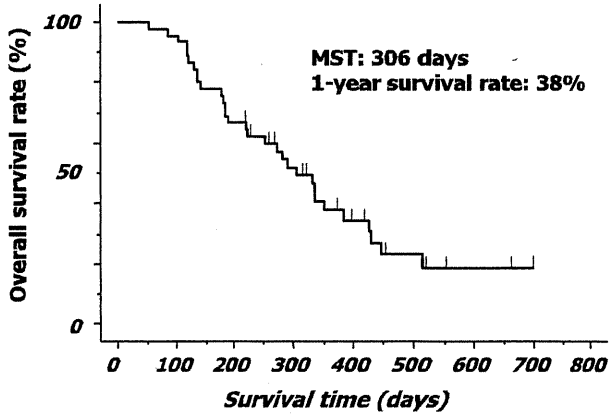

Fig. 2 Kaplan–Meier estimates of overall survival. *MST* Median survival time

Toxicity

The toxicities of the MMC/CPT-11 therapy are summarized in Table 3, with myelosuppression and gastrointestinal toxicity as major toxicities. Grade 3 and 4 neutropenia occurred in 24 and 29% of the patients, respectively, whereas grade 3 and 4 thrombocytopenia developed in only 7%. As for the nonhematological toxicities, the incidence rate of grade 3 diarrhea was 2%, and nausea and vomiting were mild. Early death due to interstitial pneumonitis within 30 days from the last chemotherapy occurred in 1 patient, which was considered by the JCOG Data and Safety Monitoring Committee to have been possibly related to the treatment.

Discussion

In second-line chemotherapy for AGC, the potential benefits remain unclear because of the few prospective studies that have been conducted thus far. These trials demonstrated that

Table 3 Grade 2–4 adverse events according to NCI-CTC ver. 2.0 ($n = 45$)

	Grade 2	Grade 3	Grade 4	Grade 3–4 (%)
Hematological WBC	24	8	5	29
Neutrophils	10	11	13	53
Hb	25	3	3	13
Platelets	1	2	1	7
Febrile neutropenia	0	4	0	9
Non-hematological Anorexia	13	11	0	24
Nausea	11	6	0	13
Diarrhea	4	1	0	2
Infection with grade 3/4 neutropenia	0	2	0	4
Infection without neutropenia	4	2	0	4

NCI-CTC National Cancer Institute-Common Toxicity Criteria, *Hb* hemoglobin

the RRs to second-line chemotherapy in phase II trials for gastric cancer were similar to those observed for other cancers which are more commonly treated after the failure of first-line chemotherapy. Furthermore, 2 Japanese randomized trials (i.e., SPIRITS [5] and JCOG9912 [6]) achieved a median OS of 13.0 months despite the relatively short median PFS of about 4–6 months. Although both JCOG9912 and our previous phase III study (JCOG9205 [19]) utilized 5-FU continuous infusion (c.i.) and 5-FU/CDDP, the obtained median PFS was 2 months and the OS in JCOG9912 was much longer than that in JCOG9205. In the present study, the proportion of patients who received second-line chemotherapy was >70%, which is higher than that obtained in our previous study (53%). The results of previous phase II trials consistently suggest that patients treated with second-line chemotherapy may survive longer than those provided with BSC, although the survival benefit of the second-line chemotherapy has not yet been clarified.

According to the 26 prospective phase II studies reported in the literature, obtained using the search expressions "gastric cancer" and "second-line chemotherapy" in PubMed, the average and median RRs were 18.8 and 20.0% (0–34.6%), respectively [18, 20–44]. Although the present study did not disprove the null hypothesis about RR, it is suggested that MMC/CPT-11 therapy with an RR of 28.9% may possess some antitumor activity as second-line chemotherapy.

As for survival, the present study showed a median survival time of 10.1 months (95% CI, 7.3–12.9 months), and a 1-year survival proportion of 38%. These data are similar to those obtained in the first-line chemotherapy setting and appeared to be better than those obtained using several other regimens, showing a survival period of 3.5–13 months compared with the reported median survival period of 7–10 months in untreated patients. However, it is very difficult to compare phase II studies due to differences in patient background and subsequent therapy. One reason for improved survival may be good clinical selection of a patient. At the baseline evaluation, the median age of the patients in the present study was 64 years (range, 36–75), and all the patients had a good PS of 0 or 1. Another reason for the improved survival was the high proportion of tumor stabilization (66.7%) after the administration of the MMC/CPT-11 regimen. Therefore, it is considered that MMC/CPT-11 therapy may provide some survival benefit.

The toxicity of the MMC/CPT-11 regimen can be considered tolerable and manageable. Hematological toxicity was within the expected range, including grade 4 neutropenia, observed in 13 patients (29%) and grade 3 febrile neutropenia in 4 patients (9%). According to a Japanese prospective pharmacogenomic study of CPT-11, homozygotes and double heterozygotes of *6 and *28 (*6/*6, *28/*28 and *6/*28) were significantly associated with severe neutropenia. The UGT1A1 gene test prior to receiving this regimen may be useful to decide the starting dose of CPT-11 or to decide whether the patient should receive CPT-11 and MMC combination chemotherapy or CPT-11 monotherapy [45]. Although treatment-related death was observed in 1 patient (2%) in the present study, the occurrence of adverse events was similar to that in JCOG9911-DI, a phase II study of the same regimen for colon cancer; thus, MMC/CPT-11 therapy was considered tolerable. In the present study, the proportion of patients with toxicity was similar to that of patients where MMC/CPT-11 therapy was used as second-line treatment against colorectal cancer [16].

From the above results, the present phase II study of MMC/CPT-11 therapy for FU-based chemotherapy-refractory gastric cancer is judged to be negative on the basis of the decision rule defined in the protocol. This may be due to the threshold RR being set very high owing to the lack of data as the basis for setting the threshold level and expected RR, because of the small number of phase II studies of second-line treatment when this protocol was developed. In fact, the RR cannot be considered poor compared with that in phase II studies performed in other treated patients (as shown in Table 2), with a favorable

survival time of 10 months. In conclusion, the MMC/CPT-11 regimen might be one treatment option for pretreated AGC in patients with good PS.

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Conflict of interest None.

Appendix

Investigators in participating institutions: Yamagata Prefectural Central Hospital, H. Saito; Tochigi Cancer Center, H. Fuji; Saitama Cancer Center, K. Yamaguchi; National Cancer Center Hospital East, T. Doi; Chiba Cancer Center Hospital, T. Denda; National Cancer Center Hospital Tokyo, Y. Shimada; Kitasato University East Hospital, W. Koizumi; Aichi Cancer Center Hospital, Y. Inaba; Nagoya Medical Center, H. Iwase; Osaka Medical College, H. Takiuchi; National Hospital Organization Shikoku Cancer Center, J. Nasu; Kumamoto Regional Medical Center Hospital, M. Yoshida.

