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Original article

A feasibility study of postoperative chemotherapy with S-1 and cisplatin (CDDP) for gastric carcinoma (CCOG0703)

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Abstract

Background. **The outcome of stage III gastric cancer patients treated by D2 dissection followed by adjuvant chemotherapy with S-1 remains unsatisfactory. Moreover, some patients with a preoperative diagnosis of stage II/III turn out to be stage IV after surgical exploration, and a standard postoperative treatment for this population has not been established.**

Methods. **A feasibility study of postoperative S-1/cisplatin (CDDP) was performed with patients who underwent gastrectomy for what turned out to be a stage IV gastric cancer. The primary endpoint of the trial was the relative dose intensity during five courses of S-1/CDDP. Several criteria to skip, postpone, or reduce the dose had been predetermined.**

Results. **Between 2007 and 2009, 31 patients were accrued, including 19 patients who were positive for peritoneal washing cytology, 6 with peritoneal seeding, 5 with metastasis to the paraaortic nodes, and 4 with other distant metastases. Only 7 patients completed five cycles as planned (median, two cycles). The median relative dose intensities of S-1 and CDDP were 37% and 40%, respectively. Causes of treatment failure were failure to fulfill criteria for starting a new course within 5 weeks of the last administration of S-1 in 7, patient refusal in 6, disease recurrence/progression in 4, need to reduce dose by two levels in 4, and two successive skips of CDDP in 3 patients. The median progression-free survival time of all patients was 363 days.**

Conclusions. **Although promising in the neoadjuvant and advanced/metastatic setting, S-1/CDDP is too toxic as a postgastrectomy treatment for Japanese patients.**

Key words Gastric cancer · Metastasis · S-1 · CDDP · Relative dose intensity

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Introduction

Gastric carcinoma is the second most common cause of cancer-related death worldwide [1], and remains a major health problem in the Far East. The survival of patients with gastric cancer is often dismal even if treated with potentially curative resection, and various perioperative therapies directed against micrometastases have been proposed and delivered in addition to improve the outcome [2–4].

In Japan, S-1 (1 M tegafur-0.4 M gimestat-1 M otastat potassium) has become a key drug in the treatment of gastric cancer. It was found to be remarkably active as a single agent in the treatment of unresectable/metastatic gastric cancer [5, 6], while the response rate was shown to be further enhanced by the addition of cisplatin (CDDP), exceeding 70% in a phase II trial [7]. A phase III trial has shown that single-agent S-1 administered postoperatively for 1 year significantly improves the outcome of patients with stage II/III gastric cancer over treatment with surgery alone [4]. Another phase III trial has shown the benefit of S-1/CDDP over S-1 in the treatment of unresectable/metastatic cancer [8]. These facts point to a strategy of administering S-1/CDDP instead of S-1 alone as an adjuvant therapy for the further improvement of outcome in patients with resectable disease, although the gastrointestinal toxicity of this combination casts doubt as to its feasibility when delivered postoperatively.

Advanced gastric cancer is often associated with peritoneal metastasis. Current imaging studies rarely detect peritoneal deposits, although the detection of even minute amounts of cancer, such as those represented by positive cytology of peritoneal washes, usually renders the cancer incurable [9]. This knowledge

prompted several investigators to perform staging laparoscopy prior to radical surgery [10]. However, it is not currently considered as a part of routine preoperative workup in Japan, where gastric cancer is one of the commonest types of cancer and is often treated at community hospitals in the hands of general surgeons. Consequently, a certain proportion of patients for whom curative surgery had been planned turn out to have a stage IV disease at surgery, in the form of peritoneal deposits and positive washing cytology. When peritoneal deposits are found to be minimal, these patients usually undergo resection as planned, but no evidence-based strategy as a postoperative therapy exists for this population.

In the present study, the feasibility of an S-1/CDDP combination given postoperatively was evaluated, primarily to establish a standard of care for patients who undergo gastrectomy for stage IV disease. In addition, we had an intention to test this combination as a candidate for novel postoperative adjuvant chemotherapy to be delivered to stage III patients, whose prognosis remain poor when treated with postoperative S-1 monotherapy, the current standard of care.

