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Phase II Clinical Trial of Postoperative S-1 Monotherapy for Gastric Cancer Patients with Free Intraperitoneal Cancer Cells Detected by Real-Time RT-PCR

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Abstract
Background We have previously reported the molecular detection of peritoneal micrometastases in patients with gastric cancer by quantifying carcinoembryonic antigen (CEA) mRNA in the peritoneal washes. Patients with CEA mRNA exceeding a cutoff value have a significant risk for developing peritoneal carcinomatosis, but optimal treatment for this population remains unknown.
Methods CEA mRNA (+) patients with gastric cancer were treated postoperatively with S-1 monotherapy. Overall survival, the primary endpoint of this phase II trial, was compared with the historical control, which is comprised of CEA mRNA (+) patients who were not given postoperative chemotherapy.
Results A total of 32 patients with CEA mRNA (+) gastric cancer were enrolled. Twelve patients (37.5%) relapsed; ten showed peritoneal relapse. Three-year survival was similar between the study population and the historical control (67.3% vs. 67.1%, respectively).
Conclusions S-1 monotherapy, which significantly reduced risk for recurrence in stage II/III gastric carcinoma in another phase III trial, seems not to be as effective in eradicating free cancer cells in the abdominal cavity.

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Gastric cancer is the second-most common cause of cancer death worldwide, and peritoneal carcinomatosis represents the most common route of tumor dissemination in patients with this disease [1–3]. This pathology is most likely caused by the presence of metastatic free cancer cells exfoliated from serosal surfaces of the primary cancer. We previously reported the detection of peritoneal micrometastases by reverse-transcriptase polymerase chain reaction (RT-PCR) analysis of peritoneal wash samples using carcinoembryonic antigen (CEA) mRNA as a target [3–7]. In these studies, CEA mRNA values correlated with depth of tumor invasion (pT category), and both overall survival and survival free from peritoneal relapse were significantly inferior among the CEA mRNA (+) patients. Several experimental studies have shown that micrometastases are more sensitive to chemotherapy compared with macrometastases [8–10]. Accordingly, micrometastasis detected by CEA RT-PCR could represent an important target of therapy.

Meta-analyses have suggested that adjuvant chemotherapy is effective in treating gastric cancer, but no definitive conclusion had been reached in the early 2000s regarding the efficacy of postoperative adjuvant chemotherapy for gastric-cancer patients treated with D2-lymphadenectomy [11]. S-1 (Taiho Pharmaceutical, Tokyo, Japan) is an orally active combination of tegafur (a prodrug converted by cells into fluorouracil), gimeracil (an inhibitor of dihydropyrimidine dehydrogenase, which degrades fluorouracil), and oteracil (which inhibits phosphorylation of

fluorouracil in the gastrointestinal tract, thereby reducing gastrointestinal toxic effects of fluorouracil) in a molar ratio of 1:0.4:1 [12]. Response rates for S-1 monotherapy exceeded 40% in two late phase II trials, which involved patients with advanced or recurrent gastric cancer [13, 14]. Toxicity profile was moderate, and use in the postoperative adjuvant setting was considered feasible [15]. We therefore initiated a phase II trial of postoperative S-1 therapy for patients with CEA mRNA (+) gastric cancer.

A total of 32 patients with CEA mRNA(+) gastric cancer had been enrolled by the middle of 2006, when postoperative S-1 therapy was shown to improve significantly the prognosis for patients with stage II/III gastric cancer compared with observation alone in a pivotal phase III study [16]. Because most CEA mRNA (+) patients would have been categorized as stage II/III if RT-PCR had not been performed and would thus be treated by S-1 anyway, the trial was closed and survival data were analyzed after all patients had been followed for 12 months or more.

Patients and methods

Eligibility criteria

Patients entered into this study were required to fulfill the following eligibility criteria: (1) previously untreated patients with histologically proven adenocarcinoma; (2) between 20 and 80 years old; (3) Eastern Cooperative Oncology Group performance status (PS) of 2 or less; (4) treated with R0 resection of the primary lesion, and showing no distant or peritoneal metastases on preoperative imaging or at laparotomy; (5) no tumor cells in peritoneal fluid on routine cytological examination through Papanicolaou staining; (6) positive free cancer cells in the abdominal cavity detected through CEA RT-PCR; (7) adequate organ function (leukocyte count 3,000/mm^3; platelet count 100,000/mm^3; hemoglobin 8.0 g/dl; total bilirubin 1.5 mg/dl; aspartate aminotransferase and alanine aminotransferase levels 2.5 times the upper limit of the normal range; and serum creatinine no greater than the upper limit of the normal range); and (8) life expectancy >3 months. Written informed consent was obtained from all patients, and the study protocol was approved by the institutional review board.

Peritoneal washing

Aliquots of 100–200 ml of saline were introduced into the Douglas cavity and left subphrenic space at the beginning of each operation and aspirated shortly after gentle agitation. Half of each wash was sent for routine cytopathology with conventional Papanicolaou staining and the other half was used to measure CEA mRNA levels. Intact cells collected from washes by centrifugation at 1,800 rpm for 5 min were rinsed with phosphate-buffered saline (PBS), dissolved in ISOGEN-LS RNA extraction buffer (Nippon Gene, Tokyo, Japan), and stored at −80°C.

Real-time quantitative RT-PCR

Frozen samples in ISOGEN-LS were thawed and total RNA was extracted using guanidinium isothiocyanate–phenol–chloroform, then cDNA was synthesized from total RNA using SuperScript II RNase H$^-$ reverse transcriptase (Invitrogen, Carlsbad, CA, USA) according to the instructions of the manufacturer. The resultant first-strand cDNA was stored at −80°C until analysis. Single-step real-time RT-PCR for CEA mRNA was performed using CEA-specific oligonucleotide primers and two fluorescent hybridization probes on a LightCycler instrument (Roche Diagnostics, Mannheim, Germany), as described previously [5, 7]. To quantify and confirm the integrity of the isolated RNA, glyceraldehyde-3-phosphate dehydrogenase (GAPDH) also was analyzed by real-time RT-PCR using the appropriate primers and hybridization probes. All primers and probes were synthesized and purified by reverse-phase high-performance liquid chromatography at Nihon Gene Research Laboratories (Sendai, Japan). Six external CEA mRNA standards were prepared by tenfold serial dilution (1–10^5 cells) of cDNA equivalent to 1×10^6 COLM-2 cells (a colon cancer cell line that expresses large amounts of CEA) spiked into 1×10^7 peripheral blood leukocyte. Each run comprised six external standards, a negative control without a template, and patient samples with unknown mRNA concentrations. The amount of mRNA in each sample was then automatically measured by reference to the standard curve constructed each time on the LightCycler software. CEA mRNA was quantified in each patient using the peritoneal washing samples from Douglas cavity and subphrenic space. If at least one CEA mRNA value from the two washes was above the cutoff value (>0.1), the patient was considered as CEA mRNA (+). The cutoff value had been selected by the authors to maximize the sensitivity for detection of peritoneal micrometastasis. This cutoff value was then validated using an independent set of patients in the previous study [4].