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Past and Present Achievements, and Future Direction of the Gastrointestinal Oncology Study Group (GIOSG), a Division of Japan Clinical Oncology Group (JCOG)

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Initially, Gastrointestinal Study Group in Japan Clinical Oncology Group (GIOSG/JCOG) focused on gastric cancer. In 1980s, fluoropyrimidine, cisplatin and mitomycin C were key drugs. A randomized Phase II trial (JCOG8501) comparing futrafur plus mitomycin C and uracil plus futrafur and mitomycin C showed a higher response rate of uracil plus futrafur and mitomycin C than futrafur plus mitomycin C. From the results of two Phase II trials of etoposide, adriamycin and cisplatin, and cisplatin plus 5-fluorouracil, uracil plus futrafur and mitomycin C and cisplatin plus 5-fluorouracil were adopted for the test arms of the Phase III trial (JCOG9205) comparing with continuous infusion of 5-fluorouracil as a control arm. Neither cisplatin plus 5-fluorouracil nor uracil plus futrafur and mitomycin C showed a survival benefit over continuous infusion of 5-fluorouracil. In late 1990s, new agents, irinotecan and S-1, were developed for gastric cancer in Japan. GIOSG conducted a Phase III trial (JCOG9912) investigating superiority of irinotecan plus cisplatin and non-inferiority of monotherapy with S-1 compared with continuous infusion of 5-fluorouracil, and S-1 succeeded in showing non-inferiority. Then, SPIRITS trial showed a survival benefit of S-1 plus cisplatin over S-1, resulting in the establishment of a standard care for advanced gastric cancer in Japan. GIOSG have merged with Gastric Cancer Study Group as the Stomach Cancer Study Group (SCSG) from 2011. Recent progress in the development of new drugs has been remarkable. From the point of the roles shared with many other study groups for clinical trials, including registration trials of new drugs conducted by pharmaceutical companies, SCSG should recognize its role and conduct clinical trials with high quality for establishing new standard treatment.

Key words: Gastrointestinal Oncology Study Group – Japan Clinical Oncology Group – esophageal cancer – gastric cancer – pancreatic cancer, colorectal cancer

INTRODUCTION

In Japan, there are several clinical trial groups. Japan Clinical Oncology Group (JCOG) is a clinical study group in which many multi-institutional clinical trials have been conducted mainly by the support of research aid from the Ministry of Health, Labour and Welfare in Japan. While other clinical trial groups such as Hokkaido Gastrointestinal Cancer Study Group (HGCSG), Tohoku Clinical Oncology Research and Education Society (T-CORE), Japan Clinical Cancer Research Organization (JACCRO), Tokyo Cooperative Oncology Group (TCOG), Chubu Clinical Oncology Group (CCOG), Epidemiological and Clinical Research Information Network (ECRIN), West Japan

Oncology Group (WJOG), Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG), Japanese Foundation for Multidisciplinary Treatment of Cancer (JFMC), Kyushu Study Group of Clinical Cancer (KSCC), etc. have also been contributing to establish new evidences for gastrointestinal malignancy, the Gastrointestinal Oncology Study Group (GIOSG) was one of the oldest three study groups dedicated to medical oncology at the beginning of JCOG and has been conducting clinical trials of gastrointestinal malignancy.

Table 1 shows the summary of clinical trials conducted by GIOSG (1–20). In late 1980s, GIOSG focused on gastric cancer and conducted a several Phase II trials (1–4). In early 1990s, it could launch the first Phase III trial (JCOG9205) (5), although its sample size was small. And then, GIOSG could complete a large Phase III trial (JCOG9912) (13). In the twenty-first century, GIOSG challenged to difficult clinical trials [JCOG0106 (14) and 0407 (15)] for gastric cancer patients with severe peritoneal metastasis, who are usually excluded from clinical trials especially for new drug approval, meaning that new standard treatment, including new agents, can hardly be applied to these patients. Along with these clinical trials, GIOSG has been continuing to conduct translational researches to find predictive marker for chemotherapy effects using the archived tissues of the patients enrolled to JCOG9001 (21), 9205 (22) and 9912 (23,24). Recently, GIOSG has expanded its activity for colorectal cancer [JCOG9703 (9) and 0208-DI], esophageal cancer [JCOG9906 (10), 9908-DI (11) and 0508 (18)], pancreatic cancer [JCOG0506 (17)], and head and neck cancer [JCOG0706 (20)] and has adopted non-surgical multimodality treatment such as chemoradiation for esophageal and head and neck cancer and endoscopic resection for mucosal gastric cancer [JCOG0607 (19)]. Furthermore, several institutions of GIOSG have started an investigator-initiated registration trial

Table 1. Clinical trials conducted by GIOSG

Organ	Study no.	Phase	Summary	Ref.
Gastric	8501	rII	Comparing FTM and UFTM for advanced gastric cancer	1
Gastric	8804	II	CDDP + 5′DFUR for advanced gastric cancer	2
Gastric	8903	II	EAP for advanced gastric cancer	3
Gastric	9001	II	FP for advanced gastric cancer	4
Gastric	9205	III	Comparing 5-FUci, FP and UFTM for advanced gastric cancer	5
Gastric	9207	II	MTX + 5-FU as the second line chemotherapy for advanced gastric cancer	6
Gastric	9410	II	5′DFUR for elderly patients with advanced gastric cancer	7
Gastric	9603	II	MTX + 5-FU for malignant ascites of gastric cancer	8
Colorectal	9703	II	CPT-11 + continuous infusion of 5-FU for unresectable metastatic colorectal cancer	9
Esophageal	9906	II	Chemoradiation therapy with 5-FU + CDDP for Stage II/III (except T4) esophageal cancer	10
Esophageal	9908-DI	I/II	Chemoradiation therapy with 254-S + 5-FU for locally advanced esophageal cancer	11
Colorectal	9911-DI	II	CPT-11 + MMC as the second-line chemotherapy for unresectable metastatic colorectal cancer	12
Gastric	9912	III	Comparing 5-FUci, CPT-11 + CDDP and S-1 for advanced gastric cancer	13
Gastric	0106	III	Comparing 5-FUci and MTX + 5-FU for patients with severe peritoneal metastasis of gastric cancer	14
Gastric	0109-DI	II	CPT-11 + MMC as the second-line chemotherapy after failure of 5-FU for advanced gastric cancer	15
Colorectal	0208-DI	I/II	Arterial infusion of 5-FU + systemic infusion of CPT-11 for liver metastasis of colorectal cancer	—
Gastric	0407	rII	Comparing best available 5-FU and weekly PTX as the second-line chemotherapy after failure of 5-FU containing regimen for patients with severe peritoneal metastasis of gastric cancer	16
Pancreatic	0506	II	GEM for locally advanced pancreatic cancer	17
Esophageal	0508[a]	II	Endoscopic resection followed by chemoradiation therapy with 5-FU + CDDP for clinically T1N0M0 esophageal cancer	18*
Esophageal	0604[a]	I/II	Chemoradiation therapy with S-1 + CDDP for Stage II/III (except T4) esophageal cancer: investigator-initiated registration trial	—
Gastric	0607[a]	II	Endoscopic submucosal resection for clinically mucosal cancer	19
Head and neck	0706[a]	II	Chemoradiation therapy with S-1 + CDDP for locally advanced head and neck cancer	20

FTM, futrafur plus MMC; UFTM, uracil and futrafur plus MMC; CDDP, cisplatin; 5′DFUR, 5′-deoxy-5-fluorouridine; EAP, etoposide plus adriamycin and cisplatin; FP, 5-fluorouracil plus cisplatin; 5-FU, 5-fluorouracil; MTX, methotrexate; CPT-11, irinotecan; 254-S, nedaplatin; PTX, paclitaxel; GEM, gemcitabine.
[a]Not completed yet.

