and no other non-hematological toxicities > grade 2. The criteria for the administration of CPT-11 on day 1 of the second and subsequent courses included a white blood cell count >3000/mm^3, a neutrophil count >2000/mm^3, a platelet count >100 000/mm^3, creatinine <1.5 mg/dl, absence of fever (>38°C) caused by infection, no diarrhea and no other non-hematological toxicities > grade 2. The criteria for administration of UFT on day 1 of each course included a white blood cell count >2000/mm^3, no diarrhea, no stomatitis > grade 1, no elevation of AST–ALT > grade 1 and no other non-hematological toxicities > grade 2. Dose modification for toxicity was performed as follows. If leucopenia (<1000/mm^3), thrombocytopenia (<20 000/mm^3), neutropenia (<1000/mm^3) associated with fever (>38°C) or infection, or non-hemaological toxicities > grade 3 occurred, the dose of CPT-11 was reduced by 20% for the subsequent course. In the case of stomatitis > grade 3, the dose of UFT was reduced by 60 mg/m^2/day.

Treatment

Protocol treatment consisted of two 35-day cycles of combination chemotherapy with CPT-11 and UFT. During the phase I study, CPT-11 was administered intravenously over 90 min at a starting dose of 80 mg/m^2 (level 1), followed by 100 mg/m^2 (level 2), 125 mg/m^2 (level 3), and 150 mg/m^2 (level 4). Dosing was performed on days 1 and 15. For the phase II study, the dose of CPT-11 was fixed at 150 mg/m^2 based on the results obtained during phase I. UFT was administered orally at a fixed dose of 300 mg/m^2 on days 1–28, followed by a 1-week rest during each course (35 days). In this study, UFT-E was used as tegafur/uracil (UFT). UFT-E is an enteric-coated granule of UFT and was developed for the purpose of mitigation of upper gastrointestinal toxicities of UFT. The previous study had shown that UFT-E had significantly lower occurrence of nausea and vomiting compared to UFT capsule (25). At least two courses of treatment were required for evaluation.

Trial Design

Phase I

This study was designed as a combined phase I/II study. Dose-limiting toxicities (DLT) during phase I were defined as grade 4 leucopenia, neutropenia, or thrombocytopenia, any grade 3/4 non-hematological toxicity (excluding nausea and vomiting), any non-hematological toxicity that resulted in skipping of the administration of CPT-11 on day 15 of the first course despite postponing treatment for up to 1 week, or reduced the administration period of UFT-E (28 days) to <14 days in the first course, or delayed administration of CPT-11 on day 1 of the second course. Cohorts of three to six patients were enrolled. If no DLT was observed, subsequent patients were treated at the next dose level of CPT-11. If one patient experienced DLT, the same dose level was used to treat a maximum of six patients. If two of the initial three or four out of six patients at a particular level experienced DLT, this dose level was defined as the maximum tolerated dose (MTD) and the preceding dose level was classified as the recommended dose of CPT-11 for this combined regimen. If MTD was not achieved at dose level 4, we defined the recommended dose of CPT-11 as 150 mg/m^2 because the maximum dosage of CPT-11 permitted and covered by medical insurance in Japan was 150 mg/m^2. An additional five patients were enrolled to receive this recommended dose for further confirmation and then it was used in the following phase II trial.

Phase II

In addition to the eight patients treated at dose level 4 in the phase I study, 27 patients were enrolled to receive the recommended dose of CPT-11 during the phase II study in order to assess the toxicity profile more accurately and predict the possible efficacy of this regimen.

Assessment of Toxicity and Response

Toxicity was assessed according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 2.0. Toxicities and laboratory abnormalities were assessed twice weekly during the first course of the phase I trial and during all courses of the phase II trial. Responses were evaluated according to the RECIST criteria. A complete or partial response required subsequent confirmation of the response after an interval of at least 4 weeks.

Statistical Analysis

The sample size for the study was calculated from an expected response rate of 30% and a minimum of 10% with α error of 0.05 and β error of 0.1. The required number of patients was estimated to be 32. Finally, we set it at 35 patients in order to allow for 10% of disqualified patients.

This trial was approved by the institutional review boards of all participating hospitals.

RESULTS

Patient Characteristics

Between July 2001 and February 2004, 49 patients were enrolled in this phase I/II study (22 patients in phase I and 27 in phase II). The characteristics of these patients are shown in Tables 1 and 2, respectively.

Phase I Trial

Toxicity

Twenty-two patients were enrolled in the phase I study. Among them, two patients dropped out because of a protocol

Table 1. Patient characteristics (phase I)

Sex	Male/Female	17/5
Age (median)	years	65.5 (38–74)
PS	0/1	21/1
Initial/recurrence		7/15
Histology	wel/mod/por/muc/unknown	6/12/0/3/1
Prior treatment	none/surg/chemo/surg + chemo	1/5/1/15
Metastatic sites	liver/lung/LN/other	3/12/8/9

PS, performance status; wel, well differentiated adenocarcinoma; mod, moderately differentiated adenocarcinoma; por, poorly differentiated adenocarcinoma; muc, mucinous carcinoma; surg, surgery; chemo, chemotherapy; LN, lymph node.

Table 2. Patient characteristics (phase II)

Sex	Male/Female	26/9
Age (median)	years	63 (46–74)
PS	0/1	34/1
Initial/recurrence		14/21
Histology	wel/mod/por/muc/unknown	14/17/1/2/1
Prior treatment	none/surg/chemo/surg + chemo	1/14/0/20
Metastatic sites	liver/lung/LN/other	14/17/10/8

*Including 8 patients treated at dose level 4 in phase I.

violation and refusal during the first course, respectively, and therefore 20 patients (dose level 1:4, dose level 2:6, dose level 3:3, dose level 4:7) were evaluated for toxicity and response. Hematological and non-hematological toxicities are listed in Tables 3 and 4, respectively. The only DLT was observed in one patient receiving dose level 2, who suffered from grade 4 neutropenia, and CPT-11 was well tolerated even at a dose of 150 mg/m^2 (dose level 4). Accordingly, the maximum tolerated dose (MTD) of CPT-11 was determined to be 150 mg/m^2 and another 27 patients were treated with this dose of CPT-11 during the phase II study.

Table 3. Hematological toxicities (phase I)

Grade	Level 1 ($n=4$)				Level 2 ($n=6$)				Level 3 ($n=3$)				Level 4 ($n=8$)			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Hemoglobin ↓	2	1			3								4	1		
Hypoglobulia					1				2				1			
Leukopenia	1				2	1	1		2				1	2		
Neutropenia	1				3			1(DLT)		2			1	1	2	
Thrombocytopenia					1											

DLT, Dose-limiting toxicities.

Table 4. Non-hematological toxicities (phase I)

Grade	Level 1 ($n=4$)				Level 2 ($n=6$)				Level 3 ($n=3$)				Level 4 ($n=8$)			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Stomatis													1			
Diarrhea	1				2	2			2				1			
Anorexia	2				4				1				5	2		
Nausea/vomiting	2				4				1				4	2		
Alopecia		1			2	2				1				1		
Fatigue	1				2				1				1	1		
Taste disturbance	1															
Stammering					1											
Constipation														1		
Abdominal pain						1							1	1		
AST/ALT ↑					2				1							
T-bil ↑					1											
Na ↓													1			
Cl ↑													1			
TP ↓					1				1				1			
Hyperglycemia													1			

AST, aspartate aminotransferase; ALT, alanine aminotransferase; T-bil, total bilirubin; Na, sodium; Cl, chloride; TP, total protein.

