Table II. *Patient characteristics.*

No. of patients	11
Age	
Median(range)	61.5 (49-72)
Gender	
Male/Female	8/3
Performance status	
0/1	3/8
Histology	
Adeno/Small	7/4
Stage	
IIIB/IV	3/8
Prior therapy	
None	8
Chemotherapy	3
Cisplatin-based	2
Non-platinum	1

weeks for toxicities and (g) inability to administer AMR for 3 consecutive days.

Pharmacokinetics. Pharmacokinetic (PK) studies for both AMR and CPT-11 were performed for all patients during their first course. Heparinized venous blood samples (3 ml) for AMR PK were taken to obtain plasma for the analysis of the parent compound and to isolate blood cells for the analysis of the active metabolite, amrubicinol, before administration, at the end of infusion and 15 min, 1 h, 1 h 55 min, 2 h 55 min, 4 h, 6 h 55 min, 10 h 55 min and 23 h 55 min post-infusion. CPT-11 PK (parent compound and SN-38) samples were taken in heparinized tubes before administration, at the end of infusion and 15, 30 min and 1, 3, 4, 5, 7, 9 and 22 h post-infusion. The plasma and blood cell samples were separated by centrifugation (3000xg for 10 min at 4°C) and were stored below –20°C until analysis. The AMR (Sumika Chemical Analysis Service, Ltd., Osaka, Japan), amrubicinol, CPT-11 (Yakult Honsha Co., Ltd., Tokyo, Japan) and SN-38 levels were assayed by high-performance liquid chromatography and mass spectrometry. The PK parameters were determined on the basis of non-compartment analysis (WinNonlin Professional ver. 4.1, Pharsight Corp.). The area under the concentration-time curve (AUC) was calculated by the trapezoidal rule.

Results

Patient characteristics. Between January 2003 and June 2004, eleven patients were enrolled in this study and their characteristics are listed in Table II. The median age was 62 years (range: 49 to 72 years). There were eight males and eight patients with PS of 1. Four had SCLC, while eight had not received prior treatment (level 1, two patients; level 1, three patients; level 2, three patients). Of the three previously treated patients, two had received cisplatin-based chemotherapy, while the remaining patient having received a non-platinum regimen. The total number and the median number of courses were 33 and 3 (range 1-8), respectively.

Table III. *Hematological toxicity following first course of amrubicin and irinotecan.*

		WBC grade	ANC grade	Plt grade	Hb grade
Dose level	No. of patients	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
–2	3	0 2 0 0 1	0 0 1 1 1	2 1 0 0 0	0 1 2 0 0
–1	5	0 2 2 0 1	0 0 1 1 3	4 1 0 0 0	0 3 1 1 0
1	3	0 0 0 3 0	0 0 0 0 3	2 1 0 0 0	0 2 1 0 0

WBC, white blood cell count; ANC, absolute neutrophil count; Plt, platelet; Hb, hemoglobin.

Table IV. *Non-hematological toxicity following first course of amrubicin and irinotecan.*

		Nausea	Vomiting	Fatigue	Transaminase
Dose level	No. of patients	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
–2	3	1 2 0 0 0	2 1 0 0 0	0 3 0 0 0	1 2 0 0 0
–1	5	1 1 3 0 0	2 3 0 0 0	3 1 1 0 0	4 1 0 0 0
1	3	1 2 0 0 0	2 1 0 0 0	1 2 0 0 0	2 1 0 0 0
		Infection	Appetite loss	Diarrhea	Pneumonitis
Dose level	No. of patients	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
–2	3	2 0 0 1 0	1 2 0 0 0	1 1 1 0 0	1 0 0 2 0
–1	5	3 0 0 2 0	1 1 3 0 0	0 3 0 1 1	5 0 0 0 0
1	3	1 0 0 2 0	1 2 0 0 0	2 1 0 0 0	3 0 0 0 0

Table V. *Toxicity following all courses of amrubicin and irinotecan.*

	Grade				
	0	1	2	3	4
WBC	2	13	5	10	3
ANC	0	3	12	4	14
Hb	1	20	8	4	0
Plt	26	6	1	0	0
Nausea	15	15	3	0	0
Vomiting	27	6	0	0	0
Appetite loss	18	9	6	0	0
Fatigue	21	10	2	0	0
Transaminase	22	10	1	0	0
Diarrhea	21	7	3	1	1
Infection	28	0	0	5	0
Pneumonitis	31	0	0	2	0

WBC, white blood cell count; ANC, absolute neutrophil count; Plt, platelet; Hb, hemoglobin.