Study design and treatment

The primary endpoint of the trial was overall survival, and secondary endpoints were peritoneal recurrence-free survival and the safety profile of S-1. Patients were to receive two oral doses of S-1 at 40 mg/m^2 per day for 4 weeks, followed by 2 weeks of no chemotherapy. This 6-week cycle was to be repeated throughout the first year after

surgery and was to be evaluated as effective if 3-year survival was shown to be higher than that of historical controls. The historical control was comprised of 58 patients who had CEA mRNA >0.1 at Aichi Cancer Center between 1995 and 2000 and were given no postoperative adjuvant chemotherapy. The sample size was calculated as 40 to confirm that the lower limit of the 95% confidence interval (CI) for 3-year survival among the study population exceed 65%, which is the 3-year survival proportion for historical control. The survival curve was estimated using Kaplan–Meier methods. Patients were to be followed up for 3 years postoperatively. Differences between curves were evaluated by log-rank testing. Adverse events were assessed according to the Common Toxicity Criteria of the National Cancer Institute (version 2.0).

Postoperative surveillance

The follow-up program consisted of interim history, physical examination, hematology, and blood chemistry panels including tests for CEA and CA19-9, performed every 3 months for 2 years. Computed tomography was performed every 6 months. Peritoneal recurrence, evident on the basis of clinical symptoms, digital examination, and physical and radiologic findings of bowel obstruction and ascites, was confirmed by paracentesis, laparotomy, and autopsy performed at the discretion of the surgeon.

Results

Patient demographics

Thirty-two patients with gastric cancer with CEA mRNA (+) status (23 men, 9 women) who underwent R0 surgery were registered between September 2003 and April 2006 at Aichi Cancer Center Hospital. Median duration of follow-up was 31.5 months after surgery (minimum 16.2 months, and maximum 51.4 months). Characteristics of the 32 patients with CEA mRNA (+) gastric cancer are summarized in Table 1. Mean age was 57.8 years (minimum 35 years, and maximum 75 years). Serosal invasion and lymph node metastasis was observed in 24 patients (75%) and 23 patients (71.9%), respectively. T1-stage patients and macroscopic type 0 (gross finding suggestive of early stage cancer) were more frequent among the control group, but other characteristics showed similar distributions.

Table 1 Baseline characteristics of the patients

	S-1 adjuvant ($n = 32$)	Control ($n = 58$)	P value
Age (year)	57.8	58.4	0.83
Gender			
M	23	39	0.81
F	9	19	
Location			
L	11	16	0.07
M	18	24	
U	3	18	
Macroscopic type			
0	1	15	0.01
1	2	0	
2	5	12	
3	19	19	
4	5	12	
Operative procedure			
Total	9	25	0.23
Proximal	0	1	
Distal	23	32	
Lymph node dissection			
≤D1	2	3	NS
≥D2	30	55	
Depth of invasion			
T1	1	15	<0.01
T2	7	13	
T3	23	20	
T4	1	10	
Lymph node metastases			
N0	9	18	0.25
N1	11	11	
N2	12	29	
Histological type			
pap	0	1	0.10
tub1	2	1	
tub2	5	16	
por1	3	5	
por2	20	27	
sig	0	7	
muc	0	1	
Other	2	0	

NS not significant, *pap* papillary adenocarcinoma, *tub1* well differentiated tubular adenocarcinoma, *tub2* moderately differentiated tubular adenocarcinoma, *por1* poorly differentiated adenocarcinoma solid type, *por2* poorly differentiated adenocarcinoma non-solid type, *sig* signet-ring cell carcinoma, *muc* mucinous adenocarcinoma

Overall survival and peritoneal recurrence-free survival

No significant difference in survival curves was identified between the study population and the historical control ($P = 0.46$; Fig. 1). Twelve patients (37.5%) relapsed, including 10 patients with peritoneal relapse (Table 2). Two-year survival proportion was 93.5% in the S-1 adjuvant chemotherapy group as opposed to 77.6% in the

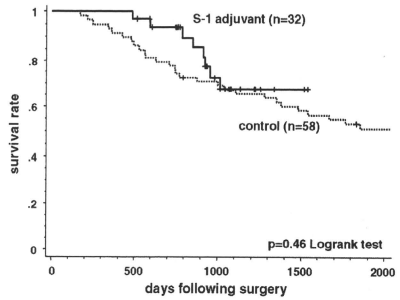

Fig. 1 Overall survival curve of patients with S-1 adjuvant therapy and historical controls. Three-year survival rates were comparable between groups. The difference in survival curves was not significant ($P = 0.46$; log-rank test)

Table 2 Site of first relapse, according to treatment group

Site	S-1 adjuvant ($n = 32$)		Control ($n = 58$)	
No. of relapses	12	(37.5%)	31	(53.4%)
Local	0	(0.0%)	4	(6.9%)
Lymph nodes	2	(6.3%)	14	(24.1%)
Peritoneum	10	(31.3%)	24	(41.4%)
Hematogenous	2	(6.3%)	7	(12.1%)

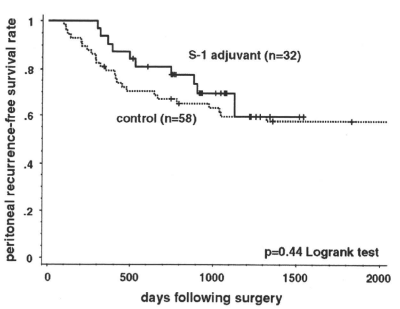

Fig. 2 Peritoneal recurrence-free survival curve of patients with S-1 adjuvant treatment and historical controls. Survival of the S-1 adjuvant group tended to be slightly favorable, but this was not significant ($P = 0.44$; log-rank test)

historical control group, but the difference was nullified by 3 years after surgery (67.3% vs. 67.1%, respectively). The difference in peritoneal recurrence-free survival curves was not significant ($P = 0.44$; Fig. 2).

Discussion

A significant survival benefit of postoperative adjuvant chemotherapy with S-1 was demonstrated for stage II/III gastric cancer in the ACTS-GC study [16]—a pivotal phase III trial comparing surgery followed by 1 year of S-1 monotherapy with surgery alone. In that study, peritoneal relapse was observed in 143 of 1,059 patients enrolled, representing the most frequent site of relapse. Peritoneal dissemination is considered to arise from free cancer cells in the peritoneal cavity exfoliated from the serosal surface of the stomach after penetration by the primary tumor. Patients with free cancer cells detectable through conventional cytological examination (CY1) had not been eligible for that trial. This suggests that conventional cytological examination lacks sensitivity and fails to detect minute quantities of free cancer cells. Our previous study revealed that RT-PCR mediated detection of CEA mRNA in the peritoneal washes offers a more sensitive tool to detect subgroups of patients at high risk for peritoneal relapse [3–5, 7, 17] and could be a powerful tool in selecting patients for postoperative adjuvant therapy.