Response

The response obtained at each dose level during the phase I trial is shown in Table 5. There were two partial responses (PR), with a response rate of 2/6 (33%) among patients receiving first-line therapy and 2/20 (10%) overall.

Phase II Trial

Toxicity

Twenty-seven patients were enrolled in the phase II study and a total of 35 patients (including eight patients given dose level 4 during phase I) were evaluated at a CPT-11 dose of 150 mg/m^2. The characteristics of these

Table 5. Response (phase I)

Dose level	CPT-11 dose (mg/m^2)	No. of patients treated	No. of patients evaluated	Response rate (%)
1	80	4	4	00.0 (0/4)
2	100	7*	6	16.7 (1/6)
3	125	3	3	00.0 (0/3)
4	150	8*	7	14.3 (1/7)
Overall		22	20	10.0 (2/20)

*No. 2-6, drop out (protocol violation); No. 4-4, dropout (patient refusal).
First-line response rate: 33.3% (2/6).
Overall response rate: 10.0% (2/20).

Table 6. Hematological toxicities (phase II)

Grade	Grade				Total		≥ Grade 3	
	1	2	3	4	No.	(%)	No.	(%)
Hemoglobin	18	6	1	0	25	(71.4)	1	(2.9)
Hypoglobulia	2	0	0	0	2	(5.7)	0	(0)
Leucopenia	4	12	1	0	17	(48.6)	1	(2.9)
Neutropenia	1	7	7	2	18	(51.4)	9	(25.7)
Thrombocytopenia	2	0	0	0	2	(5.7)	0	(0)

NCI-CTC, national cancer institute common toxicity criteria.
*Judged by NCI-CTC.

patients are shown in Table 2. The hematological and non-hematological toxicities that occurred during phase II are listed in Tables 6 and 7, respectively. There were no treatment-related deaths. The most common hematological toxicity was anemia (25/35, 71.4%), followed by neutropenia (18/35, 51.4%) and leucopenia (17/35, 48.6%). However, myelosuppression was comparatively mild, with grade 3–4 neutropenia occurring in nine patients (25.7%) and grade 3 anemia or leucopenia occurring in one patient each. The most common non-hematological toxicity was nausea/vomiting (25/35, 71.4%), followed by anorexia (24/35, 68.6%), diarrhea (13/35, 37.1%), alopecia (13/35, 37.1%) and fatigue (8/35, 22.9%). The grade 3 toxicities were anorexia in four patients (11.4%), diarrhea in two patients (5.7%), and nausea/vomiting in one patient (2.9%).

Table 7. Non-hematological toxicities (phase II)

Grade	Grade				Total		≥ Grade 3	
	1	2	3	4	No.	(%)	No.	(%)
Diarrhea	9	2	2	0	13	(37.1)	2	(5.7)
Abdominal pain	2	1	0	0	3	(8.6)	0	(0)
Nausea/vomiting	24	4	1	0	25	(71.4)	1	(2.9)
Anorexia	18	2	4	0	24	(68.6)	4	(11.4)
Constipation	0	1	0	0	1	(2.9)	0	(0)
Alopecia	6	7	–	–	13	(37.1)	–	–
Fatigue	5	2	1	0	8	(22.9)	0	(0)
Stomatitis	1	1	0	0	2	(5.7)	0	(0)
Taste disturbance	1	0	0	0	1	(2.9)	0	(0)
Neurologic—other	1	0	0	0	1	(2.9)	0	(0)
Itching	1	0	0	0	1	(2.9)	0	(0)
T-bill ↑	2	0	0	0	2	(5.7)	0	(0)
AST/ALT ↑	2	1	0	0	3	(8.6)	0	(0)

*Judged by NCI-CTC.

Table 8. Response (phase II)

	CR	PR	SD	NE	PD	Response rate (%)
Response	2	6	13	7	7	22.9 (8/35)
Prior chemotherapy (+)*	2	3	6	5	3	26.3 (5/19)
Prior chemotherapy (–)**	0	3	7	2	4	18.8 (3/16)

CR, complete response; PR, partial response; SD, stable disease; NE, not evaluable; PD, progressive disease.
*Recurrent cases less than 6 months after completion of adjuvant chemotherapy or advanced case that received one or more prior chemotherapy.
**Recurrent cases more than 6 months after completion of adjuvant chemotherapy or advanced case that received no prior chemotherapy.

Response and survival

The response to treatment during phase II is shown in Table 8. Two patients showed a complete response (CR). The measurable metastatic lesions of these two patients were lymph nodes and both patients had already received chemotherapy before the present study. Six patients achieved a partial response, including three patients with prior chemotherapy and three without it. Total response rate was 22.9% (8/35) and there was no difference in response rate in between two groups with or without prior chemotherapy (26.3% (5/19) versus 18.8% (3/16)). The median follow-up time was 16.4 months (3.5–43.4 months) and 19 deaths have occurred so far. The survival curve is shown in Fig. 1: median overall survival time was calculated to be 23.9 months and the 1-year survival rate was 67.2%.

Dose intensity

The number of courses given to 35 patients ranged from 1 to 8 (mean: 3.5 courses). The mean dose intensity of CPT-11

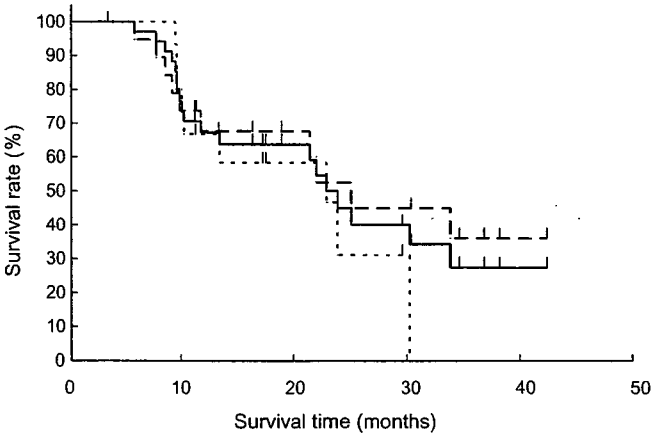

Figure 1. Survival curves of patients treated with a combination of CPT-11 and UFT (phase II). Solid line, survival curves of all patients (median survival time, 23.9 months); short dashed line, survival curves of patients without prior chemotherapy (median survival time, 23.0 months); dashed line, Survival curves of patients with prior chemotherapy (median survival time, 25.1 months).

was 51 mg/m^2/week and the relative dose intensity was 85%. Three patients required reduction of the dose of CPT-11 and administration was skipped on day 15 of treatment as a result of various toxicities in 11 patients during the second or subsequent course, as reflected in the data on dose intensity. The mean relative dose intensity of UFT was 85%.

DISCUSSION

The aim of this study was to determine the maximum tolerated dose of CPT-11 when administered in combination with UFT, an oral 5-FU derivative, to patients with advanced colorectal cancer. In addition, the activity and the toxicity profile of this regimen were assessed to determine its potential clinical usefulness.