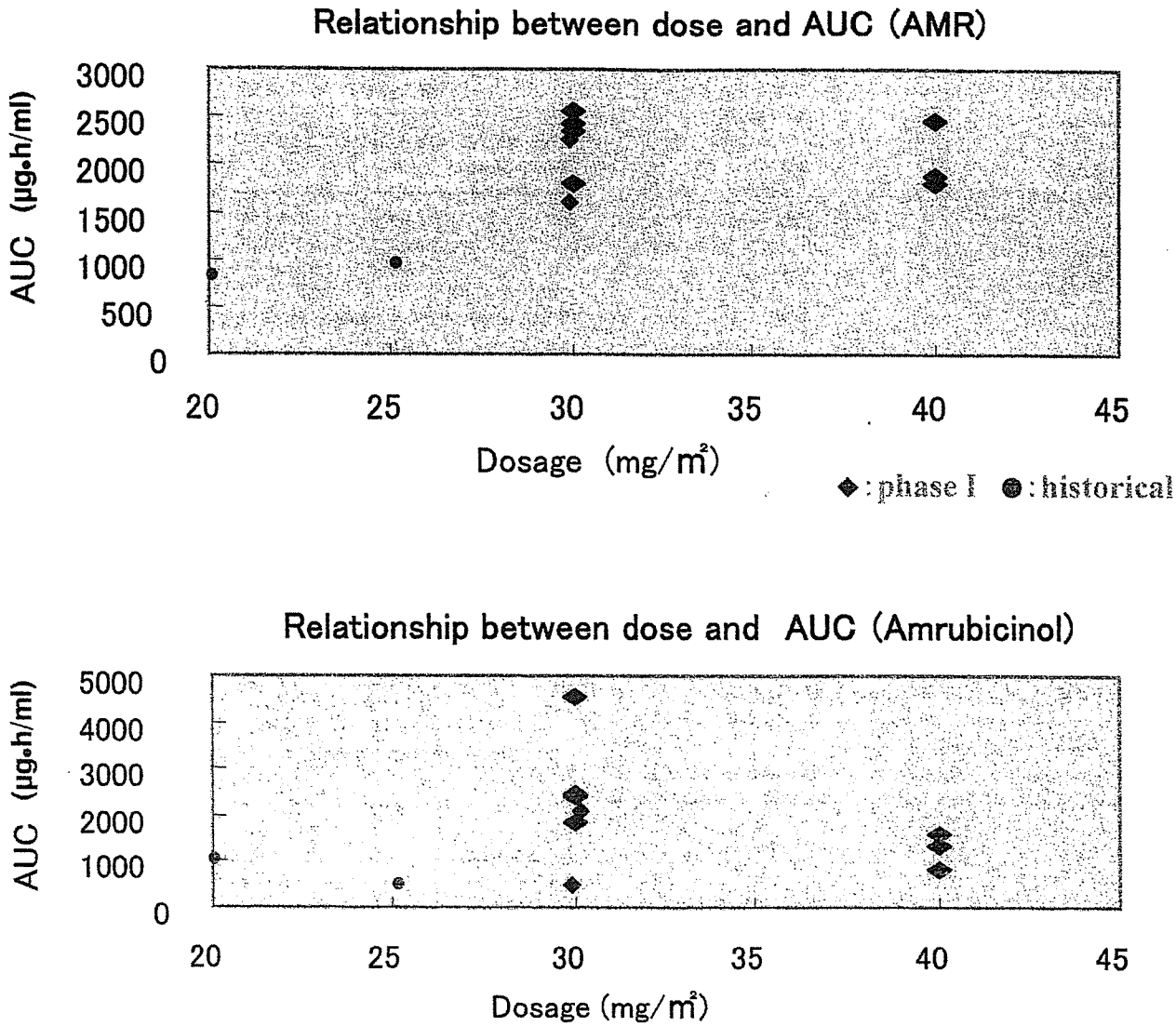

Figure 1. *Relationship between dose (mg/m²) and area under the concentration-time curve (AUC) (μg•h/ml) of (A) amrubicin; (B) amrubicinol.*

Toxicities. All patients were assessable for toxicity. The hematological and non-hematological toxicities developed during the first course are shown in Tables III and IV, respectively. Myelosuppression, especially neutropenia, was frequently observed. At level 1, two out of three patients developed febrile neutropenia and the other patient had grade 4 neutropenia which lasted for 7 days. At level 1, one patient developed febrile neutropenia and two out of five patients had grade 4 neutropenia; however, this did not last for more than 4 days. One patient had grade 3 anemia but did not receive a blood transfusion. At level 2, one patient experienced febrile neutropenia and pneumonia.