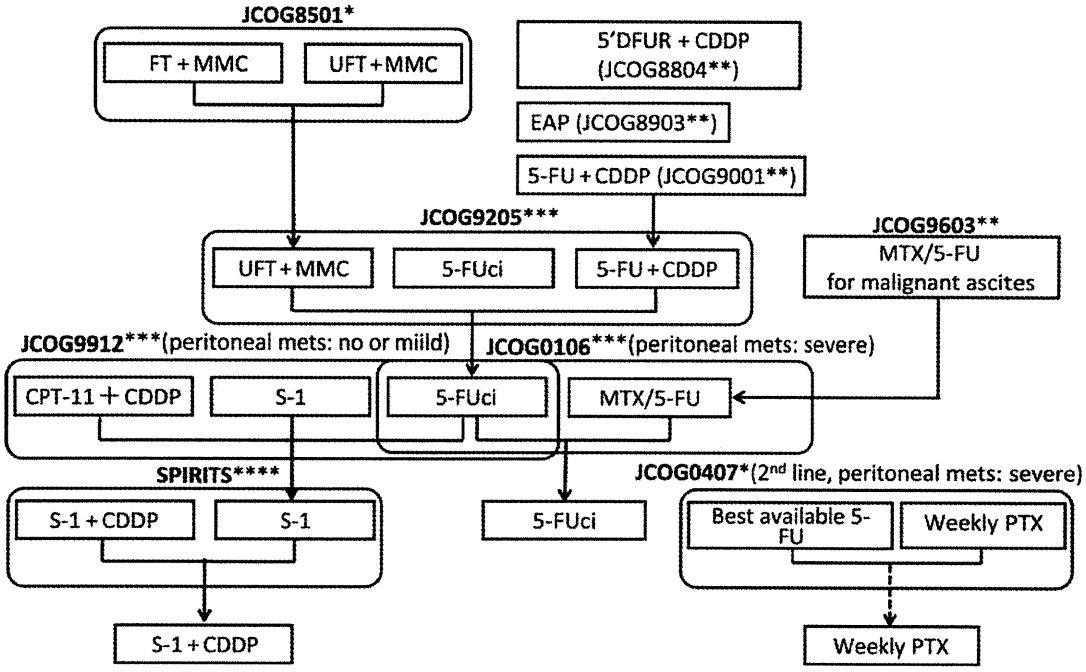

Figure 1. Flow of clinical trials for gastric cancer in GIOSG. Abbreviations are given in the text. *Randomized Phase II, **Phase II, ***Phase III and ****conducted by pharmaceutical company.

(JCOG0604) of S-1 for approval to esophageal cancer. Completion of these clinical trials leads to the establishment of new study groups such as the Hepatobiliary and the Pancreatic Oncology Group, the Gastrointestinal Endoscopy Study Group and the Head and Neck Cancer Study Group in JCOG. GIOSG has merged with Gastric Cancer Study Group as the Stomach Cancer Study Group (SCSG) from 2011. This paper reviews the history of GIOSG, introduces the present activity and proposes the future direction mainly in the field of gastric cancer (Fig. 1).

DAWN OF GIOSG

Till early 1990s, all of GIOSG trials (1–4) were Phase II. In those days, several oral fluoropyrimidines were developed and cisplatin (CDDP) was approved for gastric cancer in Japan. In the randomized Phase II study [JCOG8501 (1)] comparing futrafur plus mitomycin C (MMC) (FTM) with uracil and futrafur plus MMC (UFTM), UFTM showed a higher response rate (25%, $n = 79$) than FTM (8%, $n = 90$). In JCOG8804 (2), 5′-deoxy-5-fluorouridine (5′DFUR) plus CDDP showed a response rate of 50% in 28 patients with measurable lesion. In the Phase II trial [JCOG8903 (3)] of EAP, combination of etoposide, adriamycin (ADM) and CDDP, despite a high response rate and 5-year survival of 10%, treatment-related deaths occurred in 10%. While the dose and schedule of combination of 5-fluorouracil (5-FU) and CDDP (FP) in JCOG9001 (4) were modified from those in Western trials, it showed a response rate (43%, $n = 40$) and survival similar to those of Western trials. From these results, GIOSG concluded that FP and/or UFTM would be selected as test arms for the future Phase III trial.

Table 2. Summary of JCOG9205

Treatment	5-FUci	FP	UFTM
Number of patients	105	105	70
Response rate (%)	11	34	9
Median PFS (days)	58	118	72
Median OS (days)	216	223	176
1-year survival rate (%)	28	29	16
2-year survival rate (%)	7	7	4

PFS, progression free survival; OS, overall survival.

JCOG9205

It was reported that combination chemotherapy consisting of 5-FU, ADM, and MMC did not show a survival advantage over 5-FU alone (25). Consequently, GIOSG conducted a three-arm Phase III [JCOG9205 (5)] trial comparing FP and UFTM with continuous infusion of 5-FU (5-FUci). As a

Table 3. Summary of JCOG9912

Treatment	5-FU	CPT-11 + CDDP	S-1
Number of patients	234	236	234
Response rate (%)	9	38	28
Median PFS (months)	2.9	4.8	4.2
Median TTF (months)	2.3	3.7	4.0
Median OS (months)	10.8	12.3	11.4

TTF, time to treatment failure.

result (Table 2), 280 patients were accrued for 4.5 years, and FP did not show significantly longer survival despite its higher response rate and longer progression-free survival, associated with more severe toxicities than 5-FUci. After intensive discussion about which regimen should be adopted for a control arm in the future trial, FP (global standard) or 5-FUci (winner in JCOG9205), it was concluded that 5-FUci would be a reference arm in the next Phase III trial from the point of overall survival (true endpoint of clinical trials).

JCOG9912

In late 1990s, new anti-tumor agents such as S-1, irinotecan (CPT-11), paclitaxel (PTX) and docetaxel (DTX) were developed and approved for gastric cancer in Japan. From the promising results of Phase II trials of CPT-11 plus CDDP (26) and S-1 (27,28), GIOSG planned a three-arm Phase III study [JCOG9912 (13)] to investigate superiority of CPT-11 plus CDDP and non-inferiority of S-1 compared with 5-FUci with the primary endpoint of overall survival. Seven hundred and four patients were accrued for 5 years. Table 3 summarizes the results of efficacy of JCOG9912. At the primary analysis in March 2007, 1 year after last patient accrual, S-1 showed non-inferiority to 5-FUci [hazard ratio (HR) 0.83, 95% confidence interval (CI) 0.68–1.01, $P < 0.001$ for non-inferiority], while CPT-11 plus CDDP could not show a survival benefit over 5-FUci (HR 0.85, 95% CI 0.70–1.04, $P = 0.055$ for non-inferiority). Additional analysis, 2 years after last patient accrual in May 2008, showed that CPT-11 plus CDDP showed an HR of 0.82 (95% CI 0.68–0.99, $P = 0.0194$), while an HR of S-1 was 0.83 (95% CI 0.68–1.00, $P = 0.0233$ for superiority). In conclusion, S-1 should be considered for the standard chemotherapy of advanced gastric cancer. Thus, S-1 can also replace 5-FUci. Based on the results of JCOG9912, SPIRITS (29) trial, conducted by a pharmaceutical company, which compared S-1 plus CDDP with S-1 showed a survival benefit of S-1 plus CDDP over S-1, leading to the establishment of a standard care for advanced gastric cancer in Japan.

From the present point of view, the quality of JCOG9205 was not so good as the recent clinical trials, JCOG9912 and thereafter, lacking in (i) peer review system of protocol drafts, (ii) central monitoring of case report forms by the data center and a trial office, and (iii) feedback to each investigator. The greatest problem was the speed of patient accrual. While 280 patients were enrolled for about 4.5 years (five patients monthly) in JCOG9205, 704 were for about 6 years (10 patients monthly) in JCOG9912. Actually, JCOG9912 was completed without major violation, including only one ineligible case. It can be said that the quality of the clinical trial in GIOSG was surely improved during JCOG9912.