During the phase I study, the recommended dose of CPT-11 was determined to be 150 mg/m^2. The phase II study was conducted with this dose of CPT-11, which showed that the combined regimen could be safely administered on an outpatient basis. There were no treatment-related deaths. Hematological toxicity was comparatively mild, with grade 3–4 neutropenia being seen in nine patients (25.7%) and grade 3 anemia or leucopenia only being detected in one patient each. The incidence of grade 3 non-hematological toxicity was anorexia occurred in four patients (11.4%), diarrhea occurred in one patient (2.9%) and no grade 4 non-hematological toxicities. Douillard et al.'s regimen, infusional 5-FU/LV plus CPT-11, is one of the standard chemotherapies and the incidence of common grade 3–4 toxicities were neutropenia (28.8%), leucopenia (20.4%), diarrhea (44.4%), nausea (7.4%) and vomiting (11.1%) (16). Our study showed that the toxicity profile of CPT-11 plus UFT was similar to that for the combination of CPT-11 and infusional 5-FU/LV, but was less severe. Thus, this regimen combining CPT-11 and UFT is considered to be feasible and safe for administration on an outpatient basis.

Total response rate, 22.9% (8/35), is fairly acceptable. However, the median overall survival time (25.1 months) and the 1-year survival rate (67.5%) of the patients with prior chemotherapy enrolled in phase II were comparable to the results obtained in previous studies on the combination of CPT-11 plus 5-FU in the second-line setting (26–29), and were quite promising.

As pointed out by Ho et al., the convenience and lower cost of oral 5-FU may be preferable for many patients, particularly those receiving palliative chemotherapy (21). A recent questionnaire study performed by Borner et al. compared oral with intravenous 5-FU treatment and revealed that most patients preferred the oral regimen because of the convenience of taking medication at home, less severe toxicity (less stomatitis or diarrhea), and a general preference for tablets over injections (30). Several treatment protocols that combine oral fluoropyrimidines (e.g. UFT with or without leucovorin, TS-1, or capecitabine) with CPT-11 or oxaliplatin have been utilized for patients with advanced colorectal cancer. Although there is promising data in the combination of capecitabine and oxaliplatin (24,31), as for the combination of capecitabine and CPT-11, any useful results have not been reported yet (32,33). Moreover, TS-1 or UFT/LV combined with CPT-11 are currently under investigation.

In conclusion, the present findings suggest that the combination of CPT-11 and UFT is a promising regimen with respect to safety and efficacy for patients who have advanced/metastatic colorectal cancer in the second-line setting. Considering the excellent safety profile of this regimen and no study comparing FOLFIRI and CPT-11, it could be a very good candidate for the second-line treatment after FOLFOX failure at present. Along with the importance of establishing a standard protocol that is proven to be the most effective for colorectal cancer, we hope that the most appropriate and convenient of several possible regimens will be selected for each patient in order to improve the quality of life.

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Conflict of interest statement
None declared.

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Phase II Study of Biweekly Paclitaxel and Cisplatin Combination Chemotherapy in Advanced Gastric Cancer: Korea–Japan Collaborative Study Group Trial

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Background: Benefits of chemotherapy have generally been modest in gastric cancer, although those regimens developed more recently have produced higher response rates. Paclitaxel plus cisplatin is one such regimen and divided administration of paclitaxel has been suggested to be associated with lower neurological and hematologic toxicities and be able to achieve higher paclitaxel dose intensities than paclitaxel administration at 175 mg/m^2 every 3 weeks. This study was undertaked to assess the efficacy and toxicity of a biweekly paclitaxel and cisplatin combination treatment in advanced gastric cancer.
Methods: Twenty-five patients from Japan and Korea, 50 patients in total, were entered into this trial which was conducted from October 2004 to June 2005. Median age of the patients was 57 years (range: 26–78). Paclitaxel 140 mg/m^2 was administered intravenously on days 1 and 15 of each 4-week cycle. Cisplatin 30 mg/m^2 was also administered on days 1 and 15 with standard hydration. A total of 278 courses of treatment (two treatment courses per cycle) were conducted for 50 patients. The median number of treatment cycles per patient was two with a range of one to six.
Results: Nine of the 50 patients responded to the treatment, with an overall objective response rate of 18% (95% CI, 12–41), which included one complete response. Two patients were not evaluable and 14 patients had stable disease as best response. The median survival duration of the 50 patients was 333 days (range: 52–637+ days). The main toxicity was neutropenia. Significant toxicity (NCI-CTC grade 3 or 4) included neutropenia in 19 patients (38%), anorexia in four (8%), infection in three (6%), anemia in three (6%), and abdominal pain in three (6%).
Conclusions: Biweekly paclitaxel and cisplatin combination chemotherapy showed modest activity in advanced gastric carcinoma with a favorable toxicity pattern.

Key words: gastric cancer – paclitaxel – cisplatin – combination chemotherapy

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INTRODUCTION

Although the incidence of gastric carcinoma has fallen in most Western countries, it remains a significant problem in terms of global health and is the second most common cause of cancer mortality worldwide (1). Surgical resection is the only therapeutic modality capable of cure, while improvements in early diagnosis, pre-operative assessment, and surgical techniques have increased the number of potentially curative resections over the last 20 years. However, despite these improvements prognosis remains poor with less than a 30% 5-year survival rate in the USA (2).

The reasons for this grim outlook are that both local and distant relapses, even after apparently complete resection, are common and that many patients present inoperable disease at the time of diagnosis. Although it was previously not clear whether chemotherapy contributed to the survival of patients with unresectable advanced gastric cancer, recent studies that compared patients who received chemotherapy with those not treated with chemotherapy (best supportive care: BSC) strongly suggest that chemotherapy improves survival in advanced gastric cancer (3–5).

5-FU and/or cisplatin (CDDP)-based combination chemotherapy continues to be widely used, but the continuing lack of progress of chemotherapy for the treatment of gastric cancer has prompted the evaluations of new agents and/or combinations including taxanes, irinotecan, capecitabine, S-1 and others.

Paclitaxel (TXL) was originally extracted from the bark of Taxus brevifolia. It causes stabilization/hyperplasia of microtubules by facilitating microtubule protein polymerization, and thereby inhibits mitosis to display anti-tumor effects. TXL has shown encouraging activity as a single agent for gastric cancer treatment, with reported response rates ranging from 17 to 28% (6–9). A late phase II study in Japan produced favorable results with response rates of 23.3% for the entire population and 25.8% for cases that had undergone prior chemotherapy (7,10).

TXL and CDDP have different modes of action and fewer overlapping toxicities than other regimens. Moreover, TXL and CDDP combination therapy has been used across the world, including Japan and Korea. In particular, large-scale clinical studies have been conducted on this regimen in lung and ovarian cancers, and its clinical usefulness (including survival benefits) has been proven by comparisons with existing standard regimens. Weekly and biweekly administrations of both drugs have also been examined as short-term treatment and as means of increasing dose intensity (11–14).

Although cytotoxic chemotherapy has been widely used in advanced gastric cancer and has been demonstrated to be an effective palliative management, response duration of first-line chemotherapy is brief and survival gain is modest in gastric cancer. Moreover, the overall prognosis of patients failing first-line chemotherapy is poor, and although many of these patients are candidates for second-line chemotherapy at the time of first-line chemotherapy failure, no established second-line chemotherapeutic regimen is now available. Candidate regimens for first- or second-line chemotherapy for advanced/recurrent gastric cancer should have a good response rate and improve survival without compromising patient quality of life. We have thus sought to define optimal divided doses for TXL and TXL/CDDP-based therapies. In a Japanese phase I study, CDDP was fixed at 30 mg/m^2 and TXL increased in increments of 20 mg/m^2 from 100 mg/m^2. The maximum tolerable dose (MTD) in this phase I study was set at TXL 180 mg/m^2 + CDDP 30 mg/m^2. Although the sample size was small, the response rate achieved was 46.1% (6/13), and median survival duration was 288 days. Subsequently, a pilot phase II study was conducted in Japan to examine the efficacy/safety of treatment at TXL 160 mg/m^2 + CDDP 30 mg/m^2; 20 patients were registered in this study. Unfortunately, a dose of TXL 160 mg/m^2 + CDDP 30 mg/m^2 was not feasible in this group of patients, because for 11 of the 20 patients (55%) it could not be administered on a biweekly schedule due to delayed myelosuppression recovery at this level (15). Therefore, at a core meeting of the Japan–Korea Cooperative Gastric Cancer Study Group, it was decided to reduce the dose to TXL 140 mg/m^2 + CDDP 30 mg/m^2.