Patients and methods

Patient eligibility

Eligible patients had to meet all of the following criteria: (i) a confirmed diagnosis of gastric adenocarcinoma, (ii) age less than 75 years, (iii) gastrectomy performed within 6 weeks of initiation of chemotherapy (iv), stage IV disease according to the *Japanese classification of gastric carcinoma* [11] as confirmed by preoperative imaging studies and/or histopathological examinations, (v) no prior treatment besides surgery, (vi) European Cooperative Oncology Group performance status of 0 to 1, (vii) adequate organ functions, defined as white blood cell count 4000–12000/mm^3, total neutrophil count 2000/mm^3 or more, platelet count 100000/mm^3 or more, hemoglobin 9.0 g/dL or more, serum creatinine within the normal range according to the criteria of the hospital where the study was performed, total serum bilirubin less than 1.5 mg/dl, serum aspartate aminotransferase and alanine aminotransferase less than 100 IU/l, and creatinine clearance 60 ml/min or more. Patients had to have a life expectancy of more than 3 months, with no other active malignancies or uncontrolled concomitant diseases. Written informed consent was obtained from all participants after they had received a full explanation of the nature of the study. The study was approved by the institutional review board of Nagoya University Hospital and all other hospitals belonging to the Chubu Clinical Oncology Group (CCOG) that participated in this multicenter trial.

Pretreatment evaluation, treatment plan, and dose attenuation

At baseline, a complete medical history was taken, and a physical examination was performed. Laboratory assessment at baseline included blood cell counts, serum chemistry profiles, serum tumor markers (carcinoembryonic antigen; CA19-9), and urinalysis. Patients also underwent a baseline electrocardiographic examination and computed tomography (CT) scans of the chest, abdomen, and pelvis. At surgery, the intraperitoneal cavity was searched for peritoneal deposits and a cytologic examination of the peritoneal washes collected at the Douglas pouch was routinely performed. Histopathological detection of cancer cells by this examination is designated in the *Japanese classification of gastric carcinoma* [11] as CY1 and the patient is subsequently classified as stage IV.

Chemotherapy was to be started at 2–6 weeks after surgery. Patients received S-1 orally at the following doses twice daily for 3 weeks, followed by 2 weeks without chemotherapy. Patients with a body surface area of less than 1.25 m^2 received 80 mg daily; those with a body surface area of 1.25 m^2 to less than 1.5 m^2 received 100 mg daily; and those with a body surface area of 1.5 m^2 or greater received 120 mg daily. This 5-week cycle was repeated mainly in an outpatient setting. The exception was the delivery of CDDP, for which the patients were to be admitted for three nights and given continuous intravenous fluid administration with the antiemetics granisetron and dexamethasone. Five cycles of S-1/CDDP were to be delivered as a protocol treatment, after which the patients were recommended to receive further chemotherapy with single-agent S-1 in the absence of disease progression. If the patients had either hematological toxicity of grade 3 or greater, nonhematological toxicity of grade 2 or greater, serum creatinine exceeding the normal range according to the criteria of the hospital, or creatinine clearance of less than 50 ml/min during the previous course, the daily dose of S-1 was decreased from 120 mg to 100 mg, from 100 mg to 80 mg, or from 80 mg to 50 mg, and the dose of CDDP was decreased by 10 mg/m^2. If the patients failed to fulfill the above criteria on day 1 of the new course, the new course was to be postponed until recovery. If such toxicity occurred on day 8, CDDP was to be skipped. Under these strict rules, the protocol treatment was to be discontinued in the event of (i) postponement of the new course for 3 weeks in a row, (ii) dose reduction of S-1 or CDDP by two levels, (iii) skipping CDDP for two cycles in a row, (iv) other adverse events that were considered unmanageable, (v) withdrawal of consent from the patient, or (vi) disease recurrence or progression. Patients who failed the treatment were allowed to be given a second-

line chemotherapy at the discretion of the surgeons/oncologists.