Non-hematological toxicities were comparatively mild, except for diarrhea and pneumonitis. None of the patients experienced more than grade 3 non-hematological toxicities in the first course. All five patients at dose level 1 suffered from diarrhea, two patients experiencing grades 3 and 4. The patient with grade 3 water diarrhea, experienced on day 10, was accompanied by infection and required *i.v.* antibiotic therapy. The other patient with grade 4 diarrhea, experienced on day 5, required continuous *i.v.* hydration therapy. This patient was not able to receive CPT-11 from day 8 because of severe grade 4 diarrhea.

Eight out of eleven patients received two or more courses, but three patients did not receive the second course because two had severe water diarrhea and the other had febrile neutropenia. The toxicities following all courses are listed in Table V. The incidences of more than grade 3 leucopenia and neutropenia were 39.4% and

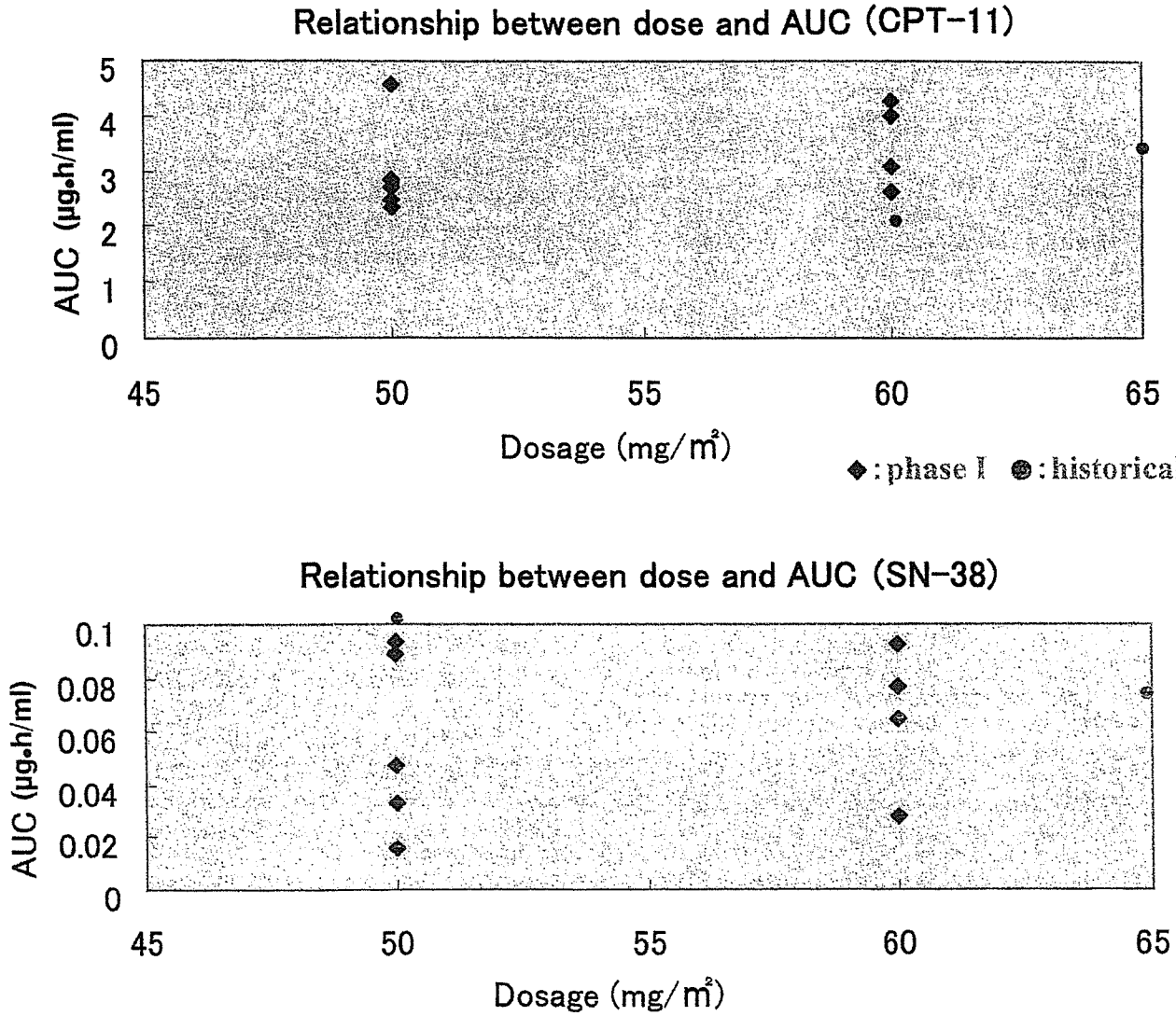

Figure 2. *Relationship between dose (mg/m^2) and area under the concentration-time curve (AUC) (μg•h/ml) of (A) irinotecan; (B) SN-38.*

54.5%, respectively, while that of febrile neutropenia was 21.2%. At level 2, two out of three patients suffered from grade 3 pneumonitis. Pneumonitis occurred during the second and third courses, respectively, which improved after the administration of steroid therapy. There was no treatment-related death.

MTD and DLTs. At level 1, all three patients had developed DLT for febrile neutropenia, with those showing grade 4 neutropenia lasting for more than 7 days. Therefore, the dosages of CPT-11 and AMR were changed to 60 mg/m^2 and 30 mg/m^2, respectively, as level 1. At level 1, three out of five patients had developed DLTs. Two patients experienced grades 3 and 4 diarrhea, while the other experienced a febrile neutropenia. In addition, the dosage of CPT-11 was decreased to 50 mg/m^2 as level 2. At level 2, one patient developed a DLT with febrile neutropenia. Two patients had not developed DLTs during their