PATIENTS AND METHODS

Eligibility

Between October 2004 and June 2005, 50 patients from Japan and Korea were enrolled in this study. Patients with histologically or cytologically proven metastatic or locally advanced inoperable gastric carcinoma were eligible. Patients were required to be 20–80-years old with a life expectancy of >3 months and to have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2. All patients were required to have at least one target lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Patients who had received less than one palliative chemotherapy (considering that patients receive one palliative chemotherapy if recurrence occurred within 6 months of adjuvant therapy) were eligible and patients should not be under the influence of the effects or side effects of previous treatments; at least 4 weeks must have passed since the last drug administration, excepting the administration of oral fluoropyrimidine or its derivatives (e.g. capecitabine or TS-1), in which case, a 2-week drug-free period was required. All eligible patients were also required to have adequate hematological counts (an absolute neutrophil count of ≥2000/μl, a platelet count of ≥100 000/μl and hemoglobin ≥9.0 g/dl), laboratory results within the following limits (serum aspartate aminotransferase [AST] and alanine aminotransferase [ALT] < 2 × UNL (excepting patients with liver metastasis: <UNL × 3), serum bilirubin ≤1.5 mg/dl), and renal function (creatinine clearance >50 ml/min, according to the Cock–Loft formula).

Exclusion criteria were as follows: cardiac disease, such as, ischemic heart disease or arrhythmia; a history of

myocardial infarction within the previous 6 months; liver cirrhosis of Child class B or C; fresh gastrointestinal bleeding requiring repeated blood transfusion; psychotropic disease requiring major tranquilizer or major anti-psychotic medication; poorly controlled diabetes; a history of hypersensitivity to the treatment drugs or preparations containing polyoxyethylene castor oil (Cremophor EL®); a history of previous treatment with taxane compounds (TXL, docetaxel) or platinum compounds (excepting adjuvant chemotherapy undertaken prior to 6 months before study registration); or peripheral neuropathy of at least Grade 2 during previous chemotherapy. Pregnant or nursing women were also excluded. Finally, all patients provided informed consent and this study was approved by the review boards of each of the 15 participating institutions.

Treatment

TXL (Taxol®; Bristol-Myers-Squibb Company, Princeton, NJ) 140 mg/m^2 was administered intravenously (i.v.) in 250–500 ml glucose solution or physiological saline solution for 1–3 h on days 1 and 15 of each 4-week cycle. Cisplatin 30 mg/m^2 was also administered as a 1- or 2-h i.v. infusion on days 1 and 15 with standard hydration. As prophylactic agents, dexamethasone (i.v., 20 mg), diphenhydramine (p.o., 50 mg), and ranitidine hydrochloride (i.v., 50 mg) were given 30 min before TXL administration. All patients received adequate anti-emetic therapy prior to chemotherapy. Granulocyte colony-stimulating factor (G-CSF) was administered at physician's discretion or taking insurance status of the countries in considerations. Treatment was repeated every 4 weeks as toxicity permitted and continued in the absence of disease progression or unacceptable toxicity.

Subsequent treatment cycles were started only when the neutrophil count was $\geq$1500/mm^3 and the platelet count was $\geq$100 000/mm^3. Planned treatment was withheld until recovery in cases with: a fever of 38°C or higher, an ECOG performance status of 3, or non-hematologic toxicity of grade 3 or higher. When drugs could not be administered owing to adverse events even after a 2-week postponement from the planned day of the next administration, treatment was stopped. If febrile neutropenia, thrombocytopenia $\geq$ grade 3, non-hematological toxicity $\geq$ grade 3 or peripheral neutropathy $\geq$ grade 2 were had occurred during the previous treatment, the dose of TXL was reduced to 120 mg/m^2 for the following treatment. A second episode required a dose reduction of TXL to 100 mg/m^2 on subsequent treatments. If repeated episodes of febrile neutropenia, thrombocytopenia $\geq$ grade 3, non-hematological toxicity $\geq$ grade 3, or peripheral neuropathy $\geq$ grade 2, occurred despite in spite of dose reduction of TXL to 100 mg/m^2, treatment was stopped. Dose escalation after dose reduction was not permitted. Complete blood, differential and platelet counts were evaluated once a week or more frequently when patients were myelosuppressed during treatment resting periods. Serum creatinine, blood urea nitrogen, electrolyte and magnesium levels were checked before each chemotherapy cycle.

Response to Treatment and Adverse Effects

Before entering the study, all patients received physical examination, and full blood count and serum chemistry analyses. Chest X-ray, ECG, upper gastrointestinal endoscopies, abdominal computer tomographic scans and other appropriate procedures were also performed. Patients were given a physical examination, a subjective/objective symptom evaluation and routine blood tests twice-weekly. Every 4 weeks, a biochemistry blood examination was added to this basal evaluation. After every two cycles of treatment, response was evaluated using RECIST criteria. Of the lesions observed prior to treatment, a maximum of five measurable lesions from each metastasized organ up to a total of 10 lesions were selected as target lesions. In cases of partial or complete response, a confirmative computer tomographic (CT) scan was performed 4 weeks later and this was followed by a CT scan after every two treatment cycles. Toxicity was reported using a National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 2.0 toxicity scale.

Statistical Analysis

The present study was a confirmatory phase II study, and was undertaken to determine the response rate of biweekly TXL and CDDP combination chemotherapy for unresectable locally advanced or metastatic gastric cancer. The secondary objective was to evaluate the toxicity of this regimen and to determine survival duration and time to progression. The 95% confidence interval (CI) for response was calculated. Survival probabilities were estimated using the Kaplan–Meier method. Response duration was calculated from the date of response confirmation to the date when progressive disease was first observed. Survival duration was calculated from the first day of treatment until death or the last follow up. The target sample size was 50 cases. Because the response rate for TXL was determined to be 23% during its development, the threshold efficacy rate was set at 20% for combination chemotherapy. In addition, based on the prior phase I study and the results of other studies, the necessary sample size was calculated to be 50 cases when the expected efficacy rate for the combination chemotherapy was set at approximately 40%, and this corresponded to an α of 0.05 and power $(1 - \beta)$ of 0.9.