There are several reports describing the detection of minimal residual disease in gastric cancer using peritoneal washes and other body fluids, using both RT-PCR based and other techniques [18]. Of these, studies using peritoneal washes had been the most successful. CEA had been the commonest target, but false-positive cases have often been an issue, given that the expression of CEA is not confined to cancer cells. Use of multiple markers combining highly specific molecules and use of microarray tips would eventually minimize this problem [19]. Analysis of other samples, such as peripheral blood and bone marrow aspirates, have led to inconsistent results and had been less convincing as prognostic markers for gastric cancer [20, 21]. We have shown again in the current study that a CEA mRNA (+) population who are negative for conventional cytology (CY0) exists and has a risk for peritoneal carcinomatosis. Survival of our 32 patients was shown not to be dismal compared with CY1 patients [22] or those with stage IV disease in general, however. The notion that CEA RT-PCR may be useful to identify patients who are not indicated for surgery [23] could be challenged by the opinion that the CY0/CEA mRNA(+) population may benefit from adequate multimodal treatments.

Needless to say, a one-arm phase II study comparing survival data with a historical control is seriously flawed. Because the study involved CEA RT-PCR, which is not commercially available, a single institutional study was the only feasible option. Given the low incidence of CY0/CEA mRNA (+) patients, a more sophisticated study design had been considered unrealistic. Of note is that S-1, irinotecan, and taxanes were available by the time patients in the

historical control group relapsed. Thus, most patients in the control group were treated by essentially the same anticancer drugs in the same sequence, and the major difference between the current phase II patients and the historical control was whether chemotherapy had been started immediately after surgery or after relapse. Whereas the current trial was ongoing, CEA mRNA in the peritoneal washes also had been quantified in several patients outside of the trial as referent data. Some of CEA mRNA (+) patients were not treated with S-1 because they were allocated to the surgery alone group in another trial or did not wish to be registered to the present study. The 3-year survival proportion of these 11 cases was 63.6%, equivalent to the historical control of our study.

In the recent phase III trial, postoperative S-1 led to significant improvements in overall and relapse-free survival over observation alone at the first interim analysis and became a standard of care for stage II/III gastric cancer in Japan. Because the CY0/CEA mRNA(+) population, the target of the current study, mostly fall into the same stage II/III category, exploring the efficacy of identical treatment in this particular population seemed to have lost meaning, and we decided to close the trial. However, it remains unclear whether the improved survival of the interventional group as observed in the interim analysis eventually leads to cure of the corresponding number of patients or just a delay in relapse. In the present study, although more patients were alive at an earlier phase of follow-up compared with historical controls, the fates of patients at 3 years after surgery were basically identical. This suggests that gastric cancer relapse, at least in a high-risk population identified through CEA RT-PCR, is only delayed by S-1 monotherapy; not cured.

The specificity of CEA RT-PCR in detecting peritoneal relapse was 81.6% and occasional false-positive results were deemed unavoidable [24]. In the current analysis, 15 pathologically T1-stage cancers were included in the control group and 1 T1 cancer was identified in the treatment group. This difference is due to characteristics of patients between the control and treatment groups. We rarely examined lavage cytology nor CEA mRNA test in surgically T1 patients after the time of treatment group, because our previous analysis showed uselessness of CEA mRNA detection in pT1 patients. After analyzing only surgical T3 patients, no significant difference in survival curves was identified between the study population and the historical control ($P = 0.18$; Fig. 3). The difference in peritoneal recurrence-free survival curves was not significant ($P = 0.27$; Fig. 4). Considering that the rate of risk reduction was lower among stage IIIB than among stage II in the ACTS-GC trial, there is a potential need for more powerful chemotherapy than S-1 for high-risk populations among those who are eligible for postoperative adjuvant

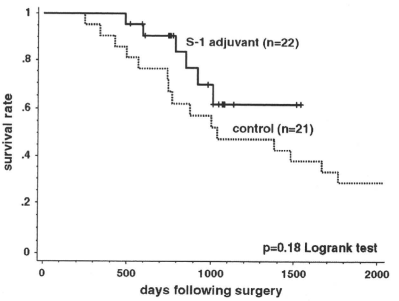

Fig. 3 Overall survival curve of surgical T3 patients with S-1 adjuvant treatment and historical controls. Survival of the S-1 adjuvant group tended to be slightly favorable, but this was not significant ($P = 0.18$; log-rank test)

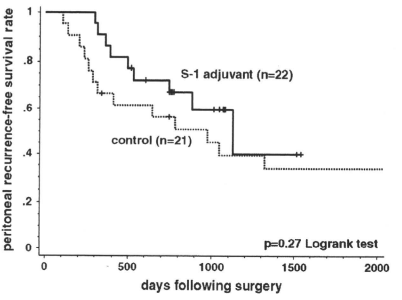

Fig. 4 Peritoneal recurrence-free survival curve for surgical T3 patients with S-1 adjuvant therapy and historical controls. Survival of the S-1 adjuvant group tended to be slightly favorable, but was not significant ($P = 0.27$; log-rank test)

therapy. Results of the current study reinforce the notion that S-1 monotherapy may be insufficient for some high-risk patients.

To combat peritoneal micrometastasis, sequential use of paclitaxel and S-1 or UFT (tegafur and uracil) is currently being explored in another pivotal phase III trial using a 2×2 factorial design with S-1 or UFT monotherapy as active controls [25]. Furthermore, the feasibility of S-1 combined with cisplatin or taxotere has been tested in the postoperative adjuvant setting. However, addition of cytotoxic agents to S-1 may lead to increased frequencies of adverse events, leading to poor compliance. Conversely, intraperitoneal administration of anticancer drugs has the theoretical advantage of exposing higher levels of

anticancer agents with lower systemic doses [26]. Indeed, a recent study [27] showed that adjuvant chemotherapy containing intraperitoneal cisplatin significantly improved RFS and OS in patients with grossly serosa-positive advanced gastric cancer. The pharmacokinetic and therapeutic advantages of paclitaxel when administered intraperitoneally have been well documented for gastric cancer as well [28, 29]. Studies to improve the cure rate among high-risk subsets of stage II/III patients using a combination of S-1 with other drugs or modalities are warranted.

Conclusions

Adjuvant chemotherapy with S-1 may delay cancer relapse but does not always eradicate micrometastases in the abdominal cavity. More effective treatments, possibly directed toward peritoneal micrometastasis, could be proposed to treat high-risk subsets of curatively resected gastric cancer, and CEA RT-PCR might be used to identify these high-risk patients.

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Conflict of interest There are no conflicts of interest to report.

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ORIGINAL ARTICLE

The Kampo medicine, Goshajinkigan, prevents neuropathy in patients treated by FOLFOX regimen

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Abstract

Background Oxaliplatin is now considered a standard treatment for advanced or unresectable colorectal cancer, but its main dose-limiting toxicity is sensory neuropathy. The OPTIMOX (stop and go) approach offers a reasonable strategy, but the preventive agent is not established. It is reported that the Kampo medicine, Goshajinkigan (GJG), has recently been considered an effective agent for the neuropathy of taxanes and for vibration sensation in patients with diabetic neuropathy. The aim of this study was to clarify the efficacy of GJG for peripheral neuropathy associated with oxaliplatin therapy.