Disease status was assessed once every 3 months on the basis of serum tumor markers and at least once every 6 months by CT scanning until the completion of five cycles of treatment. Adverse events were monitored by interviews, blood chemistry profiles, and blood cell counts once every 2 weeks. All toxic effects were graded according to National Cancer Institute Common Toxicity Criteria (NCI-CTC; version 2.0).

Endpoints and study design

The primary endpoint of the study was the relative dose intensity (percentage of the dose actually administered out of the planned dose calculated from the body surface area) during five cycles of treatment with S-1/CDDP. The secondary endpoints were the proportion of patients who tolerated five cycles, safety, progression-free survival time, and overall survival time.

No data on relative dose intensity actually exist for the present combination therapy in the postoperative setting. A relative dose intensity of 80% is generally considered acceptable. Postoperative S-1/CDDP could be considered feasible for further exploration if the parameter in this study fell between 66% and 95% (95% confidence interval when a relative dose intensity of 80% was obtained with 27 patients). Thus, the accrual of 30 patients was planned to prove this point.

Results

Patient population

Thirty-one patients were enrolled between October 2007 and February 2009. The demographic and clinicopathological characteristics of the patients are shown in Table 1. The mean age of the patients was 61.5 years (range, 34–73 years). The male/female ratio was 22:9. Ten patients underwent distal gastrectomy and the other 21 received a total gastrectomy. Splenectomy was performed in 10 patients, of whom 1 also underwent resection of the pancreatic tail. Three patients underwent coresection of the transverse colon and 1 patient received a hepatectomy. Surgery in 19 patients was R2 resection, mostly due to peritoneal deposits, whereas surgery turned out to be R1 in 9 patients who were positive for cytologic examination of the peritoneal washes (CY1) without any other distant metastasis. Three other patients underwent R0 resection. One of these had been classified as stage IV due to pT4bpN2 disease but had a curative resection. One patient had metastasis to the paraaortic lymph node and underwent D3 dissection (eradication of the paraaortic lymph nodes). Another patient had a liver metastasis which was coresected.

Compliance, relative dose intensity, and toxicity

The median relative dose intensity of CDDP was 40% and that of S-1 was 37% (Fig. 1). Patients tolerated a median of two cycles of treatment, and only seven patients (22%) completed all five cycles. The reasons for discontinuation of the treatment were failure to start S-1 within 3 weeks after the end of the previous course in seven patients, patient refusal due to adverse events in six patients, disease progression in four patients, dose reduction of S-1 or CDDP by two levels in four patients, and skipping CDDP for two cycles in a row in three patients. Time to treatment failure was 70 days (Fig. 2). Most patients (15/20; 75%) who discontinued the designated treatment due to adverse events received chemotherapy with single-agent S-1. Only S-1 delivered as the protocol treatment was included in the calculation of relative dose intensity.

The most frequent grade 3/4 toxicity was neutropenia, observed in 29% of the patients (Table 2). Grade 3/4

Table 1. Patient demographics ($n = 31$)

Variables		
Age (years)	Mean (range)	61.5 (34–73)
Sex	Male/female	22/9
PS (ECOG)	0/1	21/10
pT	T3/T41/T4b	2/18/10
pN (JCGC)	N0/N1/N2/N3/NX	1/10/14/5/1
pN (TNM)	N0/N1/N2/N3/NX	1/2/7/20/1
Liver metastasis	Negative/positive	29/2
Peritoneal metastasis	Negative/positive	23/8
M (TNM)	M0/M1	15/16
Peritoneal washing cytology	Negative/positive	8/20

PS, performance status; ECOG, Eastern Cooperative Oncology Group; JCGC, Japanese classification of gastric carcinoma; TNM, tumor node metastasis classification by the International Union Against Cancer