RESULTS

Patient Characteristics

Twenty-five patients from Japan and Korea (a total of 50 patients) were enrolled into this trial from October 2004 to June 2005. Patient characteristics are listed in Table 1. Forty-eight patients (96%) had a relatively good performance

Table 1. Patient characteristics

Patient characteristics	Japan ($n = 25$)	Korea ($n = 25$)	Total ($n = 50$)
Median age (range)	65 (50–78)	46 (26–78)	56 (26–78)
Gender (male/female)	23/2	18/7	41/9
ECOG performance status (0/1/2)	16/8/1	8/16/1	24/24/2
Histology			
Papillary adenocarcinoma	1	0	1
Tubular adenocarcinoma	14	7	21
Poorly differentiated adenocarcinoma	6	14	20
Signet ring cell carcinoma	2	4	6
Mucinous adnocarcinoma	2	0	2
Metastatic sites			
Liver	14	10	24
Lung	2	0	2
Lymph node	15	19	34
Others	2	5	7
Previous treatment			
Surgery	17	11	28
Adjuvant chemotherapy	8	5	13
Palliative chemotherapy	13	2	15
Radiation therapy	1	0	1

ECOG, Eastern Cooperative Oncology Group.

status of grade 0 or 1. Median patient age was 57 years with a range of 26–78 years. Korean patients tended to be younger than Japanese patients (median age 46 years (range: 26–78) versus 65 years (range: 50–78), respectively). Forty-one patients were male and 28 patients (17 Japanese and 11 Korean) had undergone surgical resection. Eleven (eight Japanese and three Korean) of the 28 had previously received adjuvant chemotherapy after curative surgery. The post-operative chemotherapy regimens of Korean patients were; 5-FU alone one patient, 5-FU + cisplatin (FP) one, and 5-FU + adriamycin + mitomycin (FAM) one, respectively. The post-operative regimens of Japanese patients were; TS-1 alone, 6, and UFT alone, 2. Fifteen patients had previously received palliative chemotherapy. The palliative chemotherapy regimens of the two Korean patients were Heptaplatin (Sunpla®, Sunkyung Pharm., Seoul, Korea) + 5-FU + leucovorin and TS-1 alone, respectively. The palliative chemotherapy regimens of the 13 Japanese patients were: 5-FU 1 patient, 5-FU + leucovorin 2, FP 1, TS-1 8, and TS-1 + irinotecan 1, respectively. Twenty-one patients were treatment naïve and one patient had received palliative radiation therapy for metastatic bone disease before enrollment.

Response to Chemotherapy

A total of 278 treatment courses (two treatment courses per cycle) were conducted for the 50 patients. The median

Table 2. Response rate

	Japan No. (%)	Korea No. (%)	Total No. (%)
Complete response	0 (0)	1 (4)	1 (2)
Partial response	3 (12)	5 (20)	8 (16)
No change	9 (36)	5 (20)	14 (28)
Progressive disease	13 (52)	12 (48)	25 (50)
Not evaluable	0 (0)	2 (8)	2 (4)
Response rate	3/25 (12)	6/25 (24)	9/50 (18)

number of treatment cycles per patient was two with a range from one to six. As nine of the 50 enrolled patients responded to treatment, the overall objective response rate was 18% (95% CI, 12–41), which including one complete response (Table 2). Two patients were not evaluable (one for treatment refusal after the first treatment cycle, one for treatment refusal after the third cycle due to grade 4 anemia) and 14 patients achieved a best response of stable disease. Of the 15 patients, who had been previously received palliative chemotherapy, two (13%) achieved a response. The overall response rate was 22.2% (7/35) among chemotherapy naïve patients and the Korean patient response rate was twice that of the Japanese patients (6/25, 24% versus 3/25, 12%). After a median follow-up of 659 days, 42 patients had disease progression or had died and thus the median progression-free survival was 86.5 days (range: 27–608+ days; Fig. 1). At the last follow-up, which was performed during October 2006, median survival duration of the 50 patients was 333 days (range: 52–637+ days; Fig. 2). Thirty seven patients (74%) had subsequent therapy after failure, 12 patients did not get further therapy and post-treatment is unknown in one patient. All 37 patients (18 patients in Korea and 19 patients in Japan) were treated with chemotherapy after failure to biweekly TXL + cisplatin regimen. Although, palliative surgery and radiation therapy were given in five patients, respectively, chemotherapy was given concurrently or subsequently with those local treatments. Most commonly used chemotherapeutic regimen was irinotecan-based chemotherapy in 23 patients (12 patients in Korea and 11 patients in Japan).

Toxicity

Seven patients completed six treatment cycles without progression and 32 patients could not complete treatment as a result of progressive disease. Other reasons for treatment discontinuation were; consent withdrawal after the third treatment cycle for one, treatment refusal after experiencing severe adverse events in five (grade 4 anemia, fatigue, sensory neuropathy, abdominal pain and fatigue), and repeated adverse events of more than grade 3 after two dose reductions in two (grade 3 anorexia and grade 4 neutropenia), unrecovered drug toxicity given the time limitation

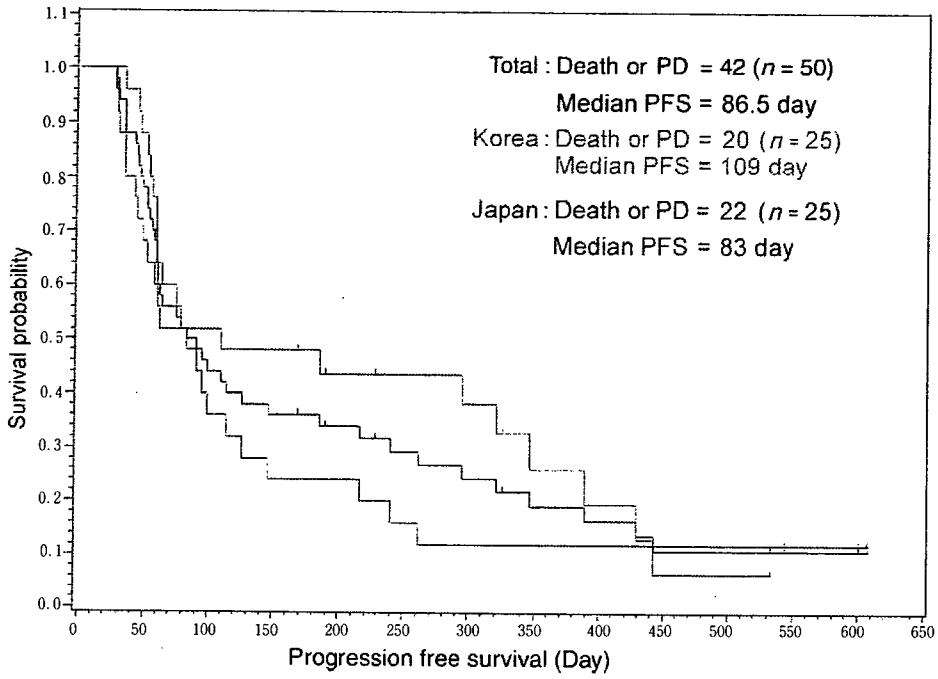

Figure 1. Progression free survival. PD, progressive disease; PFS, progression free survival.

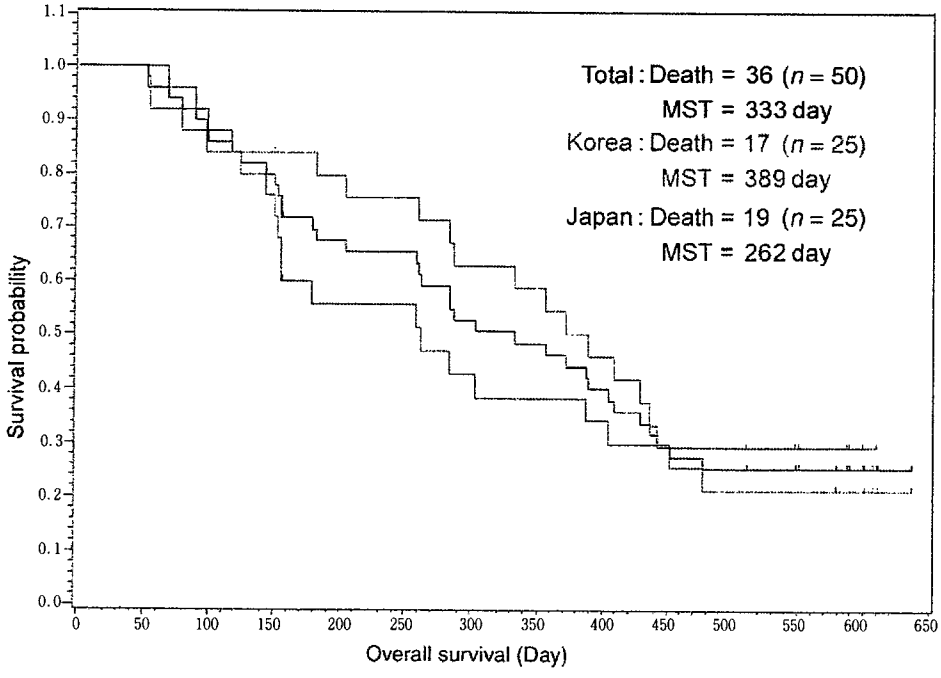

Figure 2. Overall survival. MST, median survival times.

in two (neutropenia and neuropathy) and the need for another treatment in one (emphysema).