Patients and method From 2007, 45 patients treated with modified FOLFOX6 for non-resectable or recurrent colorectal cancer participated in the study. Twenty-two patients (GJG group) received oral administration of 7.5 g/day of GJG every day during mFOLFOX6 therapy and 23 patients (control group) did not receive GJG. Neuropathy was evaluated during every course according to DEB-NTC (Neurotoxicity Criteria of Debiopharm).

Results The median number of cycles per patient in the GJG group was 13 (range 4–32), and in the control group was 12 (range 4–28). The cumulative dose of oxaliplatin was 1105 mg/m^2 (GJG group) and 1120 mg/m^2 (control group). The incidence of grade 3 peripheral neuropathy in the GJG group was significantly lower than in the control group ($p < 0.01$, log-rank test). The incidence of grade 3 peripheral neuropathy after 10 courses was 0% in the GJG group and 12% in the control group, and after 20 courses was 33% in the GJG group and 75% in the control group. The percentage of grade 2 and 3 peripheral neuropathy in the GJG group was lower than that in the control group. There were no differences in adverse effects between the two groups except for peripheral neuropathy and influence on tumor response.

Conclusion The Kampo medicine, Goshajinkigan, is useful in preventing neuropathy in non-resectable or recurrent colorectal cancer patients treated with a FOLFOX regimen.

Keywords Neuropathy · Kampo medicine · Goshajinkigan · Oxaliplatin · Colorectal cancer

Introduction

Oxaliplatin, a third-generation platinum analog, has demonstrated efficacy as first-line chemotherapy in metastatic colorectal cancer [1] and as adjuvant therapy [2]. Although all platinum analogs are potentially neurotoxic, oxaliplatin is associated with a unique spectrum of neurologic symptoms. Acute neuropathy develops immediately after infusion, characterized by cold-exacerbated paresthesia, muscle spasms, and fasciculations [1, 3]. Although acute symptoms typically resolve within a week, at higher cumulative doses oxaliplatin induces dose-limiting sensory neuropathy leading to sensory ataxia and functional impairment [1, 3]. Severe oxaliplatin-induced neuropathy occurs in 10–20% of

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patients receiving over 750–850 mg/m^2 [1, 2]. Neuropathy limits treatment tolerability, often necessitating treatment delay or cessation, and neuropathic symptoms may persist for a long time [4, 5].

The OPTIMOX (stop and go) approach [6] offers a reasonably good strategy, but attempts to prevent oxaliplatin-induced neuropathy have not been successful. Gamelin et al. [7, 8] reported that administration of calcium gluconate and magnesium sulfate (Ca/Mg) before and after oxaliplatin therapy could alleviate peripheral neurotoxicity. Other similar treatments have been described, including glutathione [9], *N*-acetylcysteine [10], xaliproden [11], carbamazepine [12], or glutamine [13], but a preventive agent for oxaliplatin-induced neuropathy has not yet been established. The Kampo medicine, Goshajinkigan (GJG), is composed of 10 natural ingredients and is classified as a drug that affects sensory nerves [14, 15]. Some studies suggested that GJG improved taxanes-induced neuropathy [16] and vibration sensation in patients with diabetic neuropathy [17]. Recently, Kono et al. [18] reported in a retrospective study that GJG was effective for peripheral neurotoxicity of oxaliplatin in patients with advanced or recurrent colorectal cancer.

We conducted the present prospective randomized study to confirm the efficacy of GJG for preventing oxaliplatin-induced peripheral neuropathy in patients with non-resectable or recurrent colorectal cancer who received modified FOLFOX6 (mFOLFOX6) therapy. The aim of this study was to clarify the efficacy of GJG for peripheral neuropathy associated with oxaliplatin therapy.

Materials and methods

Patients

In a study that investigated the neuropathy of various agents, including oxaliplatin, the incidence of more than grade 2 (National Cancer Institute's Common Toxicity Criteria; NCI-CTC) neuropathy was 5% in the Ca/Mg group and 54% in the control group when the mean total dose of oxaliplatin was 500–550 mg/m^2 (equivalent to six cycles at an oxaliplatin dose of 85 mg/m^2) [7]. The number of patients required to reproduce these results was calculated using a type I error (a) of 0.05, a type II error (b) of 0.2, and a control-to-treated data number ratio of 1:1. Therefore, the number of subjects for this study was set at 45 to allow for a 10% dropout rate. From January 2007 to December 2009, a total of 45 advanced or recurrent colorectal cancer patients who received mFOLFOX6 therapy at Tokushima University Hospital were eligible for this study. Patients signed the consent form and fulfilled the following criteria before treatment: Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2, normal bone marrow function (white blood count $\geq$4000/mm^3, platelet count $\geq$100000/mm^3), liver function (serum total bilirubin <1.5 mg/dl), renal function (creatinine <1.5 mg/dl), and heart function (stable cardiac rhythm, no active angina, no clinical evidence of congestive heart failure). Patients were excluded from the study if they had clinical neuropathy, diabetes mellitus, alcoholic disease, or brain involvement, or if they were on vitamin B, magnesium or calcium therapy. Clinical data was collected as follows; age, gender, performance status, primary tumor site, metastatic tumor site, and details of mFOLFOX6 therapy (previous chemotherapy, use of bevacizumab, number of courses, cumulative oxaliplatin dose). Informed consent was obtained from all patients included in the study, which was approved by local ethics committees. This study was registered in UMIN (000002494).

Treatment plan

Therapy was administered on an outpatient basis and patients were premedicated with appropriate antiemetics. Patients were randomly assigned to receive mFOLFOX6 therapy with GJG (GJG group) or without (control group). Random allocation of participants to GJG group or control group was performed by a person not involved in the care or evaluation of the patients. GJG (7.5 g/day divided into 2–3 doses) (Tsumura and Co., Japan), was administered during mFOLFOX6 therapy, given orally before meals or between meals on a daily basis. Other sensory neuromodulatory agents such as calcium–magnesium infusions or antiepileptic-like agents were forbidden. The mFOLFOX6 chemotherapeutic regimen consisted of a 2-h intravenous infusion of oxaliplatin (85 mg/m^2) combined with l-LV (100 mg/m^2), followed by a rapid intravenous infusion of 5-FU (400 mg/m^2), and then a 46-h continuous infusion of 5-FU (2400 mg/m^2). This regimen comprised one course of therapy and was repeated once every 2 weeks.