first courses; however, pneumonitis appeared after the second and third courses, respectively. Although pneumonitis is not a DLT according to conventional criteria, such pneumonitis events are included in the criteria of DLTs as they are fatal toxicities. Therefore, we were unable to establish the MTD and to determine the RD in this trial as all three levels were found to be intolerable.

Response. Nine patients were assessable for response. There were two partial responses, which included one patient with previously treated SCLC and the other with previously untreated NSCLC.

Table VIa. *C_{max}, AUC and clearance of plasma levels of amrubicin and metabolites.*

	30 mg/m^2 (mean)	40 mg/m^2 (mean)
No. of patients	6	3
AMR (plasma)		
C_{max} (μg/ml)	3735.5	3533.3
AUC (μg•h/ml)	2231.4	2235.1
CL (l/h/m^2)	15.29	18.33
AMR (blood cells)		
C_{max} (μg/g)	2582.8	2248.6
AUC (μg•h/g)	2035.7	2044.3
Metabolite (plasma)		
C_{max} (μg/ml)	29.9	21.4
AUC (μg•h/ml)	362.4	1036.1
Metabolite (blood cells)		
C_{max} (μg/g)	115.3	90.0
AUC (μg•h/g)	2368.3	1244.1

Table VIb. *C_{max}, AUC and clearance of plasma levels of CPT-11 and SN-38.*

	50 mg/m^2 (mean)	60 mg/m^2 (mean)
No. of patients	5	4
CPT-11		
C_{max} (μg/ml)	0.83	1.12
AUC (μg•h/ml)	3.01	3.489
CL (l/h/m^2)	17.65	17.89
SN-38		
C_{max} (μg/ml)	0.02	0.029
AUC (μg•h/ml)	0.05	0.066

C_{max}, concentration$_{max}$, CPT-11, irinotecan; AMR, amrubicin; AUC, area under the concentration-time curve; CL, clearance.

Pharmacokinetics. Plasma samples were obtained from nine patients during the first course. The relationships between the mean concentration-time curve of CPT-11, SN-38, AMR and amrubicinol are shown in Figures 1 and 2. The pharmacokinetic parameters derived from the plotted data are listed in Tables VIa and b. Though only two dose levels for CPT-11 and SN-38 were examined, there seemed to be a linear association between dose and AUC. However, no similar association was apparent for AMR and amrubicinol. Moreover, the PK parameters for AMR showed marked inter-patient variability.