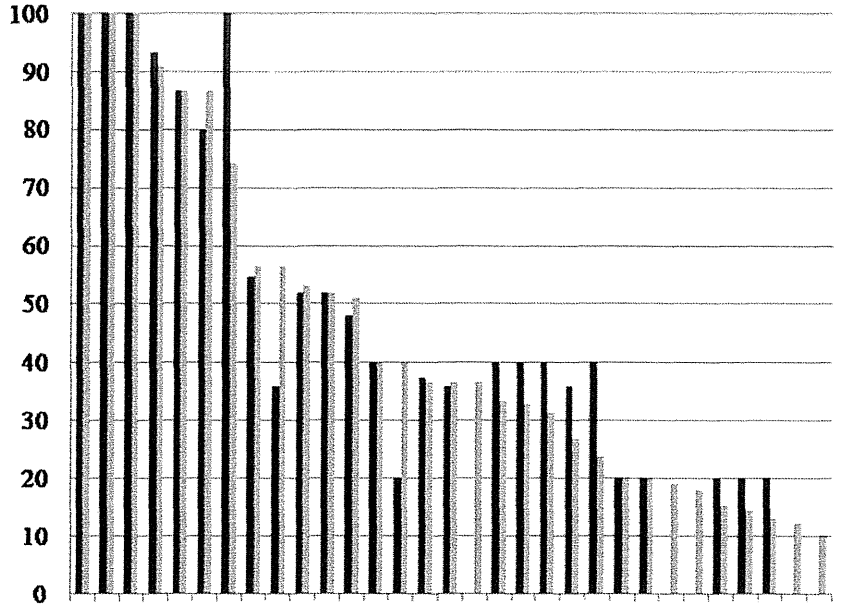

Fig. 1. Relative dose intensity of S-1 (*gray bars*) and cisplatin (*CDDP; black bars*) in each patient registered. The median relative dose intensities of S-1 and CDDP were 37% and 40%, respectively. S-1 given as monotherapy after failure of the protocol treatment was excluded from the calculation of relative drug intensity

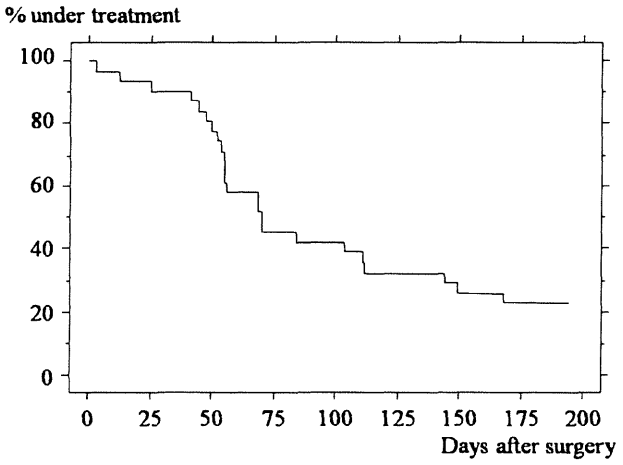

Fig. 2. Curve showing time to treatment failure. The median number of cycles delivered was two, with only 7/31 patients completing the five cycles as originally planned

Table 2. Adverse events

Events	All grades (%)	Grade 3 and 4 (%)
Leukopenia	21 (68)	2 (6.5)
Neutropenia	21 (68)	9 (29)
Anemia	30 (97)	5 (16)
Thrombocytopenia	13 (42)	0 (0)
Anorexia	24 (77)	7 (23)
Nausea	23 (74)	3 (10)
Vomiting	7 (23)	0 (0)
Fatigue	17 (55)	3 (10)
Diarrhea	13 (42)	1 (3.2)
Pigmentation	12 (39)	0 (0)
Stomatitis	8 (26)	0 (0)
GOT	13 (42)	0 (0)
GPT	12 (39)	0 (0)
Bilirubin	3 (9.6)	0 (0)
Creatinine	6 (19)	0 (0)

nonhematological toxicity included anorexia (23%), nausea (10%), and fatigue (10%). Anemia of all grades was observed in 97% of the patients, possibly reflecting the fact that the treatment was given postoperatively. Anorexia and nausea of all grades was observed in 77% and 74%, respectively. The most prominent skin manifestation was pigmentation, a symptom peculiar to S-1, showing diffuse darkening of skin color, which is sometimes observed in various parts of the body.