Patient evaluation

Patients enrolled in this study were evaluated at baseline (prior to chemotherapy) and before each course of treatment. The differences between the two groups, GJG group and control group, were evaluated as follows: the incidence of grade 3 peripheral neuropathy, the number of patients in each course, the percentage of grade 2 and 3 peripheral neuropathy in each course, adverse effects (grade 3) except for neuropathy, and influence of tumor response to mFOLFOX6. Peripheral neuropathy evaluations were based on the Neurotoxicity Criteria of Debiopharm (DEB-NTC) [19]. If patients had grade 3 neuropathy, the oxaliplatin dose was reduced to 75% of the previous dose. Adverse effects of

grade 3 except for neuropathy were assessed using the NCI-CTC. Chemotherapy was delayed until recovery if the neutrophil count decreased to less than 1500/L or the platelet count decreased to less than 100000/L. 5FU and oxaliplatin doses were reduced when NCI-CTC grade 3 or 4 non-neurological toxicity occurred. The anti-tumor effect of chemotherapy was assessed by the Guidelines for Evaluation of the Response to Treatment in Solid Tumors (RECIST) [20].

Data analysis

The primary end point of this study was the incidence of grade 3 peripheral neuropathy. The secondary end points were the percentage of grade 2 and 3 peripheral neuropathy in each course, adverse effects except for neuropathy, and tumor response to mFOLFOX6. The assessment of the occurrence of peripheral neuropathy was based on Kaplan–Meier analyses. The two groups were compared with the log-rank test to identify differences in the incidence of peripheral neuropathy. The chi-squared test was used to assess differences in incidence of grade 3 peripheral neuropathy at each course between the two groups. Quantitative data were given as median (range). Comparisons of other clinical data were performed using a chi-squared test, Fisher's exact probability test or Mann–Whitney U test, as appropriate. All statistical tests performed were two-sided and declared at the 5% significance level. All statistical analysis was performed using StatMate version 3 software (Japan).

Results

Patient characteristics

All patients were randomly allocated to the GJG group ($n = 22$) or the control group ($n = 23$). The population in the GJG group consisted of 14 men and 8 women with a median age of 67. The population in the control group consisted of 8 men and 15 women with a median age of 65. The majority of patients in the two groups were PS 0 and 1. The primary tumor sites in the GJG group were 15 colon and 7 rectum, and those in the control group were 16 colon and 7 rectum. The metastatic site was similar in the two groups. There was no statistically significant difference between the two groups based on any of these parameters. The patients' characteristics are listed in Table 1.

Table 1 Patient characteristics

	GJG	Control	p value
n	22	23	
Age	67 (48–77)	65 (52–80)	0.21
Sex			
Male	14 (64%)	8 (35%)	0.1
Female	8 (36%)	15 (65%)	
Performance status			
0	9 (41%)	10 (43%)	0.87
1	10 (45%)	11 (48%)	
2	3 (14%)	2 (9%)	
Primary tumor			
Colon	15 (68%)	16 (70%)	0.82
Rectum	7 (32%)	7 (30%)	
Metastatic site			
Liver	12 (54%)	12 (53%)	0.84
Lung	3 (14%)	4 (17%)	
Local	3 (14%)	1 (4%)	
Lymph node	2 (9%)	3 (13%)	
Other	2 (9%)	3 (13%)	

Details of mFOLFOX6 therapy

The details of mFOLFOX6 therapy are listed in Table 2. The presence of previous chemotherapy treatment and the use of bevacizumab were similar in the two groups. The median number of chemotherapy courses was 13 (range 4–32) in the GJG group and 12 (range 4–28) in the control group. The median cumulative oxaliplatin (L-OHP) dose was 1105 mg/m^2 (range 340–2720) in the GJG group and 1120 mg/m^2 (range 340–2380) in the control group. There was no statistically significant difference between the two groups based on any of these parameters. In the GJG group, 13 patients discontinued chemotherapy; nine showed progressive disease and four patients experienced an allergic reaction to oxaliplatin. In the control group, 11 patients discontinued chemotherapy; nine showed progressive disease, one had an allergy to oxaliplatin and one patient complained of persistent grade 3 oxaliplatin-induced neuropathy.

Table 2 Details of FOLFOX therapy

	GJG ($n = 22$)	Control ($n = 23$)	p value
Previous treatment			
Yes	4 (18%)	4 (17%)	0.75
No	18 (82%)	19 (83%)	
Use of bevacizumab			
Yes	18 (82%)	18 (78%)	0.94
No	4 (18%)	5 (22%)	
No. of courses	13 (4–32)	12 (4–28)	0.87
Cumulative L-OHP dose (mg/m^2)	1105 (340–2720)	1120 (340–2380)	0.87

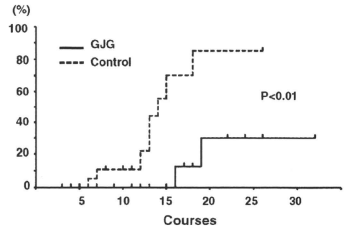

Fig. 1 Kaplan–Meier analyses showed that the incidence of grade 3 peripheral neuropathy occurred significantly less frequently in the GJG group than the control group ($p < 0.01$, log-rank test)

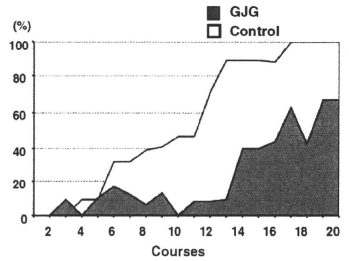

Fig. 2 The percentage of grade 2 and 3 peripheral neuropathy in each cycle was lower in the GJG group than the control group

Effect of GJG on neuropathy

The compliance in the GJG group was 100%. Compliance was checked on the starting day of each course. The number of patients in each course was similar in the two groups. Kaplan–Meier analyses showed that the incidence of grade 3 peripheral neuropathy occurred significantly less frequently in the GJG group than the control group ($p < 0.01$, log-rank test). The incidence of grade 3 peripheral neuropathy after 10 courses was 0% in the GJG group and 12% in the control group, and after 20 courses was 33% in the GJG group and 75% in the control group (Fig. 1). There was no statistically significant difference between the two groups in regard to the incidence of grade 1 or worse and grade 2 or worse peripheral neuropathy (data not shown). The percentage of grade 2 and 3 peripheral neuropathy in each course was lower in the GJG group than the control group (Fig. 2).

Adverse effects and influence on tumor response

Table 3 summarizes adverse effects (grade 3) except for neuropathy. There were no chemotherapy-related deaths during the study. The main toxicities were neutropenia, nausea and diarrhea. In regard to tumor response to mFOLFOX6, no complete response was observed in either group. A partial response was observed in 15 patients (68%) in the GJG group and in 13 patients (57%) in the control group. Stable disease was observed in 5 patients (23%) in the GJG group and in 8 patients (35%) in the control group. The response rate (complete response and partial response) and the disease control rate (complete response, partial response and stable disease) were 68 and 91% in the GJG group and 57 and 92% in the control group, respectively. There were no statistically significant differences in incidence and severity of adverse effects except for peripheral neuropathy and influence on tumor response to mFOLFOX6 between the two groups. The tumor response to mFOLFOX6 is shown in Table 4.