Discussion

A phase I study was conducted regarding the combined use of CPT-11 and AMR, as a topo I and II inhibitor, respectively, for advanced lung cancer, which demonstrated that the combination of CPT-11 and AMR was inactive against both NSCLC and SCLC. It was indicated that the combination of CPT-11 and AMR is not tolerated. As this combination mediated an unexpectedly strong myelosuppressive effect, the MTD and the RD for combination therapy with CPT-11 and AMR could not be determined.

JCOG compared cisplatin plus CPT-11 with cisplatin plus etoposide within a standard regimen in patients with previously untreated ED-SCLC. The response rate and MST for the patients treated with cisplatin plus CPT-11 were 84.4% and 12.8 months, respectively, which are considered a good outcome. On the other hand, Masuda *et al.* conducted a phase II trial of CPT-11 and etoposide with rhG-CSF in patients with previously treated SCLC. The response rate was 71% and the MST was 8.9 months. CPT-11-containing regimens, such as CPT-11 plus cisplatin and etoposide, seem to generate high response rates for both previously treated and untreated patients with SCLC. Our study showed that only two out of eleven patients responded to treatment. The overall response rate of 18.1% was lower than expected. Of the four patients with previously untreated SCLC, only one responded to treatment. In the case of the SCLC patients, the response rate was 25%, but was 14.3% in the cohort of NSCLC patients. Although several recent trials have reported that the efficacy of a non-platinum regimen is equivalent to that of a platinum regimen for advanced NSCLC (12, 13), the results of the present study were disappointing. These response rates were lower than those found historically and than those shown in a phase II study of CPT-11 and AMR monotherapy. An attempt was made to rationalize the underlying basis of these phenomena. Firstly, it was reasoned that the combination therapy with CPT-11 and AMR did not appear to have an additive or synergistic effect. Secondly, the dosage of either drug was not increased since the effects of CPT-11 and AMR on myelosuppression overlapped when used in combination. In the present study, CPT-11 and AMR were used as a combination therapy to inhibit topo I and II. Preclinical and phase I studies have shown that the combined use of topo I and II inhibitors has a synergistic or antagonistic effect. Although cross-resistance between topo I and topo II inhibitors is uncommon in drug-resistant cell lines (14-16), topo I inhibitors were reported to have shown competitive activity in the presence of topo II inhibitors *in vitro* (6). Furthermore, the dose could not be increased since toxicity was marked at all dose levels. The most severe adverse reactions were bone marrow toxicities, particularly leucopenia and neutropenia, followed by infection, diarrhea and pneumonitis. The incidence of more than grade 3 leucopenia was 39% and that of neutropenia was 55%. Four out of eleven patients developed febrile neutropenia in the first course. At level 2, no DLTs occurred in the first course, but two patients experienced interstitial pneumonia in the second and third courses.

None of the patients with previously untreated SCLC were able to complete four courses of treatment. Several studies have investigated combination therapy with CPT-11 and etoposide and some have reported marked toxicity after simultaneous administration of the two drugs (17, 18). This suggests that, when using topo I and II inhibitors in combination, it may be better to administer the drugs sequentially rather than simultaneously. The present study supports these theories. Myelosuppression may be overcome with G-CSF. If G-CSF is used prophylactically, the adverse event of myelosuppression is surmountable, perhaps allowing dosage increases.

The PK investigation showed no difference in the AUC and C_{max} of CPT-11 and SN-38 when compared with historical data. Moreover, CPT-11 did not display a drug-drug interaction with AMR. The PK parameters for AMR showed marked inter-patient variability. The parameters in blood cells were measured since these cells contain the same reductase as found in tumors; however, no relationship between the PK, toxicity and efficacy data could be demonstrated. Although there was no correlation between the PK parameters and toxicity in this study, this schedule cannot be recommended. Future studies should investigate combination therapies with G-CSF or sequential administration.