Survival

At a median follow-up time of 536 days or until death, the median progression-free survival time was 363 days, and the median overall survival time was 813 days (Fig. 3).

Discussion

Preoperative or perioperative adjuvant therapy with cytotoxic agents with or without radiation is considered promising for the treatment of gastric cancer [2–4]. In a trial testing perioperative chemotherapy, chemotherapy was more easily delivered preoperatively than postoperatively [3], partially because patients are more vulnerable to the drug-related adverse reactions shortly after gastrectomy. Accurate staging by arrays of examinations including staging laparoscopy followed by several months of preoperative therapy is not suitable for

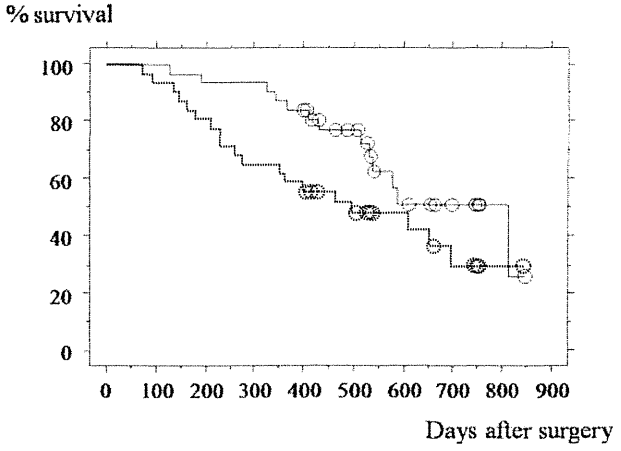

Fig. 3. Overall survival (*solid line*) and progression-free survival (*dotted line*) of all patients obtained after the mean follow up of 536 days or until death

delivery in general practice worldwide, and the standard of care in the United States, for example, is surgery followed by postoperative chemoradiation [2]. The optimal moment to perform curative surgery during the course of multimodal treatment is actually unknown, and is often decided upon according to common medical practice in each country.

Gastric cancer is more often diagnosed at an early stage in Japan compared with the timing in Western countries, due in part to nationwide screening, and this has led to a favorable outcome [12]. Early diagnosis and early treatment has therefore been considered the gold standard, and surgery is generally performed as soon as possible for fear of disease progression. Owing to the limitations in the sensitivity of preoperative imaging studies, with staging laparoscopy still not a standard practice in community hospitals, peritoneal metastases are sometimes found at surgery, either as macroscopically recognizable deposits or as micrometastases (CY1). In such circumstances, surgeons often proceed with gastrectomy as originally planned, and what is considered as the best available chemotherapy is given afterwards. Whether this strategy is superior to stomach-conserving therapy (staging laparoscopy followed by chemotherapy) is unknown, and the question is currently under investigation by a Japan Clinical Oncology Group (JCOG) randomized trial [13]. In the meantime, identification of the best available chemotherapy in the postoperative setting is warranted. It was logical to consider S-1/CDDP as a candidate for the standard of care in this setting, because this combination achieved a significantly longer median survival time in a phase III trial for advanced/metastatic gastric cancer when compared with S-1 monotherapy [8].