The main toxicities encountered were neutropenia (Table 3). NCI-CTC grade 3 and 4 neutropenia was observed in 12 (24%) and seven (14%) patients, respectively. Other noted hematologic toxicities of over grade 3 were anemia (10%), leucopenia (6%), and thrombocytopenia (2%), respectively. The incidence of hematologic toxicities over grade 3 was similar in both countries (Table 3). Of the 228 treatment courses administered, 42 (18.4%) were delayed as a result of myelosuppression. Overall, eight patients (16%) required dose modification during treatment. After the first treatment course, four patients required TXL dose reduction (three with grade 4 neutropenia and one with a grade 3 elevation of AST and ALT. Of the three patients requiring a TXL dose reduction after the first course of treatment as a result of neutropenia, two required a second dose reduction owing to repeated grade 4 neutropenia during the second treatment cycle and one patient terminated treatment owing to progressive disease). During the second treatment cycle, two patients required a TXL dose reduction (one patient requiring dose reduction as a result of grade 4 neutropenia during the second cycle, required a second dose reduction owing to repeated grade 4 neutropenia at the fifth cycle, and one patient requiring a dose reduction owing to anorexia during the second cycle, required another dose reduction owing redeveloped grade 3 anorexia during the third cycle). Another two patients required a dose reduction as result of a grade 4 neutropenia during their third and fourth cycles, respectively. The commonest non-hematologic toxicities in Korean patients were alopecia, nausea, myalgia and vomiting, each of which affected more than 10 patients (Table 4). Non-hematologic toxicities were more infrequent in Japanese patients than in Korean patients, and alopecia, fatigue, anorexia and sensory neuropathy were the commonest non-hematologic toxicities in Japanese patients, each of which affected seven patients. Grade 3 anorexia was observed in four (8%) of the 50 patients and grade 3 abdominal pain and grade 3 infection developed in three (6%) patients apiece (Table 4). Although 14 patients had sensory neuropathy, most patients had mild to moderate degree (10 patients with grade 1 and 3 patients with grade 2). No severe infection or treatment related death was observed.

DISCUSSION

The aim of this study was to assess the efficacy and toxicity of biweekly TXL + CDDP combination treatment. Since the response rate for TXL was determined to be 23% during its development, the threshold efficacy rate was set at 20% for combination chemotherapy in this study. In addition, the expected efficacy rate for the combination chemotherapy was set at approximately 40%. Although, the study confirms that the biweekly TXL + CDDP have favorable patterns of toxicity, we have failed to prove the expected efficacy rate of TXL + CDDP in this study. Its clinical objective response rate was 18%, with that of 22.2% (7/35) in chemotherapy naïve patients and 13% (2/15) in non-chemotherapy naïve patients. In advanced gastric cancer, a first-line TXL and platinum doublet combination administered 3-weekly produced a response rate of 33–46% (16–18). In terms of biweekly treatments, Kornek et al. (19) reported a study on TXL 160 mg/m^2 + CDDP 60 mg/m^2, and observed a response to treatment in 44.4% of the 41 cases, which included five cases of complete remission. Moreover, when administered as a second-line treatment, a response rate of 22–28% was observed when TXL was administered with carboplatin (20,21). Our response rate is inferior to the response rate of a similar regimen reported by Kornek et al. (19), but is similar to that of a phase II part of the study performed by the East Japan Gastric Cancer Study Group (15). The relatively low response rate of the present study may be due to our inclusion of 15 previously treated patients. In addition, multi-institute cooperative studies such as the present one tend to produce lower response rates than single institute studies.

TXL and CDDP have different modes of action and fewer overlapping toxicities than other combinations. The most widely used TXL + CDDP regimen involves high dose TXL (175–200 mg/m^2) and CDDP (60–75 mg/m^2) administered 3-weekly. However, treatment is sometimes delayed by neurotoxicity and higher dose of CDDP is associated with higher neurotoxicity and more severe renal damage. Rosenberg et al. performed a comparative study on TXL administration modalities in patients with ovarian cancer and reported that weekly administration of TXL is better than a 3-weekly administration even though treatment effects are comparable, because the incidences of side effects are

Table 3. Hematologic toxicities

Adverse events	Japan ($n = 25$)		Korea ($n = 25$)		Total ($n = 50$)	
	Grade 3 events No. (%)	Grade 4 events No. (%)	Grade 3 events No. (%)	Grade 4 events No. (%)	Grade 3 events No. (%)	Grade 4 events No. (%)
Leukopenia	2 (8)	0 (0)	1 (4)	0 (0)	3 (6)	0 (0)
Neutropenia	7 (28)	5 (20)	5 (20)	2 (8)	12 (24)	7 (14)
Anemia	2 (4)	0 (0)	2 (8)	1 (4)	4 (8)	1 (2)
Thrombocytopenia	0 (0)	0 (0)	1 (4)	0 (0)	1 (2)	0 (0)

Table 4. Non-hematologic toxicities

Adverse events	All events no. (%)		Grade 3 or 4 events ($n = 50$) no. (%)
	Japan ($n = 25$)	Korea ($n = 25$)	
Infection	2 (8)	1 (4)	3 (6)
Fever	2 (8)	3 (12)	2 (4)
Vomiting	1 (4)	11 (44)	2 (4)
Stomatitis	2 (8)	4 (16)	0 (0)
Diarrhea	0 (0)	5 (20)	0 (0)
Arthralgia	2 (8)	5 (20)	0 (0)
Myalgia	1 (4)	13 (52)	1 (2)
Dyspnea	0 (0)	5 (20)	1 (2)
Neuropathy [motor]	1 (4)	0 (0)	1 (2)
Neuropathy [sensory]	7 (28)	7 (28)	1 (2)
Anemia	12 (48)	9 (36)	3 (6)
Anorexia	7 (28)	9 (36)	4 (8)
Nausea	1 (4)	13 (52)	0 (0)
Fatigue	7 (28)	6 (24)	0 (0)
Alopecia	7 (28)	14 (56)	–
Abdominal pain	1 (4)	7 (28)	3 (6)

clearly lower for the weekly administration (particularly with respect to myelosuppression and peripheral neuropathy) (22). In addition, Seidman et al. conducted a phase II clinical study in which TXL was administered weekly at 80–120 mg/m^2 to patients with adriamycin-resistant breast cancer and reported a response rate of 53% with high tolerability (23). Moreover, the weekly application of TXL 80 mg/m^2 as an 1-h infusion has been suggested to be associated with lower hematologic toxicity while capable of achieving a higher dose intensity than TXL administration at 175 mg/m^2 3-weekly (24). These results show that the divided administration of TXL may reduce myelosuppression and neurotoxicity. Two phase II studies using biweekly TXL + CDDP have been conducted and both reported a high response rate in esophageal cancer (biweekly administrations of TXL 180 mg/m^2 + CDDP 30 mg/m^2) (25) and in gastric cancer (biweekly administration of TXL 160 mg/m^2 + CDDP 60 mg/m^2) (19). However, grade 4 neutropenia occurred in 31 and 11% of patients, respectively, which required hospital admission or prophylactic G-CSF. Here, we conducted a multi-institutional cooperative phase II study of a biweekly regimen (biweekly administration of TXL 140 mg/m^2 + CDDP 30 mg/m^2) followed by a phase I–II study (15), because this biweekly schedule was suitable for outpatient clinical with modest efficacy and a safe toxicity profile.

