

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/m² 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/m² 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/m² 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/m² + CDDP 30 mg/m²) (25) and in gastric cancer (biweekly administration of TXL 160 mg/m² + CDDP 60 mg/m²) (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/m² + CDDP 30 mg/m²) 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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Randomized phase II trial for gastric cancer

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 except 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/mm³ or neutrocytes \geq 1500/mm³; platelets \geq 100 000/mm³; 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 [$<75/\geq75$ 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 weeks

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.

Randomized phase II trial for gastric cancer

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