Table 3 Adverse effects (grade 3) except for neuropathy

	GJG ($n = 22$)	Control ($n = 23$)	p value
Neutropenia	3 (14%)	1 (4%)	0.27
Anorexia	0 (0%)	1 (4%)	0.32
Nausea	4 (18%)	2 (9%)	0.34
Vomiting	1 (5%)	1 (4%)	0.97
Diarrhea	2 (9%)	4 (17%)	0.41
Mucositis	2 (9%)	2 (9%)	0.96
All grade 3 toxicity	8 (36%)	8 (35%)	0.84

Table 4 Tumor response to FOLFOX

	GJG ($n = 22$)	Control ($n = 23$)	p value
Tumor response			
Complete response	0 (0%)	0 (0%)	0.86
Partial response	15 (68%)	13 (57%)	
Stable disease	5 (23%)	8 (35%)	
Progressive disease	2 (9%)	2 (8%)	
Response rate	15 (68%)	13 (57%)	0.62
Disease control rate	20 (91%)	21 (92%)	0.96

Discussion

Although the OPTIMOX (stop and go) approach [6] offers a reasonably good strategy, there are several problems, such as the period of use of oxaliplatin and the use of bevacizumab, which are yet to be solved. On the other hand, attempts to prevent oxaliplatin-induced neuropathy have not been sufficiently successful. There are previous randomized controlled studies [9–13, 21] regarding prevention of oxaliplatin-induced neuropathy, including this present report. Five of the seven studies showed the efficacy of the

agent in preventing oxaliplatin-induced peripheral neuropathy. The efficacy of glutamine was reported by Wang et al. [13] and glutathione, a byproduct of glutamine metabolism, was reported by Cascinu et al. [9]. Additionally, Lin et al. [10] reported the efficacy of *N*-acetylcysteine which could increase whole blood concentrations of glutathione in patients with *N*-acetylcysteine supplementation. A major role of glutamine in the prevention of platinum-induced neuropathy has been suggested by several experimental findings. Because glutamine is known to upregulate nerve growth factor (NGF) mRNA in an animal model [22], glutamine supplements may prevent chemotherapy-induced neuropathy via upregulating the NGF level. On the other hand, it has also been hypothesized that high systemic levels of glutamine may downregulate the conversion of glutamine to an excitatory neuropeptide, glutamate, which may also account for the reduced symptoms observed in patients receiving glutamine [23]. Next, a large randomized controlled trial [11] tested xaliproden, a neurotrophic and neuroprotective drug, 11and found that it reduced the risk of grade 3–4 peripheral neuropathy by 39% in metastatic colorectal cancer patients receiving oxaliplatin.

In contrast, two studies of calcium gluconate and magnesium sulfate (Ca/Mg) [21] and carbamazepine [12], the sodium channel blocker, could not show the efficacy of the agent in preventing oxaliplatin-induced peripheral neuropathy. The mechanism of platinum drug neurotoxicity may involve drug accumulation within the peripheral nervous system, especially in the dorsal root ganglia [24]. This suggested that sodium channels may only be involved in acute peripheral neuropathy.

This present study is the first report proving the efficacy of the Kampo medicine, Goshajinkigan, against oxaliplatin-induced peripheral neuropathy using a prospective control study. Neuropathy is the major cause of dose reduction and discontinuation of oxaliplatin treatment [2], with severe neuropathy occurring in 15–20% patients with a cumulative dose of 750–850 mg/m^2 [1, 2]. In the present study, the mean cumulative oxaliplatin dose administered was 1105 mg/m^2 in the GJG group and 1120 mg/m^2 in the control group. Recently, Kono et al. [18] reported in a retrospective study that GJG was effective against peripheral neurotoxicity of oxaliplatin. Additionally, a larger placebo-controlled double-blind randomized phase II study [25] to confirm the usefulness of GJG is taking place in Japan.

A major concern is that GJG might protect tumor cells from the cytotoxic effects of chemotherapy. Although Ca/Mg infusion was suggested to decrease antitumor activity [26], in the current study GJG did not have an influence on tumor response to mFOLFOX6 therapy. Kono et al. [18] reported that the tumor response rate was lower in the group that received GJG + Ca/Mg than in the GJG group and suggested that some interaction might have occurred when GJG and Ca/Mg were combined. Additionally, in the current study GJG did not have an influence on adverse effects except for peripheral neuropathy.

Several mechanisms have been suggested by which GJG may alleviate peripheral neuropathy [27–29]. The first is that GJG promotes the release of dynorphin, and thus improves numbness/pallesthesia via the opiate system. The second is that GJG promotes nitric oxide production, and thus improves the circulation and the blood supply to the nerves. Recently, Joseph et al. [30] reported that oxaliplatin acted on IB4-positive C-fiber nociceptors to induce an oxidative stress-dependent acute painful peripheral neuropathy. Imamura et al. [31] reported that GJG reduced transmitter proteins and sensory receptors associated with C-fiber activation. This effect may be one of the mechanisms of GJG which prevents oxaliplatin-induced neuropathy.

In regard to combination treatment, Kono et al. [18] reported that the patients who received GJG + Ca/Mg developed worse neuropathy than those who received GJG alone and suggested that GJG alone (rather than combined with Ca/Mg) may be more effective in suppressing peripheral neurotoxicity. Although it will be necessary to confirm the usefulness of combination treatment by performing larger prospective studies in the future, a candidate may be either GJG + glutamine or GJG + xaliproden.

The key weaknesses of this report are as follows: no placebo control, no double-blinding and a small sample. However, Kampo medicines in Japan are strictly monitored by means of three-dimensional high-performance liquid chromatography (3D-HPLC), and therefore their reliability is of a high level. We firmly believe that the result of a placebo-controlled double-blind randomized phase II study [25] to confirm the usefulness of GJG reinforces our findings.

Conclusions

The Kampo medicine, Goshajinkigan, safely reduced the incidence of severe neuropathy by mFOLFOX6 regimen without any adverse influence on the response rate to mFOLFOX6. Therefore, Goshajinkigan is useful in preventing oxaliplatin-induced neuropathy in patients with non-resectable or recurrent colorectal cancer.

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Conflict of interest No author has any conflict of interest.

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ORIGINAL

Intraperitoneal infusion of paclitaxel with S-1 for peritoneal metastasis of advanced gastric cancer : phase I study

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Abstract : Background : Intraperitoneal administration of taxanes revealed excellent anti-tumor effect for peritoneal metastasis of gastric cancer in some experimental models. The aim of this study is to determine maximum tolerated dose (MTD), dose limiting toxicity (DLT) and recommended dose (RD) of intraperitoneally infused paclitaxel (PTX) with S-1 as a phase I study. Patients and Methods : Eighteen patients with advanced gastric cancer in addition to confirmed peritoneal metastasis using laparoscopy were enrolled in this study. The regimen consists of oral administration of S-1 (Dose 80 mg : BSA< 1.25 m^2, 100 mg : 1.25<BSA<1.5 m^2, 120 mg : BSA>1.5 m^2) for 14 days and intraperitoneal infusion of PTX (Dose escalation : level I : 40, II : 60, III : 80, level IV : 90, V : 100 mg/m^2) at day1 and 14. PTX concentrations in serum and ascites were determined at 4, 8, 12, 24, 48 hours after the infusion, which was repeated twice every 4 weeks. Results : The number of patients were as follows : Level I : 3, Level II : 6, Level III : 3, Level IV : 3, Level V : 3. Grade 3 leukocytopenia was confirmed in 1 (Level II) and 2 (Level V). MTD is 90 mg/m^2, RD is 80 mg/m^2 and DLT is Grade 3 leukocytopenia. The average serum PTX concentrations remained in optimal range except for all 3 of level V patients. In all cohorts, the PTX concentrations in the ascites were approximately 1000 folds higher than those in serum for 48 hours after the infusion. Conclusions : MTD and RD were PTX 90 mg/m^2, 80 mg/m^2, respectively. These findings were supported by pharmocokinetics of PTX J. Med. Invest. 58 : 134-139, February, 2011