TRANSLATIONAL RESEARCH

Personalized medicine is one of most important treatment strategies for advanced gastric cancer patients treated with not only molecular target agents but cytotoxic agents because gastric cancer shows very heterogeneous behaviors. GIOSG challenged to a translational research to find predictive marker for chemotherapy effects using the archived tissues of the patients enrolled to JCOG9001 (21), 9205 (22) and 9912 (23,24). The methods of evaluating chemosensitivity-related factors were initially limited to immunohistochemistry using formalin-fixed samples in JCOG9001 and 9205, and recently have progressed to laser-captured microdissection and real-time RT–PCR in JCOG9912. The explorative study along with a Phase II trial of FP (JCOG9001) showed that the number of favorable phenotypes out of five chemosensitivity factors, p53(−), bcl-2(−), vascular endothelial growth factor (VEGF)(+), glutathione *S*-transferase p(−) and thymidylate synthase(−), was a prognostic factor (21), and this result was recapitulated in the confirmative translational study of JCOG 9912 in which pretreatment biopsy were available in 131 of 210 (62%) patients allocated to 5-FUci or FP in the JCOG9205 trial (22). And it was also shown that FP showed a longer survival than 5-FUci among the VEGF(+) patients, while there was no difference in overall survival between the two arms among the VEGF(−) patients. These results suggested that multiple factors may be implicated to chemosensitivity and personalized medicine should be investigated in randomized trials. Then, pretreatment tumor tissue was available from 365 of 704 (52%) patients enrolled in JCOG9912 trial. It was suggested that dihydropyrimidine dehydrogenase might be a selective marker between CPT-11 plus CDDP and S-1 (23) and excision repair cross-complementing group 1 may be an independent prognostic factor for overall survival after first-line treatment of advanced gastric cancer (24).

COMBINED ANALYSIS OF JCOG9205 AND 9912

While both JCOG9205 (5) and 9912 (13) trials contained 5-FUci as control arms, their median overall survivals were 7.1 months in JCOG9205 and 10.8 months in JCOG9912. While about half of the patients received the second-line

chemotherapy in JCOG9205, more than 70% of the patients did in JCOG9912. It is speculated that the second-line chemotherapy might contribute to prolongation of advanced gastric cancer patients. After harmonizing the inclusion criteria of both trials and adjusting patient backgrounds, while time to treatment failure was almost similar (hard ratio, 0.95), overall survival (OS) and survival after treatment failure (OS-TTF) were better in JCOG9912 than JCOG9205 (HR; OS 0.71, 95% CI 0.56–0.99, OS-TTF 0.72, 95% CI 0.57–1.01) (30). Although survival benefit of the second-line chemotherapy for advanced gastric cancer has not been confirmed by randomized Phase III trials, these results suggest that the second-line chemotherapy with new agents approved in late 1990s such as CPT-11, PTX, and DTX might have contributed to the prolongation of the OS because there were no active drug for the second-line chemotherapy in the era of JCOG9205.

JCOG0106 AND 0407

Peritoneum is one of the common metastatic sites as well as liver and lymph nodes. The incidence of peritoneal metastasis is higher than 50% among patients with advanced gastric cancer. The prognosis of patients with severe peritoneal metastasis is considered to be poor because it causes various complications such as ascites, bowel obstruction and hydronephrosis, and deteriorates patient's general condition. Moreover, these patients usually do not have target lesions according to RECIST. For these reasons, patients with severe peritoneal metastasis are usually excluded from clinical trials. Thus, evidence from clinical trials can hardly be applied to these patients and the standard chemotherapy for them has not been established.

GIOSG challenged to the Phase III trial [JCOG0106 (14)] targeting to the patients with severe peritoneal metastasis, comparing sequential therapy of 5-FU and methotrexate (MTX) (MF) based on the results of JCOG9603 (8), in which massive ascites remarkably decreased in 13 out of 37 patients (35%) by MF therapy. In JCOG0106, a total of 237 patients were enrolled for 4.5 years, and MF could not show a survival benefit over 5-FUci [median survival time (MST); 5-FUci/MF 9.4/10.6 months, HR 0.94, 95% CI 0.72–1.22, $P = 0.31$].

Although not a few patients are complicated with severe peritoneal metastasis after failure in the first-line chemotherapy, the second-line chemotherapy is limited by patient's poor condition. Thus, GIOSG conducted a randomized Phase II trial [JCOG0407 (16)] comparing best available 5-FU with weekly administration of PTX for the patients with severe peritoneal metastasis in the second-line chemotherapy after failure in the first-line chemotherapy containing fluoropyrimidine. MST in each arm was the same, 7.7 months, and survival at 1 year was 31.4% in weekly PTX and 27.1% in best available 5-FU (HR = 0.887, 95% CI 0.571–1.377, $P = 0.298$), associated with less toxicity of PTX. Thus, JCOG0407 suggested activity and feasibility of weekly PTX for gastric cancer patients with severe peritoneal metastasis in the second line.

AT PRESENT

In 2006, Japanese guideline changed and requires a Phase III trial for approval of new anti-cancer agents. Before JCOG9912, new agents such as CPT-11 and S-1 had been approved only after completing Phase II trials, and JCOG could run a Phase III trial using these new agents to investigate survival benefit of these new drugs. Top 5 of 37 institutions in GIOSG enrolled more than half of the patients of JCOG9912, and top 10 institutions covered two-thirds of all. After JCOG9912, many industry-sponsored registration Phase III trials of new molecular target agents, such as trastuzumab, bevacizumab and cetuximab in the first line and lapatinib and everolimus in the second line, have been conducted globally, and some of top institutions with high activity in GIOSG have participated to them. This means leading institutions of GIOSG have contributed to both JCOG and registration trials. However, it was difficult to participate simultaneously both in JCOG trials and to registration trials, and actually there has been no clinical trial of chemotherapy for advanced gastric cancer since completion of JCOG0407 in 2008.

At present, GIOSG has been planning two Phase III trials. One is a trial of triplet chemotherapy which may cause severe hematological toxicity, investigating additional effects of DTX on S-1 plus CDDP, accompanied by translational research for personalized medicine. The other trial focuses on poor conditioned patients who cannot take even oral drugs or receive large volume hydration due to severe peritoneal metastasis with/without ascites, comparing weekly PTX

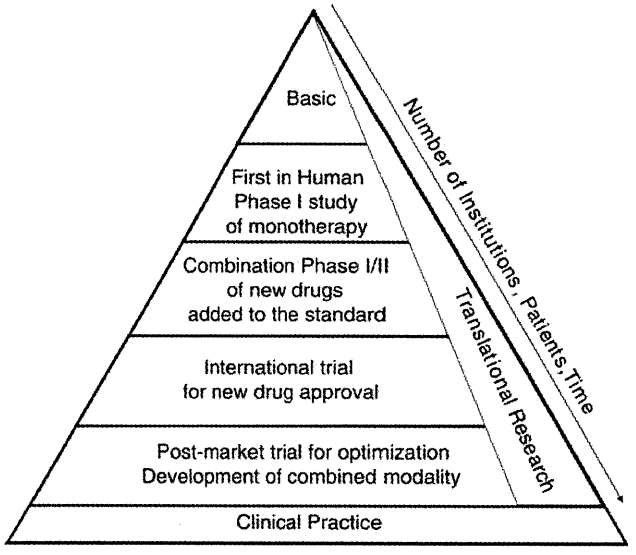

Figure 2. Step and role for progress in new drug development.

plus 5-FU/leucovorin with 5-FU/leucovorin. It is planned that this study will be conducted in collaboration with WJOG. GIOSG have merged with Gastric Cancer Study Group as the SCSG from 2011. It is expected that the activity of SCSG will be increased by synergistic effects of collaboration between medical oncologists and surgeons.