In the present study, the feasibility of postoperative S-1/CDDP was explored with patients who underwent surgery for stage IV disease. Another intention was that a positive result in this study may lead to the future application of this promising regimen as postoperative adjuvant therapy for stage III cancer, whose outcome remains unsatisfactory with the strategy of surgery followed by single-agent S-1. Difficulties had been anticipated, however, because the Japanese patients seemed vulnerable to various adverse events in the postoperative setting. S-1/CDDP has been feared because of its gastrointestinal and renal toxicity. Nausea and anorexia are commonly observed adverse reactions after the administration of CDDP, and dehydration due to impaired oral food intake could enhance the renal toxicity of CDDP. Despite the use of serotonin antagonists that have decreased the incidence of severe vomiting, patients already with some degree of gastrectomy-related discomfort might suffer from even mild gastrointestinal toxicities; much more so than those who have received other types of surgery. Renal toxicity in turn affects the clearance of gimestat, a component of S-1 that inhibits the metabolism of tegafur, leading to myelotoxicity and other adverse events [14]. Actually, the toxicity profile of S-1 monotherapy observed in a phase II study for advanced/metastatic cancer [6] was far less intense compared with that reported in a feasibility study in the postoperative adjuvant setting [15]. Myelotoxicity of all grades was increased by twofold and gastrointestinal toxicity by three-old in the feasibility study. Surprisingly, patients who received the same treatment in a subsequent randomized trial comparing postoperative S-1with surgery alone in curatively resected stage II/III cancer did better [4], owing to the establishment of more precise rules regarding dose attenuation, alteration of the treatment schedules, and discontinuation of the protocol treatment.

In addition to adhering to these rules for the safe postoperative delivery of S-1, the present study paid particular attention to renal function: serum creatinine level had to be within the normal range and creatinine clearance had to be no less than 50 ml/min for a patient to continue with the treatment. Consequently, 14 patients failed to fulfill either of several criteria to continue treatment, and had to refrain from receiving all five cycles, in addition to the 6 patients who refused further treatment. No long-lasting or life-threatening toxicity occurred, and the treatment could be considered safe as long as one adhered to the protocol. On the other hand, more patients might have completed the treatment as planned had the criteria been less stringent.

Anemia was the commonest adverse event, observed in 97% of our patients, and this may have enhanced general fatigue. Anorexia, nausea, and fatigue were the

commonest nonhematological adverse events. Toxicities generally tended to linger on, preventing the treatment from being delivered on schedule. Surprisingly, a comparison with the phase III trial comparing S-1/CDDP with S-1 monotherapy for advanced/metastatic cancer [8] revealed that the incidences of various toxicities observed in the S-1/CDDP group of that study, including those of grade 3 or greater, were actually similar to those observed in the present study. Presumably, it took longer to recover from these toxicities to fulfill the criteria for the initiation of a new cycle of treatment among the postoperative patients. In addition, even grade 1 or 2 gastrointestinal toxicities may have significantly affected patients who had just received gastrectomy.

In the present study, discontinuation of S-1/CDDP did not mean termination of chemotherapy, because 21 of the 24 patients who could not tolerate S-1/CDDP were treated with a second-line chemotherapy. Fifteen of the 20 patients who discontinued S-1/CDDP for reasons other than disease progression were given S-1 monotherapy. Thus, most patients who were entered in the trial eventually received S-1 until progression, and this presumably led to the median progression-free survival of 363 days. In another trial, the authors evaluated the efficacy of S-1 monotherapy among patients with free cancer cells in the peritoneal cavity (CY1 stage patients) treated with R1 resection [16]. Overall survival time in that trial was 705 days and progression-free survival was 496 days. With several patients treated by R2 resection included, the progression-free survival obtained in the present study could be considered as acceptable. With the relative dose intensity of less than 40%, however, S-1/CDDP did not meet the expectation as a candidate for further evaluation in the postoperative setting.

S-1 being a key drug for chemotherapy for gastric cancer in Japan, one may need to turn to other combinations if S-1 alone is deemed insufficient [17–19]. Taxanes with a lower incidence of gastrointestinal toxicities may be particularly good candidates as a partner of S-1 in the postoperative setting, although the superiority of these combinations over S-1 alone is yet to be proven by randomized trials. Another option could be oxaliplatin, which has been shown not to be noninferior to CDDP [20] and is associated with a lower incidence of gastrointestinal and renal adverse events. A combination of S-1 and oxaliplatin has been established and evaluated in a phase II trial [21], and further steps for its approval for gastric cancer treatment in Japan are awaited.