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A Phase II Study of the Global Dose and Schedule of Capecitabine in Japanese Patients with Metastatic Colorectal Cancer

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Background: Although the standard 3-week capecitabine regimen (1250 mg/m^2 twice daily for 2 weeks followed by a 1-week rest) has shown superior activity and improved safety over bolus 5-fluorouracil/leucovorin in two large randomized phase III trials in Europe and in the United States, only a 4-week regimen of capecitabine (828 mg/m^2 twice daily for 3 weeks) has been studied in Japan. Therefore, we performed a phase II study to investigate the 3-week regimen of capecitabine in Japanese patients with metastatic colorectal cancer (MCRC).
Methods: Previously untreated patients with MCRC received oral capecitabine 1250 mg/m^2 twice daily for 2 weeks. Treatment was repeated every 3 weeks. Blood and urine samples were collected for pharmacokinetic analysis.
Results: Sixty patients were enrolled. The overall response rate was 35% [95% confidence interval (CI), 23–48%], and 52% of patients had stable disease. The median time to progression was 5.5 months (95% CI, 4.2–6.7 months). The median overall survival was 20.2 months (95% CI, 16.6–27.8 months). The most frequently occurring adverse drug reaction was hand-foot syndrome (all-grade 73%; grade 3 13%). Diarrhea, anorexia, nausea and stomatitis were each seen in 37% of patients. The pharmacokinetic profiles of capecitabine and its metabolites were similar to those reported in Caucasian patients.
Conclusions: The 3-week regimen of capecitabine was effective and well tolerated in Japanese patients with MCRC as well, and could be used as the basic regimen for future combination therapies.

Key words: capecitabine – colorectal cancer – phase II study

INTRODUCTION

For more than 40 years, 5-fluorouracil (5-FU) has been the mainstay of treatment for patients with metastatic colorectal cancer (MCRC). Many incremental improvements to 5-FU regimens, such as biomodulation with leucovorin (LV) and schedule modification, have been made. For example, infusional 5-FU offers not only improved response rates, but also a small survival benefit, compared with those of bolus 5-FU according to data from randomized trials and meta-analyses (1,2). However, continuous infusions require venous access lines and pumps with significant associated costs. Consequently, patients prefer to receive oral rather than intravenous chemotherapy (3,4).

Several new fluoropyrimidines, including uracil plus tegafur (UFT), capecitabine and S-1, have been developed and evaluated in the treatment of colorectal cancer. Capecitabine (Xeloda®) is an oral fluoropyrimidine carbamate designed in Japan to deliver 5-FU predominantly to tumor cells. After oral administration, capecitabine is rapidly and extensively absorbed through the intestine as an intact molecule, and then metabolized to 5-FU in three steps. In the first step, capecitabine is hydrolyzed to 5′-deoxy-5-fluorocytidine (5′-DFCR) by carboxylesterase primarily in the liver. 5′-DFCR is then converted to 5′-deoxy-5-fluorouridine (5′-DFUR) by cytidine deaminase, which is highly active in

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tumor cells and in the liver. Thymidine phosphorylase, which is significantly more active in tumor tissues than in adjacent normal tissues, finally converts 5'-DFUR to 5-FU (5,6). With each successive conversion step, the potential for systemic exposure to 5-FU is reduced while 5-FU delivery to tumor tissues is increased. Consequently, capecitabine avoids many of the gastrointestinal toxicities commonly observed with 5-FU.

Many clinical studies of capecitabine in MCRC have been conducted worldwide. In a Japanese phase I study using continuous administration of capecitabine, the maximum tolerated dose was 1255 mg/m^2 twice daily; skin fissures and gastric ulcers were noted as the dose-limiting toxicities (7). Another phase I study showed that a 1-week rest period appealed to patients and also maintained the activity of capecitabine therapy (8). From these findings, a 4-week intermittent regimen (3 weeks of capecitabine 828 mg/m^2 twice daily followed by a 1-week rest period) was recommended for Japanese phase II studies. This 4-week intermittent schedule of capecitabine was active and well tolerated in Japan, resulting in response rates of 25% (5/20) in a small pilot study (9), and 27% (15/56) in a phase II study (10) in patients with advanced or MCRC. However, it was a 3-week regimen of capecitabine (1250 mg/m^2 twice daily for 2 weeks followed by a 1-week rest period) that was shown to have superior activity and improved safety over bolus 5-FU/LV (Mayo Clinic regimen) as the first-line therapy in two large randomized phase III studies (11–13), and has been approved for MCRC in Europe and in the United States. Since then, this 3-week regimen has been used as a platform for combination therapy with other active agents, such as irinotecan, oxaliplatin and bevacizumab (14–18).

To date, the efficacy and safety of the 3-week capecitabine regimen in Japan remains unclear. Therefore, we conducted this phase II trial as a registration trial, which included a pharmacokinetic analysis, of the 3-week capecitabine regimen in Japanese patients with previously untreated MCRC.