The main toxicity of this regimen used in the present study was neutropenia. Hematologic toxicities consisted of neutropenia grade 3 in 24% and grade 4 in 14%, which is substantially lower than that reported by Polee et al. (25). Although the incidence of neutropenia was found to be similar with higher dose TXL and CDDP regimen (19), our study did not use prophylactic G-CSF. In the present study, only two patients could not complete treatment as a result of delayed or repeated severe neutropenia. The other significant toxicity was anorexia: four patients experienced grade 3 anorexia.

The median survival duration for all 50 patients was 333 days and considering that a substantial number of patients in the present study had been exposed to previous chemotherapy or surgery (56% of patients had undergone gastric resection, 22% had received adjuvant chemotherapy, and 30% had been received another palliative chemotherapy), this result appears to be promising. Furthermore, side effects of this regimen were tolerable and controllable in most patients, and only a small number of patients did not tolerate the treatment. Of the 11 patients who discontinued treatment owing to a severe adverse event or to delayed recovery from an adverse event, most had an unfavorable clinical characteristic (seven patients underwent previous surgery, three patients had received adjuvant chemotherapy and three previous palliative chemotherapy, and six patients were older than 60). Except those patients with severe adverse events or delayed recovery from an adverse event, 37 patients (74%) proceeded to salvage chemotherapy. Subsequent chemotherapies might contribute to prolongation of survival in our patient group.

It was interesting to note that patients' characteristics were different between Korea and Japan. Korean patients tended to be younger (median age 46 versus 65), which is consistent with a review of surgically resected gastric cancer patients at a Korean and a Japanese hospital, which showed that patients under 40-years old composed 14.8% of Korean patients and only 6% of Japanese patients, whereas patients over 70 years of age accounted for 3.2 and 19.2% of the gastric cancer populations at Korea University Hospital and the Japan National Cancer Center Hospital, respectively (26). In particular, Korean gastric cancer cases tended to be of the poorly differentiated pathologic type (poorly differentiated adenocarcinoma, signet ring cell carcinoma and mucinous adenocarcinoma), whereas Japanese gastric cancer cases had a differentiated histology (papillary adenocarcinoma and tubular adenocarcinoma). Although Mok et al. suggested that such a difference in histologic type between two hospitals was mostly as a result of a greater frequency of early gastric cancer in Japan National Cancer Center Hospital patients (51.2%) than in Korea University Hospital patients (19.0%), this discrepancy in histologic type may represent the real difference of patient populations between two countries, because only advanced stage patients were enrolled in this study. The response rate of Korean patients was twice that of the Japanese patients (6/25, 24% versus 3/25, 12%) and the survival duration of Korean patients was also longer than that of Japanese patients (389 days versus 262 days). Non-hematologic toxicities were more infrequent in Japanese patients than in Korean patients, especially nausea, vomiting, myalgia and alopecia were infrequently noted in Japanese patients. However, the incidence of grade

3/4 neutropenia was more common in Japanese patients (12/25, 48% versus 7/25, 28%). Japanese patients tend to have been older and more pretreated patients, which might contribute to poor prognosis, resistance to treatment and high incidence of severe neutropenia. However, it is difficult to prove that the difference in treatment result was related with patient background or other prognostic factors.

In conclusion, biweekly TXL and CDDP combination chemotherapy showed modest activity in advanced gastric carcinoma and was characterized by a favorable toxicity pattern. However, this regimen has failed to achieve a superior efficacy to TXL monotherapy in this group of patients. Nonetheless, because of the 1-day infusion schedule used this regimen, it can be administered on an outpatient basis without disrupting daily life.

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Conflict of interest statement

None declared.

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Clinical Trial Note

A Randomized Phase II Selection Trial in Patients with Advanced/Recurrent Gastric Cancer: Trial for Advanced Stomach Cancer (TASC)

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A randomized phase II clinical trial is being conducted for patients with advanced or recurrent gastric cancer, in order to select the most promising treatment for subsequent evaluation in a large-scale phase III trial. We compare four chemotherapeutic treatments, which include two sequential and two combination regimens using paclitaxel with 5-fluorouracil or S-1, an oral fluorouracil derivative. The primary endpoint is 10-month overall survival rate, while the secondary endpoints are adverse events, time to treatment failure and progression-free survival. A Bayesian method is used to provide a statistical rule for monitoring the trial. Forty patients per treatment regimen (160 in total) were randomized into one of the four regimens using a centralized dynamic method.

Key words: Randomized phase II trial – gastric cancer – chemotherapy – Bayesian trial monitoring

INTRODUCTION

In Japan, where the incidence of gastric cancer is the highest in the world, many clinical trials have been performed to investigate its optimal chemotherapeutic treatments (1,2). Based on the results of those trials,fluorinated pyrimidines such as 5-fluorouracil (5-FU) and tegafur/gimeracil/oteracil potassium (S-1), cisplatin (CDDP), paclitaxel (TXL), and irinotecan (CPT-11), have been used as key drugs for advanced gastric cancer.

To date, the Japan Clinical Oncology Group (JCOG) has conducted clinical trials to compare many combination therapies most often of two drugs, taking 5-FU monotherapy as control. For example, the JCOG Study 9205 compared two chemotherapeutic regimens, including UFT (uracil plus tegafur) plus mitomycin C (MMC) and 5-FU plus cisplatin (CDDP) to 5-FU monotherapy in patients with unresectable advanced gastric cancer (3). Inferiority of UFT plus MMC was demonstrated, while no significant survival difference was shown between 5-FU plus CDDP and 5-FU alone. Recently, many phase II and phase III studies have been conducted to examine S-1 containing regimens and S-1 monotherapy in Japan. Thus, a new phase III study (JCOG 9912) comparing two chemotherapeutic regimens of CPT-11 plus CDDP and S-1, with 5-FU as control, has been conducted. Patient enrollment in this trial was completed in January 2006 and the final data analysis will be performed in early 2007.

While initial treatment for patients with unresectable advanced gastric cancer in Western countries commonly

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includes combination therapy with three drugs, monotherapy and combination therapy with two drugs are more favored in Japan. There is an urgent need to develop more efficacious first-line and second-line treatment regimens for unresectable advanced gastric cancer. We are therefore performing a randomized phase II trial to compare the following four treatment regimens: (Group A) sequential 5-FU monotherapy followed by TXL monotherapy, (Group B) sequential S-1 monotherapy followed by TXL monotherapy, (Group C) concurrent 5-FU and TXL, and (Group D) concurrent S-1 and TXL.