FUTURE DIRECTION

It is well known that many steps from basic reach to Phase III trial for new drug approval. Furthermore, optimization of new drug is necessary to obtain better outcome in clinical practice such as multimodality treatment, treatment strategy covering all through clinical course and personalized medicine. All these steps are very important for progress in cancer treatment (Fig. 2). From the point of the roles shared with many other clinical trial groups, and pharmaceutical companies which are the main promoters of new drugs development, SCSG should recognize its own role. It is considered that the most important role of SCSG is to conduct a post-market trial for establishing new standard treatment in clinical practice, containing multimodality treatments, translational research, second-line chemotherapy and personalized medicine. Especially, because the recent indication of new drugs has been limited for 'unresectable or recurrent disease' and not for perioperative setting of resectable disease, SCSG consisting of both medical oncologist and surgeons should collaborate to conduct an investigator-initiated Phase III trial for expanding the indication of new drugs to perioperative chemotherapy (e.g. herceptin in the adjuvant setting for Her-2-positive gastric cancer) in the near future. Finally, the future trials should be large scale and focus on optimization of new drugs in multimodality treatments. Thus, collaboration with the other clinical trial groups, pharmaceutical companies and government, not only in Japan but in the global, will be dispensable. In conclusion, SCSG should make efforts to conduct clinical trials with high quality for new standard treatment.

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Conflict of interest statement

None declared.

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ORIGINAL ARTICLE

Comparison of safety and efficacy of S-1 monotherapy and S-1 plus cisplatin therapy in elderly patients with advanced gastric cancer

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Abstract
Background Although S-1 plus cisplatin (SP) therapy is recognized as the standard treatment for advanced gastric cancer (AGC) in Japan, its safety and efficacy in elderly patients have not been investigated sufficiently.
Methods We retrospectively reviewed the data of 58 patients with AGC selected from 82 consecutive patients who were ≥70 years old and were treated with SP or S-1 monotherapy as the first-line therapy. In SP, S-1 (40 mg/m^2, bid) was administered for 3 weeks and cisplatin (60 mg/m^2) on day 8, every 5 weeks. In S-1 monotherapy, S-1 (40 mg/m^2, bid) was administered for 4 weeks, every 6 weeks.
Results SP and S-1 was administered in 21 and 37 patients, respectively. There were some differences in patient characteristics between the treatment groups, such as histological type ($P = 0.16$); the presence of liver metastasis ($P = 0.07$); and the presence of peritoneal metastasis ($P = 0.02$). The incidences of grade 3/4 hematological toxicities were 57% (12/21) in the SP and 35% (13/37) in the S-1 group ($P = 0.17$). Those of non-hematological toxicities were 14% (3/21) and 14% (5/37) for anorexia, 10% (2/21) and 14% (5/37) for fatigue, and 5% (1/21) and 5% (2/37) for nausea in the SP and S-1 groups, respectively. Median progression-free survival and median overall survival in the SP and S-1 groups were 5.0 and 5.2 months, and 14.4 and 10.9 months, respectively.
Conclusion SP and S-1 therapy were both feasible in elderly patients, though there is the risk of a high incidence of hematological toxicities.

Keywords S-1 · Cisplatin · Elderly · Feasibility · Efficacy

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Introduction

With more than 800,000 new cases per year reported globally, gastric cancer is the second most common cause of cancer death [1, 2]. Systemic chemotherapy prolongs survival and improves quality of life in patients with advanced gastric cancer (AGC), compared to the best supportive care provided alone [3–5]. In Japan, the combination chemotherapy of S-1 plus cisplatin (SP) is recognized as a standard treatment for AGC from the results of pivotal phase III studies [6–8].

The population of elderly patients is increasing rapidly all over the world, and age is the most significant risk factor for the survival of various kinds of cancer patients [9]. However, it is uncertain whether evidence on the safety and efficacy of treatments from clinical trials is also

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applicable to patients who are 70 years or older, because the proportion of elderly patients included in most clinical trials is small: patients over 70 years old accounted for less than 25% in the Japan Clinical Oncology Group (JCOG) 9912 trial [6] and only 17% in the S-1 plus cisplatin versus S-1 alone for first-line treatment of AGC (SPIRITS) trial, which compared SP therapy to S-1 monotherapy alone [7]. The subset analysis of the SPIRITS trial showed that the hazard ratio for overall survival in elderly patients between 70 and 74 years old was 0.95, while that in the whole study population was 0.77. Therefore, a different treatment strategy might be necessary for elderly cancer patients.

In the present single-institution retrospective study, we assessed the safety and efficacy of SP therapy and S-1 monotherapy in elderly patients with AGC.

Materials and methods

Patients

The subjects of this study were patients with unresectable or recurrent gastric cancer who received SP therapy or S-1 monotherapy at the Shizuoka Cancer Center between September 2002 and March 2008. The patient selection criteria were as follows: age 70 years or older; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2; histologically proven adenocarcinoma; absence of history of prior chemotherapy; adequate oral intake; adequate bone marrow, renal, and hepatic functions (absolute neutrophil count of 1,500/μl or more, platelet count 10,000/μl or more, serum creatinine of 1.5 mg/dl or less, serum transaminase levels less than 100 IU/l or less than 200 IU/l if hepatic metastasis existed); presence of at least one non-curative factor other than positive peritoneal washing cytology; and absence of concomitant malignancy. A measurable lesion was not mandatory.

Treatment dose and schedule

In SP therapy, S-1 was administered orally at a dose of 40 mg/m^2 bid on day 1 through day 21 followed by 14 days of rest, with cisplatin 60 mg/m^2 being administered intravenously on day 8. This regimen was repeated every 35 days until detection of disease progression, appearance of unacceptable toxicities, or the patient's refusal to continue treatment. In S-1 monotherapy, S-1 40 mg/m^2 bid was administered on day 1 through day 28, followed by 14 days of rest, until any of the above-mentioned events occurred. In each treatment group, the dose of S-1 was determined according to the body surface area (BSA), as follows: 40 mg bid for BSA less than 1.25 m^2; 50 mg bid for BSA 1.25–1.5 m^2; 60 mg bid for BSA over 1.5 m^2.

These treatments were administered according to standard clinical practice. All physicians generally adhered to the following treatment modification criteria. If a grade 3 or higher adverse event, grade 2 increase of creatinine, or grade 2 infection occurred, treatment was suspended during the cycle or the start of the subsequent cycle was delayed until recovery of non-hematological toxicities grade 1 or lower, the neutrophil count reached more than 1,500/μl, and the platelet count reached more than 7.5 × 10^4/l. The dose of S-1 and cisplatin was reduced if any of the following adverse drug reactions occurred during the previous cycle: grade 4 leukocytopenia, anemia, or thrombocytopenia; or grade 3 or higher non-hematological toxicities.

Efficacy and toxicity evaluation

We retrospectively obtained all the clinical data from the medical records. Physical examinations and laboratory tests were repeated at least once every 3 weeks. Data on adverse events were collected until 30 days from the last administration or initiation of the subsequent chemotherapy, whichever occurred earlier. We evaluated adverse events on the basis of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Response evaluation was repeated at least once every 2 months. Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0.

Statistical analysis

Differences in the distribution of variables were evaluated using the Fisher exact test or Mann–Whitney *U* test, as appropriate. Patients who did not have a target lesion were excluded from the response analysis.

Overall survival (OS) was defined as the period from the date of the first administration of S-1 to the date of death from any cause or to the last date of confirmation that the patient was alive in the census. Progression-free survival (PFS) was defined as the period from the date of the first administration of S-1 to the earliest date of detection of tumor progression by imaging, or symptomatic deterioration clinically judged to be caused by disease progression, or the last date that the patient was confirmed to be alive without disease progression in the census. Survival curves were drawn by the Kaplan–Meier method.

The following variables were examined in the univariate analysis of OS and PFS: treatment, age, sex, PS, presence of complications, prior gastrectomy, creatinine clearance, histological type, presence of target lesions, number of metastatic sites, presence of liver metastasis, peritoneal metastasis, and lymph node metastasis. Multivariate analysis included potentially predictive variables for the risk of

disease progression or death in univariate analysis. $P < 0.05$ was considered significant.