PATIENTS AND METHODS

Study Design

The primary endpoint of this open-label multicenter phase II study was response rate. Secondary endpoints were safety, time-to-tumor progression (TTP), survival and pharmacokinetic analysis. This study was conducted in accordance with the Good Clinical Practice guidelines for clinical trials in Japan and the Declaration of Helsinki. The study protocol was approved by the ethics committee of each institution. Written informed consent was obtained from all patients.

Patients

All patients had to have histologically confirmed colorectal adenocarcinoma with at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) (19). Patients were also required to have the following laboratory values: neutrophils $\geq 1.5 \times 10^3/mm^3$; platelet count $>10 \times 10^4/mm^3$; serum creatinine $<1.5 \times$ upper limit of normal (ULN); serum bilirubin $<1.5 \times$ ULN; ALT (GPT), AST (GOT) $\leq 2.5 \times$ ULN (or $\leq 5 \times$ ULN in the case of liver metastases); alkaline phosphatase $\leq 2.5 \times$ ULN (or $\leq 5 \times$ ULN in the case of liver metastases or $\leq 10 \times$ ULN in the case of bone disease) and creatinine clearance >50 ml/min. Patients had received no chemotherapy for metastatic disease (excluding adjuvant chemotherapy completed more than 6 months before registration) and no radiotherapy to target lesions. Patients were not included if they had received radiotherapy within the previous 4 weeks, or had not fully recovered from the major surgery within 4 weeks. Other eligibility criteria were as follows: Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; expected survival time of more than 3 months and age at enrollment of 20–74 years.

Exclusion criteria were as follows: pregnant or lactating women; sexually active men/women unwilling to practice contraception during the study; a history of hypersensitivity to 5-FU; organ allografts; clinically significant cardiac disease or myocardial infarction within the last 12 months; metastases of the central nervous system; a history of epilepsy; psychiatric disability precluding compliance with oral drug intake or giving informed consent; history of another malignancy within the last five years, except for cured basal cell carcinoma of skin, cured carcinoma *in situ* of uterine cervix, or cured esophago-gastric carcinoma removed by endoscopic procedures; serious uncontrolled infection; malabsorption syndrome; participation in any investigational drug study within 4 weeks preceding the start of treatment.

Evaluation of Response and Safety

Anti-tumor efficacy was evaluated by the investigators according to RECIST guidelines (19). An Independent Review Committee (IRC) confirmed tumor responses. Adverse events were assessed according to the National Cancer Institute—Common Toxicity Criteria, Version 2.0 (20). Hand-foot syndrome (HFS) was classified as follows: grade 1 (numbness, dysesthesia, painless swelling or erythema not disrupting daily living activities); grade 2 (erythema with painful swelling or disruption of daily living activities) or grade 3 (moist desquamation, ulceration, blistering or severe pain, or any symptoms leading to an inability to work or to perform daily living activities).

Study Assessments

Tumor responses were assessed every 2 cycles up to the cycle 10, and then every 3 cycles. Tumor markers (CEA and CA19-9) were also assessed at these times. Laboratory tests were performed before treatment, on day 8 of cycle 1 and on day 22 of each cycle. Drug compliance was reviewed at regular patient visits by checking unused tablets. Survival in all patients was monitored for 2 years after the last patient was enrolled.

Dosage and Dose Modifications

Capecitabine (Xeloda®) 1250 mg/m^2 was taken orally twice daily within 30 min after breakfast and dinner. The actual dose of capecitabine administered was determined according to the patient's body surface area (BSA) as follows: 3000 mg/day if BSA was <1.33; 3600 mg/day if BSA was between 1.33 and 1.56; 4200 mg/day if BSA was between 1.57 and 1.80; and 4800 mg/day if BSA was >1.80. Each cycle of therapy consisted of 2 weeks of capecitabine administration followed by a 1-week rest period. Patients received treatment unless they had disease progression or unacceptable toxicity, or withdrew consent.

Treatment interruption or dose reductions were made if patients experienced grade 2–4 toxicities, but not if the toxicity was considered unlikely to become serious or life-threatening. Treatment was interrupted in cases of grade 2 or grade 3 toxicities and was not resumed until adverse drug reactions improved to grade 1. The dose of capecitabine was not reduced for the subsequent treatment cycle in cases of the first appearance of grade 2 toxicity. Capecitabine dose was reduced by 25% when patients experienced any grade 2 toxicity for a second time or for any grade 3 toxicity. It was reduced by 50% when patients experienced any grade 2 toxicity three times, any grade 3 toxicity twice, or any grade 4 toxicity. Treatment was discontinued if such toxicities were observed despite dose reduction.