On the other hand, further attempts to reevaluate postoperative S-1/CDDP may not be futile. Aprepitant, a novel anti-emetic recommended by the National Comprehensive Cancer Network guideline that became available after the termination of the present study, could significantly improve tolerability to CDDP. In the meantime, members of the Japan Clinical Oncology Group proposed a modified version of the postoperative treatment in which the first course consisted of S-1 alone while CDDP was to be added only from the second course onwards, thus delaying the administration of CDDP. This strategy led to a significant improvement in compliance, and final analysis and publication of their data is eagerly awaited.

Of note, the combination of 5-fluorouracil (5FU) and CDDP has repeatedly failed to show prognostic benefit as a postoperative adjuvant therapy in Western countries [22, 23]. This could eventually be the fate of the S-1/CDDP combination given postoperatively. S-1/CDDP can be administered more easily in the neoadjuvant setting [24, 25], and this strategy is currently being explored in the JCOG0501 study (a phase III trial comparing a group treated by two to three courses of S-1/CDDP followed by surgery and S-1 monotherapy with a group treated by surgery followed by S-1 monotherapy) in a population with linitis plastica-type cancer. This trial could result in a paradigm shift in Japan, after which more patients with newly diagnosed advanced cancer would initially undergo chemotherapy.

To conclude, the combination of S-1 and CDDP in the dose and schedule used in the present study cannot be recommended as a candidate for postoperative chemotherapy in Japanese patients with gastric cancer. The use of less toxic drug combinations and a greater focus on neoadjuvant chemotherapy are among future strategies to improve the outcome of advanced gastric cancer.

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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

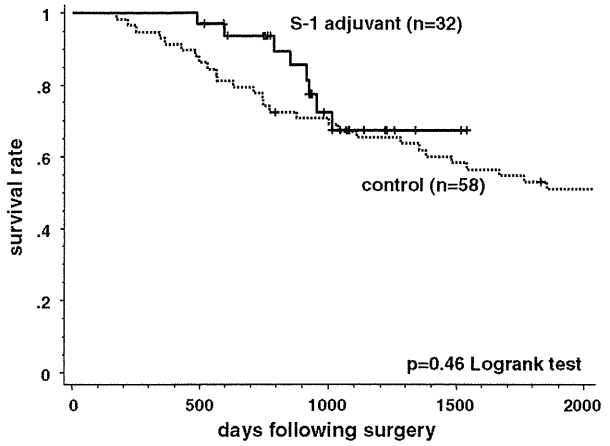

Fig. 1 Overall survival curve of patients with S-1 adjuvant therapy and historical controls. Three-year survival rates were comparable between groups. The difference in survival curves was not significant ($P = 0.46$; log-rank test)

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%)

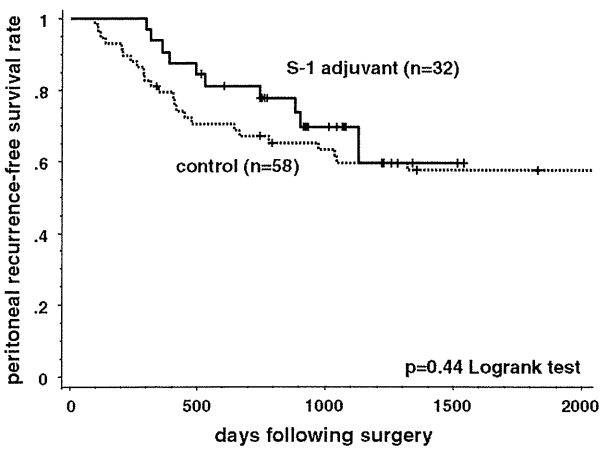

Fig. 2 Peritoneal recurrence-free survival curve of patients with S-1 adjuvant treatment and historical controls. Survival of the S-1 adjuvant group tended to be slightly favorable, but this was not significant ($P = 0.44$; log-rank test)