All statistical analyses were performed using Dr. SPSS II (SPSS Japan Inc., Japan). Written informed consent was obtained from all the patients before starting the chemotherapy.

Results

Patient characteristics

A total of 82 consecutive patients with gastric cancer who were 70 years or older received SP therapy or S-1 monotherapy between September 2002 and March 2008 at the Shizuoka Cancer Center. Among them, 24 patients were excluded for the following reasons: absence of non-curative factor other than positive peritoneal washing cytology (10 patients), organ dysfunction (7 patients), absence of histological confirmation of adenocarcinoma (6 patients), and concomitant malignancy (1 patient). Therefore, 58 patients were included as subjects in this study; of them, 21 patients were treated with SP therapy and 37 were treated with S-1 monotherapy.

Patient characteristics are shown in Table 1. There were some differences in background between subjects in the SP and S-1 groups, such as histologically determined intestinal type (48 vs. 62%, respectively; $P = 0.16$); the presence of liver metastasis (57 vs. 32%, respectively; $P = 0.07$); and the presence of peritoneal metastasis (14 vs. 43%, respectively; $P = 0.02$).

Table 1 Patient backgrounds

	SP group	S-1 group	*P* value
Number of patients	21	37	
Age (years), median (range)	73 (70–82)	73 (70–80)	0.51
Age ≤75	17 (81%)	25 (68%)	0.27
Age >75	4 (19%)	12 (32%)	
Sex			0.97
Male	16 (76%)	28 (76%)	
Female	5 (24%)	9 (24%)	
ECOG performance status			0.78
0	7 (33%)	14 (38%)	
1	13 (62%)	21 (57%)	
2	1 (5%)	2 (5%)	
Complications			0.28
+	10 (48%)	23 (62%)	
−	11 (52%)	14 (38%)	
Prior gastrectomy			0.82
+	9 (43%)	17 (46%)	
−	12 (57%)	20 (54%)	
Creatinine clearance			0.60
Median (range) (ml/min)	63.2 (40–125.8)	63.9 (35.9–98.7)	
Histological type			0.16
Intestinal	10 (48%)	23 (62%)	
Diffuse	11 (52%)	14 (38%)	
Tumor status			0.22
Metastatic	14 (67%)	30 (81%)	
Recurrent	7 (33%)	7 (19%)	
Metastatic sites			
Liver	12 (57%)	12 (32%)	0.07
Peritoneum	3 (14%)	16 (43%)	0.02
Lymph node	14 (66%)	21 (57%)	0.46
Target lesions			0.65
+	18 (86%)	30 (81%)	
−	3 (14%)	7 (19%)	
Number of metastatic sites			0.64
0	1 (5%)	0 (0%)	
1	7 (33%)	13 (35%)	
2	11 (52%)	19 (51%)	
≥3	2 (10%)	5 (14%)	

Exposure to treatment

The median number of treatment cycles for SP was 3 (range 1–8) and for S-1 was 4 (range 1–18). Treatment modification was required in 11 SP patients (52%) and in 21 S-1 patients (57%) as follows: dose reduction in 3 patients (14%) and in 14 patients (38%), and delay of the subsequent cycle in 9 patients (43%) and in 14 patients (38%), respectively. Both dose reduction and subsequent cycle delay were required in 1 SP patient and in 7 S-1 patients. The median relative dose intensity per patient of S-1 and cisplatin was 80% (range 42–96%) and 82% (range 55–100%), respectively, in the SP group, and that of S-1 was 86% (range 54–100%) in the S-1 group. The main reason for treatment failure was disease progression in both treatment arms: 76% in SP and 92% in S-1 groups. In addition, 19% of patients in the SP group stopped treatment because of adverse events.

Adverse events

The adverse events are shown in Table 2. The incidences of grade 3 or higher hematological toxicities were greater in the SP group (12/21: 57%) than in the S-1 group (13/37: 35%), although the difference was not statistically significant ($P = 0.10$). Incidences of specific hematological toxicities for the SP and S-1 groups were 33% (7/21) and 5% (2/37) for neutropenia, 43% (9/21) and 32% (12/37) for anemia, and 19% (4/21) and 0% (0/37) for thrombocytopenia, respectively. The incidence of grade 3 or higher

non-hematological toxicities was similar in both treatment groups: 14% (3/21) and 14% (5/37) for anorexia, 10% (2/21) and 14% (5/37) for fatigue, and 5% (1/21) and 5% (2/37) for nausea in the SP and S-1 groups, respectively. The median creatinine clearance calculated by the Cockcroft–Gault equation was 53.4 and 56.0 ml/min, respectively, in the 10 patients of SP and 14 of S-1 who experienced grade 3 or 4 toxicity (excluding that of anemia). The median creatinine clearance was 64.1 and 66.8 ml/min in patients who did not experience grade 3 or 4 toxicity in the SP and S-1 groups, respectively.

One patient from each treatment group died within 30 days of the last administration of chemotherapy. One was a 74-year-old man from the SP group, who started S-1 at the standard dose after palliative total gastrectomy. After administration of cisplatin on day 8, he received hydration therapy from day 11 to 14 for the treatment of anorexia (grade 2) and diarrhea (grade 1). After recovering from these symptoms, he was discharged from the hospital on day 15. On day 18, he suffered from diarrhea again, and was admitted to another hospital. Despite intensive care, he died on day 27 because of arrythmia. In this case, the possibility of treatment-related death could not be excluded, because dehydration due to severe diarrhea might have caused the arrythmia. The other patient from the S-1 group was a 74-year-old man who presented after gastrojejunostomy for obstruction due to the primary tumor. He received the standard dose of S-1, and visited our hospital on days 15 and 29 in the first cycle without any serious adverse events. However, he was found dead at home on day 38. He had no specific concomitant disease except mild hypertension. The cause of death was diagnosed as acute heart failure, and it is possible that S-1 contributed to his death.

Table 3 Response in patients with target lesions

	SP group ($n = 18$)	S-1 group ($n = 30$)
Best overall response		
CR	1	2
PR	8	12
SD	3	8
PD	6	7
NE	0	1
Response proportion (%)	50.0	46.7

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluated

Response and survival

Eighteen patients in the SP group and 30 in the S-1 group had measurable lesions. The objective response rate was 9/18 (50.0%) in the SP group and 14/30 (46.7%) in the S-1 group. Among the responders, complete response was obtained in one patient in the SP group and 2 in the S-1 group (Table 3).

Twenty-one patients in the SP group and 37 in the S-1 group were involved in the PFS and OS analysis. The curves of PFS and OS for the SP and S-1 groups almost overlapped (Figs. 1, 2). The median PFS was 5.0 months in the SP group and 5.2 months in the S-1 group [hazard ratio (HR): 1.18, 95% confidence interval (CI): 0.68–2.06]. The median survival time (MST) was 14.4 months in the SP group and 10.9 months in S-1 (HR: 0.99, 95% CI: 0.57–1.71). The proportion of patients who received subsequent chemotherapy was similar in the SP and S-1 groups: 62% (13/21) and 65% (24/37), respectively.