PROTOCOL DIGEST OF THE STUDY

Purpose

The purpose of the study is to select the most promising chemotherapy regimen among four regimens using paclitaxel (TXL) concurrently and as a second-line treatment, with fluorouracil (5-FU) or tegafur/gimeracil/oteracil potassium (S-1), for a future randomized phase III trial in patients with advanced or recurrent gastric cancer.

Study Setting and Protocol Review

The study is an open-label, randomized phase II clinical trial (4,5). The protocol has been approved by the Protocol Review Committee of the Japan South West Oncology Group (JaSWOG).

Resources

Research grants are from the Epidemiological and Clinical Research Information Network (ECRIN) and the Kyoto University EBM Collaborative Research Center.

Endpoints

The primary endpoint is 10-month overall survival (OS) rate. The secondary endpoints are incidence of adverse events, time to treatment failure, progression-free survival time and OS time. In addition, objective tumor response is to be evaluated in a subpopulation of patients with measurable disease.

Eligibility Criteria

Patients with a histologically confirmed diagnosis of advanced or recurrent gastric cancer are eligible.

Inclusion Criteria

(i) Histologically confirmed gastric adenocarcinoma;
(ii) No previous antitumor therapy expect for operation and postoperative adjuvant chemotherapy using an oral fluoropyrimidine, completed six months before enrollment into this trial;
(iii) Age $\geq$ 20 years;
(iv) ECOG performance status 0–1;
(v) Sufficient organ function before chemotherapy according to the following laboratory data: WBC $\geq$ 3000/mm^3 or neutrocytes $\geq$ 1500/mm^3; platelets $\geq$ 100 000/mm^3; hemoglobin $\geq$ 8.0 g/dl; bilirubin $\leq$ 1.5 mg/dl; SGOT $\leq$ 100 IU; SGPT $\leq$ 100 IU; creatinine $\leq$ 1.5 mg/dl; creatinine clearance $\geq$ 50 ml/min; ECG showing no serious arrhythmia and no serious ischemic heart disease;
(vi) Oral food intake possible; and
(vii) Written informed consent.

Exclusion Criteria

(i) Serious complications including: cerebrovascular disease, poorly controlled diabetes or hypertension, serious infectious diseases, lung fibrosis, interstitial pneumonia, dyspnea, pleural effusion, ascites, hemorrhage, active intestinal ulcer, serious psychiatric disease;
(ii) Symptomatic metastasis to the central nervous system;
(iii) Patients with active synchronous or metachronous malignancy;
(iv) Medical history of serious drug allergy or hypersensitivity to any drugs;
(v) Hypersensitivity to Cremophor EL;
(vi) History of alcoholic anaphylaxis;
(vii) Women with ongoing pregnancy or breast-feeding, or contemplating pregnancy;
(viii) Mental disorders which may affect ability or willingness to provide informed consent or abide by the study protocol;
(ix) Continual administration of a steroid; or
(x) Patients judged inappropriate for the study by the clinician.

Registration

Participating investigators are instructed to send an eligibility criteria report to the Data Center at the EBM Collaborative Research Center at Kyoto University. Eligible patients are registered and then randomized to one of the four groups (A, B, C and D) described in the next section by a centralized dynamic method using the following factors: measurable disease according to the RECIST criteria [yes/no], disease type [inoperable advanced/post-operative recurrent (with post-operative chemotherapy)/post-operative recurrent (with no post-operative chemotherapy)], PS [0/1], peritoneal metastasis based on diagnosis with images [yes/no], age [$<$75/$\geq$75 years] and institution as balancing variables. Information regarding the necessary follow-up examinations and chemotherapy schedule are then sent from the Data Center. The accrual started in December 2005 and is to continue for two years.

Treatment Methods

The following four treatment groups are examined in the present trial.

Group A: Sequential 5-FU monotherapy followed by TXL monotherapy

5-FU	800 mg/m^2	c.i.v.	daily for five days, every four weeks
TXL	80 mg/m^2	d.i.v.	days 1, 8, and 15, every four cweeks

Group B: Sequential S-1 monotherapy followed by TXL monotherapy

S-1	80 mg/m^2	p.o.	daily for 28 days, every six weeks
TXL	80 mg/m^2	d.i.v.	days 1, 8, and 15, every four weeks

Group C: Concurrent 5-FU + TXL

5-FU	600 mg/m^2	c.i.v.	daily for five days from day 1
TXL	80 mg/m^2	d.i.v.	days 8, 15, and 22, every four weeks

Group D: Concurrent S-1 + TXL

S-1	80 mg/m^2	p.o.	daily for 14 days from day 1
TXL	50 mg/m^2	d.i.v.	days 1 and 15, every three weeks

In the sequential treatment groups A and B, the administration of 5-FU or S-1 monotherapy is to be discontinued if the following are observed: (i) disease progression or occurrence of new disease, (ii) grade 4 toxicities evaluated according to the CTCAE (Common Terminology Criteria for Adverse Events) ver.3.0, (iii) adverse events causing patients to refuse treatment or causing a clinician to discontinue treatment, (iv) increase in the tumor markers CEA and/or CA19–9 in two or more consecutive measurements or symptomatic progression (e.g. cancer pain, dysphagia). Thereafter, clinicians monitor the criteria for initiation of treatment with TXL monotherapy. A post-trial treatment, as a rule, should be a CPT-11 containing regimen.

Follow-up

Disease progression and occurrence of new disease are examined using, as needed, abdominal X-ray, abdominal computed tomography (CT) or magnetic resonance imaging (MRI), thoracic CT, and measurements of the tumor markers CEA and CA19–9, which are performed at baseline and at least every 4–5 weeks during treatment. Blood tests and symptom checks are carried out before treatment and at least every 2 weeks during treatment. In cases where therapy is discontinued owing to toxicity, clinicians should follow-up patients until they recover from the toxicity.

Study Design and Statistical Methods

The primary analysis in this study is aimed at comparing three treatment regimens B, C and D with regimen A, which is regarded as the reference regimen, in terms of the primary endpoint of 10-month OS rate. The comparisons are carried out using Bayesian statistics (6,7). The Bayesian paradigm treats a parameter characterizing important aspects of the phenomenon under study as a random quantity. The parameter of our primary interest is the 10-month OS rate of each regimen. Bayes' theorem is used to combine the observed OS data and the prior distribution that characterized our uncertainty or knowledge about the parameter before starting the trial. We asked a panel of oncologists for pretrial opinions on the endpoints, in order to construct the prior distributions of the treatment regimens (8). The posterior distribution of the parameter given the data is obtained through this Bayesian calculation. The Bayesian method (6,7) is used to provide a rule for selecting one regimen that is sufficiently efficacious to warrant termination of the phase II trial and commence with a future phase III trial. We carry out the Bayesian calculation to monitor the trial.

In addition, overall survival, progression-free survival and treatment success curves are constructed as time-to-event plots by the Kaplan-Meier method (9). Differences between the curves are estimated for superiority using the hazard ratio produced by the Cox regression model (10), accounting for the balancing variables as strata, which are used for randomization. Incidences of grade 3 or 4 adverse events are compared between the treatment groups. The number of patients to be accrued has been set at 40 per treatment regimen (160 in total).

Interim Analysis and Monitoring

The Data and Safety Monitoring Committee (DSMC) independently review the report of trial monitoring regarding efficacy and safety data from the present study. Based on the monitoring, DSMC can consider early termination of a treatment regimen during study and modification of the study protocol including increasing the sample size if any definitive selection is not possible at the end of study. Protocol compliance, safety and on-schedule study progress are also monitored by the DSMC.

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Conflict of interest statement
None declared.

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