Mini-Abstract : *In intraperitoneal infusion of PTX with S-1, DLT was leukocytopenia, MTD and RD were PTX 90 mg/m^2, 80 mg/m^2, respectively. These findings were supported by pharmocokinetics of PTX*

Keywords : *paclitaxel, S-1, intraperitoneal infusion, peritoneal metastasis, gastric cancer*

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INTRODUCTION

Median survival time, even with the best supportive care, for patients with unresectable or metastatic gastric cancer is only 3.1 months (1). Although peritoneum is the most common metastatic site of

advanced gastric cancer, a standard regimen has not been established despite the number of trials and the survival rate is very low.

Recently new chemotherapy agents have been developed. In particular S-1 revealed a high response rate of 49% for advanced gastric cancer in late phase II study (2), which has been widely accepted as a key drug even for adjuvant setting in Japan (3).

Taxanes stabilize and excessively form microtubules, which is a different mechanism from other agents. In phase II study, response rate of paclitaxel (PTX) for advanced gastric cancer was 21% and not affected by differentiation of adenocarcinoma (4, 5). High concentrations approximately 1000 times of PTX in the peritoneal cavity maintained compared with those in serum after intraperitoneal administration because of fat solubility and heavy molecular weight ; 853.92 (6). Excellent pharmacokinetics and anti-tumor effect to the peritoneal dissemination of gastric cancer was reported in the experimental model (7).

It is considered that S-1 and PTX is one of the best combinations for the treatment peritoneal metastasis of gastric cancer. The aim of this study is to determine the appropriate doses and feasibility of intraperitoneal infusion of paclitaxel (PTX) with orally administered S-1.

PATIENTS AND METHODS

Patient eligibility

Patients with peritoneal metastasis of advanced gastric cancer were eligible for this clinical trial. Before initiation of the study, relevant study documentation was submitted to and approved by the responsible ethics committee : the University of Tokushima hospital clinical research Ethical Review Board, Tokushima, Japan.

The guidelines of the World Medical Association Declaration of Helsinki in its revised edition (Edinburgh, Scotland, October 2000) and other applicable regulatory requirements were strictly followed. Written informed consent was obtained from each patient before any study-specific screening procedures were undertaken.

Inclusion criteria

Patients aged 20-75 years, had to have histologically or cytologically confirmed peritoneal metastasis of gastric cancer using laparoscopy under general anesthesia, who had not received abdominal surgery and any prior chemotherapy regimens.

Exclusion criteria

Patients with ischemic heart disease that needed medication, liver cirrhosis, lung fibrosis, pneumonia, intestinal bleeding or other severe complications were excluded.

Treatment plan

An initial laparoscopy was performed under general anesthesia for the patients with advanced gastric cancer histologically diagnosed. Peritoneal metastasis was histologically confirmed by removal of disseminated nodules or peritoneal cytology.

The catheter for intraperitoneal infusion of PTX was passed through the wound of trocar port in the right side of the umbilicus, which was connected to the port implanted in the abdominal wall for the patient diagnosed peritoneal metastasis.

S-1 was orally administered with a fixed quantity (Dose 80 mg : Body Surface Area (BSA) < 1.25 m^2, 100 mg : 1.25 < BSA < 1.5 m^2, 120 mg : BSA > 1.5 m^2) for 14 days. PTX was infused intraperitoneally through the implanted catheter at day1 and 14. Dose of PTX was escalated ; level I : 40 mg/m^2, level II : 60 mg/m^2, level III : 80 mg/m^2 level IV : 90 mg/m^2, level V : 100 mg/m^2. Intraperitoneal PTX with S-1 was repeated two cycles every four weeks.

Adverse events were coded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. Dose Limiting Toxicity (DLT) was defined two patients had nonhematologic or hematologic grade 3 or greater adverse events. If one patient had Grade 3 or more adverse events, the cohort was expanded to three patients owing to occurrence of a DLT. As a result, the dose of PTX was increased to the level that two patients had a DLT in turn. The Maximum Tolerated Dose (MTD) was defined as one escalation level lower than that DLT was confirmed. Recommended dose (RD) was defined as one level lower than MTD.

Analytic methods and pharmocokinetics

Blood samples for pharmacokinetic analysis were drawn before infusion, at 4, 8, 12, 24 and 48 h after the infusion of PTX. Ascites samples were aspirated through the catheter for PTX infusion at the same time points. High performance liquid chromatography (Ultra-Violet absorbance detector : Ultra-violet of 227 nm in wave length) was used to analyze PTX concentrations of serum and ascites in SRL, Inc

(Tokyo, Japan).

RESULTS

Patient demographics

Patient demographics are shown in Table 1. The 18 patients were enrolled in this study after histologically confirming peritoneal metastasis. Two of the 18 patients had adenocarcninoma cells in peritoneal cytology without macroscopically detected metastatic nodules. Curative operation was not impossible for all 18 patients.

Table 1 : Patient demographics

Sex (male/female)	14/4
Age (years) (median/min/max)	56/49/75
WHO Performance status (0/1)	14/4
Macroscopic types III / IV	10/8
Histological typing well/poorly differentiated	3/15
Positive adenocarcinoma cells in peritoneal cytology	18
Macroscopically detected metastatic nodules	16
Gastrectomy	12

Clinical safety and tolerability

All 18 enrolled patients were evaluated for safety. A summary of the patient- and investigator-reported drug related clinical adverse events is shown in Table 2. Current regimen was generally well tolerated, with 6 patients clinically significant drug-related adverse events. The most frequently reported adverse event was Grade 3 leukocytopenia. Grade 1 or 2 anemia, vomiting and abdominal pain were confirmed.

The 40, 80, 90 and 100 mg/m^2 cohort enrolled three patients. After the one patient had Grade 3 leukocytopenia in 60 mg/m^2 cohort, this cohort was expanded to 6 patients without Grade 3 or more adverse events. Grade 3 leukocytopenia was confirmed consecutively 2 patients in 100 mg/m^2 cohort.

DLT was leukocytopenia, MTD was 90 mg/m^2 and RD was 80 mg/m^2, respectively.