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

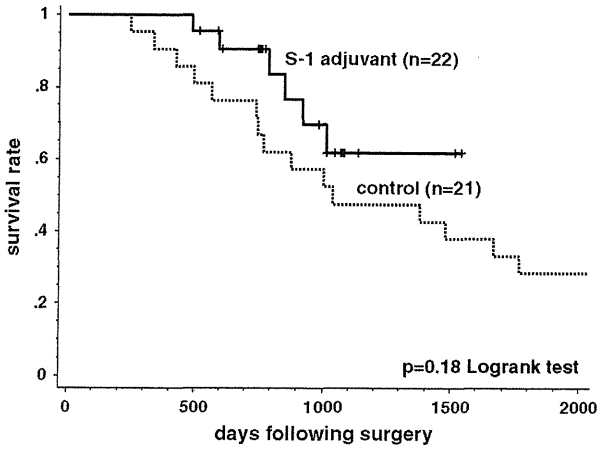

Fig. 3 Overall survival curve of surgical T3 patients with S-1 adjuvant treatment and historical controls. Survival of the S-1 adjuvant group tended to be slightly favorable, but this was not significant ($P = 0.18$; log-rank test)

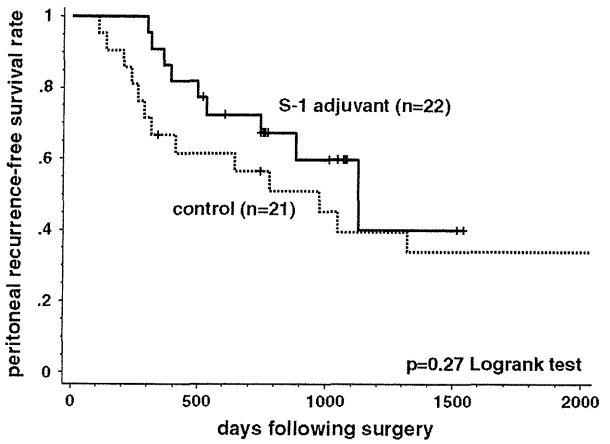

Fig. 4 Peritoneal recurrence-free survival curve for surgical T3 patients with S-1 adjuvant therapy and historical controls. Survival of the S-1 adjuvant group tended to be slightly favorable, but was not significant ($P = 0.27$; log-rank test)

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%)	

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

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.

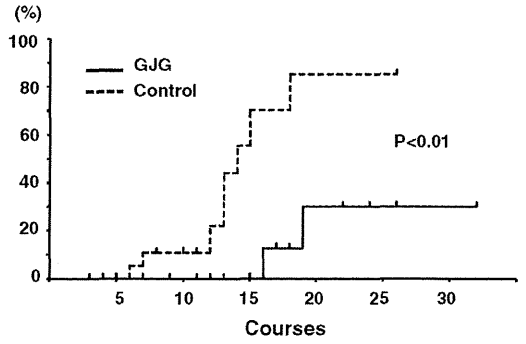

Fig. 1 Kaplan–Meier analyses showed that the incidence of grade 3 peripheral neuropathy occurred significantly less frequently in the GJG group than the control group ($p < 0.01$, log-rank test)

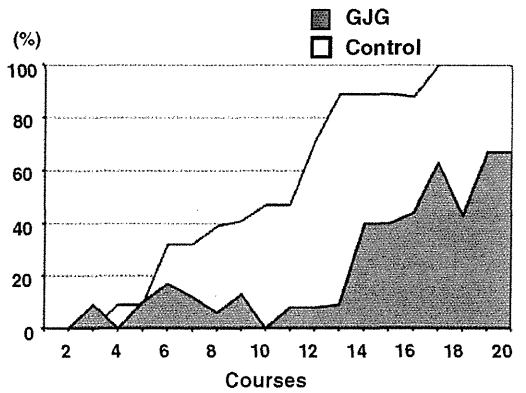

Fig. 2 The percentage of grade 2 and 3 peripheral neuropathy in each cycle was lower in the GJG group than the control group

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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