Table 2 Adverse events

	SP group ($n = 21$)				S-1 group ($n = 37$)			
	G1/2	G3	G4	≥G3 (%)	G1/2	G3	G4	≥G3 (%)
Hematological								
Leukocytopenia	8	5	1	29	16	1	0	3
Neutropenia	7	5	2	33	8	2	0	5
Anemia	12	5	4	43	24	12	0	32
Thrombocytopenia	12	3	1	19	8	0	0	0
Non-hematological								
Febrile neutropenia	–	0	0	0	–	0	0	0
Fatigue	10	1	1	10	16	5	0	14
Anorexia	16	2	1	14	18	5	0	14
Diarrhea	5	1	0	5	12	0	0	0
Stomatitis	4	0	0	0	13	1	0	3
Nausea	11	1	0	5	9	2	0	5
Vomiting	2	0	0	0	6	0	0	0

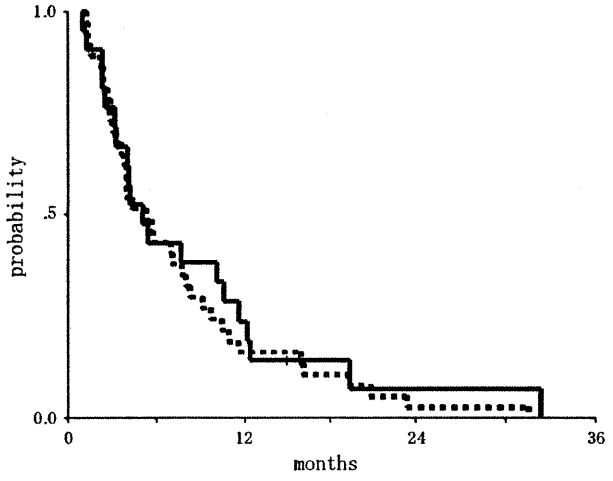

Fig. 1 Progression-free survival (PFS). The median PFS was 5.0 months in the SP group ($n = 21$, *solid line*) and 5.2 months in the S-1 group ($n = 37$, *dotted line*). The hazard ratio was 1.18, and the 95% confidence interval was 0.68–2.06

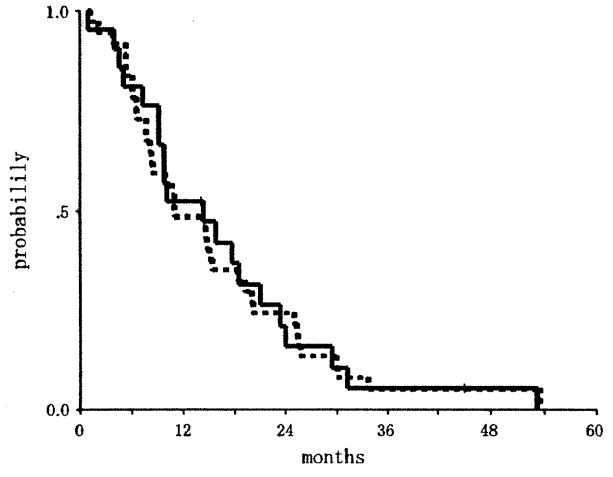

Fig. 2 Overall survival (OS). The median survival time was 14.4 months in the SP group ($n = 21$, *solid line*), and 10.9 months in the S-1 group ($n = 37$, *dotted line*). The hazard ratio was 0.99, and the 95% confidence interval was 0.57–1.71

Multivariate analysis showed that poor PS was the only factor associated with shorter OS (HR: 2.12, 95% CI: 1.37–3.26, $P = 0.001$) among the three potentially predictive variables selected by univariate analysis (age, PS, presence of peritoneal metastasis), while there was no predictive variable for PFS.

Discussion

Following the results of pivotal phase III trials, SP therapy is considered the standard chemotherapy in patients with unresectable or recurrent gastric cancer in Japan [6–8]. In the SPIRITS trial, the survival benefit of SP therapy over S-1 monotherapy was demonstrated with acceptable toxicity levels; however, the subset analysis showed that the hazard ratio in patients who were 70 years or older was 0.95 (95% CI: 0.71–1.27) [7]. However, because the subset analysis contained only 50 patients (17%) who were 70 years or older, there is uncertainty about the superiority of SP therapy over S-1 monotherapy in elderly patients with AGC. Thus, further investigation of SP therapy and S-1 monotherapy in elderly gastric cancer patients is necessary.

Because this study was retrospective, patient backgrounds between the two groups were not well balanced. In the S-1 group, the proportion of patients with peritoneal metastasis was significantly higher than in the SP group. Peritoneal metastasis is generally considered to be one of the unfavorable factors relating to shorter survival time in AGC; the patients included in the prognostic model had radiologically evident peritoneal metastasis or massive ascites [10]. In contrast, in the subset analysis of the JCOG 9912 trial, excluding the patients with severe peritoneal metastasis, patients without measurable lesions, mainly those with mild peritoneal metastasis, survived longer than those with measurable lesions [6]. Furthermore, in a randomized phase II study comparing S-1 and capecitabine, for which eligibility criteria included adequate oral intake, peritoneal metastasis was not a prognostic factor for OS [11]. Therefore, controversy exists over whether or not peritoneal metastasis is a prognostic factor in AGC. In our study, peritoneal metastasis was diagnosed in 10 out of 16 patients in the S-1 group and in 1 out of 3 patients in the SP group by laparotomy, not by radiological assessment. Because all patients had adequate oral intake, the peritoneal metastasis of most patients in this study was not so severe (only one patient had massive ascites), and therefore we consider that the presence or absence of peritoneal metastasis may not have had a major impact on survival. In the present study, the response rates in the SP and S-1 groups were 50.0 and 46.7%, respectively, and MST was 14.4 and 10.9 months, respectively. Though MST seemed longer in the SP group, the Kaplan–Meier curves of both treatment groups almost overlapped, and the hazard ratio was 0.98 (95% CI: 0.57–1.69). This hazard ratio of SP therapy over S-1 monotherapy was very similar to that of the subset analysis of elderly patients in the SPIRITS trial [7].

The relative dose intensity in the SP and S-1 groups was over 80% for each drug. Dose reduction was required in 14% of SP group subjects and 38% of S-1 group subjects. Though there was a higher incidence of grade 3 or 4 hematological toxicities in the SP group than the S-1 group, only one patient of SP needed dose reduction because of hematological toxicity. Most dose modifications were required because of non-hematological toxicities, the incidences of which were similar between the SP group and

Table 4 The incidence of grade 3 or 4 adverse events (%)

	Present study		SPIRITS trial	
	SP group ($n = 21$)	S-1 group ($n = 37$)	SP group ($n = 148$)	S-1 group ($n = 150$)
Hematological				
Leukocytopenia	28.6	2.7	11	2
Neutropenia	33.3	5.4	40	11
Anemia	42.9	32.4	26	4
Thrombocytopenia	19.0	0	5	0
Non-hematological				
Febrile neutropenia	0	0	3	1
Fatigue	9.5	13.5	4	1
Anorexia	14.3	13.5	30	6
Diarrhea	4.8	0	4	3
Stomatitis	0	2.7	0.7	0
Nausea	4.8	5.4	11	1
Vomiting	0	0	4	2

the S-1 group. Chemotherapy in both treatment groups was discontinued due to disease progression in many patients. It was evident that both treatments were feasible even in elderly patients.

The incidence of grade 3 or higher adverse events in the present study was more frequent than in the SPIRITS trial (Table 4), which could possibly be attributed to decreased creatinine clearance. In this study, patients with poor renal function experienced more severe adverse events. The pharmacokinetics of S-1 are dependent on renal function because 5-chloro-2,4-dihydroxypyridine, which is an inhibitor of dihydropyrimidine dehydrogenase [12–17], is eliminated through the kidneys. Organ functions, including renal function in the elderly, are likely to be somewhat impaired, and it has been reported that the glomerular filtration rate generally decreases with age [18]. The decreased creatinine clearance might lead to more frequent and severe toxicities associated with S-1, especially in elderly patients. Therefore, it is necessary to consider renal function before starting S-1-based chemotherapy, especially in elderly patients.