Table 2 : Drug-related adverse events

	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Hemoglobin	1 (5.6%)			
Leukocytes			3 (16.7%)	
GASTROINTESTINAL				
Vomiting	1(5.6%)			
PAIN				
Abdominal pain		1 (5.6%)		

Pharmocokinetics of PTX

The average serum PTX concentrations in 40, 60, 80 and 90 mg/m^2 cohort were maintained between the lower limit of cytotoxic effects and upper limit of blood system disorder, which were over upper limit of blood system disorder in all 3 patients of 100 mg/m^2 cohort. In all cohorts, PTX concentrations in the ascites were approximately 1000 folds higher than those in serum for 48 hours after the infusion (Figure 1).

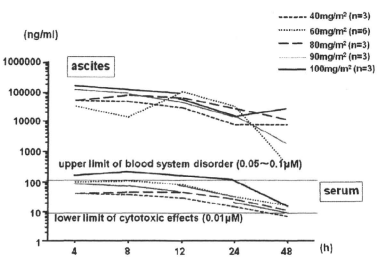

Figure 1 : Pharmacokinetics of PTX
The PTX concentrations in 40, 60, 80 and 90 mg/m^2 cohort remained in the optimal range. In 100 mg/m^2 cohort, the PTX concentrations were over upper limit of blood system. PTX concentrations in the ascites were approximately 1000 times higher than those in serum.

Clinical activity

All 18 patients were evaluated for efficacy. Objective clinical response was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST). The 2 patients had partial response. The 15 patients was recorded as stable disease, however, positive adenocarcinoma cells in peritoneal cytology became negative in 2 patients, remarkable decrease of ascites was found in 2 patients. Down staging according to the 13th Japanese Classification of Gastric Carcinoma was possible in 2 patients (2 : positive cytology became negative). There was one patient classified as having progressive disease.

Gastrectomy was performed for 12 of 18 patients, which had curative potential in the patients with down staging. The median survival time was 11 months. Survival time of the 2 patients whose positive cytology became negative was 32 and 48 months, respectively (Table 3).

Table 3 : Clinical activity

Case	Level	RECIST	Down staging	Gastrectomy	Prognosis	Survival time (months)
1	1	PR	-	+	death	8
2	1	SD	-	+	death	10
3	1	SD	+*	+	alive	48
4	2	SD	-	+	death	17
5	2	PR	-	+	death	21
6	2	SD	-	-	death	15
7	2	SD	-	-	death	14
8	2	SD	-	+	death	10
9	2	SD	-	-	death	11
10	3	SD	+*	+	alive	32
11	3	SD	-	+	alive	30
12	3	SD	-	+	death	8
13	4	SD	-	+	death	9
14	4	SD	-	-	death	6
15	4	SD	-	+	death	5
16	5	PD	-	-	death	14
17	5	SD	-	-	death	7
18	5	SD	-	+	alive	11

* Positive adenocarcinoma cells in peritoneal cytology became negative.

DISCUSSION

Intraperitoneal infusion of PTX was generally well tolerated. The most frequently reported adverse event was Grade 3 leukocytopenia. DLT was leukocytopenia, MTD was 90 mg/m^2 and RD was 80 mg/m^2, respectively. These findings were supported by pharmacokinetics of PTX.

Because S-1 is the most widely accepted drug for gastric cancer in Japan, a lot of combination trials based on S-1 have been performed (8-10). Median overall survival was significantly longer in patients assigned to S-1 plus cisplatin (13.0 months) than in those assigned to S-1 alone (11.0 months) in the Phase III trial for advanced gastric cancer, however, peritoneal dissemination held 34%, 24% of each group, respectively (8). Significant differences in overall survival compared with S-1 alone revealed in any other regimens. It has not been established standard regimens for peritoneal metastasis of gastric cancer.

Intraperitoneal PTX in the phase II trial for the patients with small-volume residual carcinomas of the ovary, fallopian tube, or peritoneum was well tolerated, which included only moderate abdominal pain (grade 2 : 15.7%, grade 3 ; 1.3%) and minimal neutropenia (grade 2 ; 3.9% ; grade 3 ; 1.3%) (11). The incidence of Grade 3 neutropenia were observed in 32% of the patients with advanced gastric cancer in the treatment schedule comprised an intravenous infusion of 80 mg/m^2 PTX , repeated weekly three times for 4 weeks (12). These data suggested that intraperitoneal administration of PTX did not increase the incidence of drug-induced toxicities (13).

A pharmacokinetics study demonstrated that the PTX concentration in ascites remained in the range of the lower limit of cytotoxic effects and upper limit of blood system disorder from 4 to 72 hours after intravenous infusion of 60 and 80 mg/m^2 PTX. On the other hand, plasma concentrations of PTX were over upper limit of blood system disorder at 4 hours (14). In contrast, the PTX concentrations in 40, 60, 80 and 90 mg/m^2 cohort in this study remained in the optimal range. In 100 mg/m^2 cohort, the PTX concentrations were over upper limit of blood system. PTX concentrations in the ascites were approximately 1,000 folds higher than those in serum.

A major advantage after intraperitoneal delivery of PTX is high concentration in the peritoneal cavity (550-2,000 folds) compared with the systemic compartment (13). Drug exposure of high concentration is considered to have an advantage because antitumor effects increased dose dependent manner

as far as could be seen there were no severe toxicities in the experimental model (7).

Although this study is a phase I study, the response rate and survival could not be described exactly, two patients with positive adnocarcinoma cells and no macroscopically detected disseminate nodules had a long survival of over 30 months. The overall 5-year survival (43.8%) of advanced gastric cancer patients with intraperitoneal free cancer cells without overt peritoneal metastasis (CY+/P-) after extensive intraoperative peritoneal lavage followed by the intraperitoneal chemotherapy (EIPL-IPC: peritoneal lavage of 10 times using 1 L of physiological saline following cisplatin at a dose of 100 mg/body into the peritoneal cavity) was significantly better than that of the intraperitoneal chemotherapy (4.6%) and the surgery alone (0%) (15). It is important to detect positive adenocarcinoma cells in the peritoneal cavity to improve survival of the patients with peritoneal metastasis (16).

Concerning patients with macroscopically detected peritoneal metastasis, the utility of peritonectomy with chemohyperthermic peritoneal perfusion (CHPP) was reported, however, there are some problems regarding peritonectomy : complicated procedures and CHPP : severe stress to the patients and needs of specific and expensive instruments (17).

Fat solubility of PTX is suitable for intraperitoneal infusion, in contrast, Cremophor EL and ethanol is necessary as a solvent for clinical use, which causes acute hypersensitivity (18). For better and safe drug delivery system, various modifications of PTX have been developed and phase I trials were reported (19-21). Intraperitoneal PTX using the water-soluble solvent revealed excellent pharmacokinetics compared with Cremophor EL (22).

Intraperitoneal PTX including new modified drugs has high potentials to improve survival for the peritoneal metastasis of gastric cancer.

CONFLICT OF INTEREST STATEMENT

Mitsuo Shimada received a research grant from Research Support Foundation of the University of Tokushima and TAIHO Pharmaceutical. Co. Ltd. ; Other authors have no conflict of interest.

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