In geriatric oncology, neither the Karnofsky Performance Scale Index nor ECOG PS may be reliable for assessing physical status because comorbidities in elderly patients might affect their physical or mental status [19]. It has been reported that assessment of the condition of elderly cancer patients measured by comprehensive geriatric assessment (CGA) is useful for predicting tolerance to chemotherapy and survival [20–22]. CGA is a multidimensional evaluation scale of an elderly patient's physical performance, comorbidity, cognition, psychological stage, socioeconomic status, nutritional status, and medications [23, 24]. In some clinical trials targeting elderly cancer patients, functional assessment scales were adopted for patient selection in addition to PS and organ function assessments [25, 26]. In this study, PS was the only factor associated with survival. In addition, CGA might interfere with measurement of PS, as demonstrated in previous studies [20, 24, 27]. Thus it is suggested that CGA might also affect the clinical outcomes, especially the survival rates, of gastric cancer patients treated with chemotherapy.

In conclusion, SP therapy and S-1 monotherapy were both feasible in elderly patients with AGC, though the superiority of SP therapy over S-1 monotherapy was not so prominent in this review. Further clinical trials are warranted to establish a new standard care, especially in elderly gastric cancer patients.

Conflict of interest No author has any conflict of interest.

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ORIGINAL ARTICLE

Leptomeningeal carcinomatosis associated with gastric cancer

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Abstract
Background Leptomeningeal carcinomatosis (LMC) is a rare but devastating complication of gastric cancer.
Methods The subjects were 12 gastric cancer patients who were diagnosed as having LMC at the Shizuoka Cancer Center between October 2002 and March 2009. We conducted a retrospective survey of the medical records of the study subjects and collected data on the clinical features, treatment modalities employed/outcomes, and survival of the patients.
Results Of the 12 patients, 9 (75%) were male, and the median age was 63 years. Histopathologically, the majority of the patients (83%) had diffuse-type adenocarcinoma. At the time of diagnosis of the LMC, the other major sites of metastasis were the peritoneum (75%) and lymph nodes (50%). The median duration from the diagnosis of gastric cancer to the diagnosis of LMC was 15.6 months. While the treatment strategy changed with time, intrathecal chemotherapy ($n = 10$), followed by whole brain irradiation ($n = 7$) and subsequent ventriculo-peritoneal shunt ($n = 3$) was performed in 10 of the patients. Improvement of neurological functions was observed in 6 of the 10 patients. The median overall survival time from the diagnosis of LMC in all the 12 patients was 60 days. One patient survived for a considerably long period of 532 days.
Conclusions Multidisciplinary treatment, including ventriculo-peritoneal shunt for LMC secondary to gastric cancer, may benefit selected patients, but further accumulation of clinical cases is necessary.

Keywords Gastric cancer · Leptomeningeal carcinomatosis · Intrathecal methotrexate therapy · Whole brain irradiation · Ventriculo-peritoneal shunt

Introduction

Leptomeningeal carcinomatosis (LMC) complicating solid tumors is most often seen in patients with breast and lung cancer and melanoma, and it is a rare complication in patients with gastric cancer. While LMC is reportedly diagnosed clinically in 2–4% of all cancer patients [1], the prevalence of LMC in gastric cancer patients is as low as 0.14–0.24% [2–4]. However, irrespective of the primary site of cancer, LMC is a devastating complication. There have only been a few reports of LMC complicating gastric cancer.

No standard therapy for LMC has yet been established. The poor general condition of patients with LMC, especially in the presence of consciousness disturbance associated with hydrocephalus, convulsions, etc., makes satisfactory treatment of LMC very difficult. On the other hand, the prognosis of the condition is extremely poor

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without treatment. Recently, the efficacy of multidisciplinary treatment for LMC associated with breast and lung cancer, such as intrathecal chemotherapy (ITC) with methotrexate, cytarabine or liposomal cytarabine [5–7], whole-brain irradiation (WBI) [8] and ventriculo-peritoneal shunt (VP shunt) [9], has been reported. However, there are currently no published reports of case series of LMC complicating gastric cancer.

At the Shizuoka Cancer Center, the treatment for gastric LMC has changed with time. ITC alone was administered initially, followed subsequently by the addition initially of WBI, and then more recently of VP shunt performed by neurosurgeons, when indicated, to control the cerebrospinal fluid pressure.

We have encountered some cases of LMC complicating the clinical course in patients with gastric cancer. In the present retrospective study, we report on the clinical features of gastric LMC and also on the outcomes of treatment for LMC secondary to gastric cancer.

Subjects and methods

The subjects were 12 gastric cancer patients who were diagnosed as having LMC at the Shizuoka Cancer Center between October 2002 and March 2009, and were selected for this study on the basis of the following inclusion criteria: (1) histologically confirmed gastric cancer; (2) LMC confirmed by cerebrospinal fluid (CSF) cytology and/or by magnetic resonance imaging (MRI); (3) no history of other/concurrent malignancies. Patients with LMC caused by direct meningeal invasion from the skull base were excluded. We conducted a retrospective survey of the medical records of the subjects to collect data on the clinical features, treatment modalities employed/outcomes, and survival of the patients.

We administered intraventricular injections of methotrexate at 2 mg/body with prednisolone at 10 mg for 5 consecutive days in all the patients who met the following criteria: (1) age $\leq$75 years; (2) no bleeding tendency; (3) no rapid progression of the lesions other than LMC. Initially, for the first three patients, we undertook no additional therapy after the intraventricular injection of methotrexate. Subsequently, for the next 7 patients who had no previous history of WBI, we added WBI at a total dose of 30 Gy, administered in 10 fractions. For the last three patients, we also performed VP shunt after completion of the WBI. The indication for VP shunt was determined based on the following criteria: (1) improvement of clinical symptoms such as headache, vomiting, and consciousness disturbance after drainage of CSF by a subcutaneous reservoir or lumbar puncture; (2) Radiation Therapy Oncology Group Neurologic Functional Classification (RTOG-NFC) of $\leq$3 (Table 1) [10]; (3) low or moderate cell counts and protein level in the CSF, associated with a reduced risk of shunt obstruction.

Table 1 Radiation Therapy Oncology Group neurologic function classification

RTOG neurologic function classification	Description
1	Able to work or perform normal activities; neurologic findings minor or absent
2	Able to carry out normal activity with minimal difficulties; neurologic impairment does not require nursing care or hospitalization
3	Seriously limited in performing normal activities; requiring nursing care or hospitalization; patients confined to bed or wheelchair or have significant intellectual impairment
4	Unable to perform even minimal normal activities; requiring hospitalization and constant nursing care feeding; Patients unable to communicate or in coma

Statistical analysis

The clinical course from the diagnosis of gastric cancer was counted from the date of the initial endoscopy confirming gastric cancer or, in the two cases for whom the date of the initial endoscopy was not available, the date of surgical resection. Overall survival was calculated from the date of diagnosis of the LMC by CSF cytology or MRI to the date of death. The median overall survival was calculated by the Kaplan–Meier method, using StatView software, version 5.0.0 (SAS Institute, Cary, NC, USA).

Results

Patients' characteristics

Between October 2002 and March 2009, 14 gastric cancer patients were diagnosed as having LMC. Two of these patients with direct meningeal invasion from a skull base metastasis were excluded. The remaining 12 patients were enrolled as the subjects of this retrospective study.

The characteristics of the subjects are shown in Table 2. Of the 12 patients, 9 (75%) were male, and the median age was 63 years old (range 30–73 years). All patients had neurological symptoms caused by the LMC, and nine patients (75%) had a poor RTOG-NFC of 3 or 4 (Table 1) [10]. All but one patient had diffuse type adenocarcinoma or small cell carcinoma. At the time of diagnosis of the