Statistical Methods

The target number of patients for accrual was 60. Given an expected response rate of 25%, a threshold response rate of 10% and a one-tailed probability of 0.025, the statistical power was 80%. All eligible patients were included in the analysis of response. The 95% confidence interval (CI) of the response rate was calculated by the exact method, assuming a binomial distribution of data. Treatment duration was defined as days from the first day of drug administration to the last regulated rest day of the final cycle. Dose intensity was calculated by dividing the cumulative dose/treatment duration by BSA. TTP was calculated as the time from the first administration of capecitabine to disease progression or death if the patient died before progression. Overall survival was defined as the time from study enrolment to death. These endpoints were calculated by the Kaplan–Meier method. Safety was evaluated in all patients who received capecitabine treatment.

Pharmacokinetic Analysis

Blood sampling was performed in the first 20 patients who gave consent to participate in the pharmacokinetic study. On day 1, the evening dose of capecitabine was not administered in order to quantify urinary recovery of capecitabine and its metabolites over a 24 h collection period. On days 1 and 14, 5 ml blood samples were collected at 0, 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8 and 11 h after the morning dose using vacutainers containing EDTA as an anticoagulant. Blood samples were centrifuged at 1500 *g* and 4°C for 10 min, and supernatant plasma was removed and stored in plastic tubes below −20°C until analysis. Urine was collected and pooled during the following time intervals: 0, 0–11 and 11–24 h on day 1; and 0–11 h on day 14. At the end of each interval, the total volume and the pH of urine were recorded; and a 15 ml aliquot was removed and stored at −20°C until analysis.

Plasma and urine concentrations of capecitabine and its metabolites were determined by a validated liquid chromatography with mass-spectrometry detection (LC/MS-MS). The lower limits of quantification (LLOQ) of capecitabine, 5′-DFCR, 5′-DFUR, 5-FU and α-fluoro-β-alanine (FBAL) in plasma were 0.01, 0.01, 0.05, 0.002 and 0.011 μg/ml, respectively. The LLOQ of capecitabine, 5′-DFCR, 5′-DFUR, 5-FU, α-fluoro-β-ureidopropionic acid and FBAL in urine were 0.02, 0.02, 0.02, 0.1, 0.02 and 0.1 μg/ml, respectively.

Pharmacokinetic parameters were assessed by standard non-compartment analysis, using WinNonlin® professional version 4.1 (Pharsight Corporation). Maximum plasma concentration (C_{max}) and the time to reach C_{max} (T_{max}) were determined. Apparent half-life ($t_{1/2}$) was estimated from ln2/λ, where the apparent rate constant of elimination, λ, was estimated by linear regression on the logarithm of the plasma concentration versus time data. The area under the plasma concentration time curve from time 0 to infinity (AUC) was estimated from the sum of AUC_{0-t} and C_{tlast}/λ, where AUC_{0-t} is the area under the curve from time 0 to the last sampling time (t_{last}) at which a concentration above the limit of quantification was measured (C_{tlast}). AUC_{0-t} was estimated using the linear-log trapezoidal rule. Percentage of dose recovered in urine as capecitabine or one of its metabolites was calculated based on the dose administered, urinary concentration and volume of urine collected.

RESULTS

Patient Characteristics

Sixty patients were enrolled at 11 centers between January 2003 and November 2003. All patients met the eligibility criteria and received at least one dose of capecitabine. Therefore, both tumor response and safety were assessed in 60 patients. The baseline characteristics of patients are shown in Table 1. Median age was 60 years (range 34–71 years). A total of 33 patients (55%) had colon cancer, and 26 (43%) had rectal cancer. Metastatic sites affected were liver (73%), lung (58%), lymph node (47%) and others (17%).

Treatment Duration and Intensity

The median duration of treatment was 186 days (range 8–508 days). The median cumulative dose of capecitabine was 370 g (range 27–1255 g). The planned dose intensity was 1667 mg/m^2/day and the actual median dose intensity was 1420 mg/m^2/day (range 940–2220 mg/m^2/day). Approximately 57 and 35% of patients completed 8 and 10 cycles of therapy, respectively. The reasons for treatment discontinuation were progressive disease (54 patients), adverse reactions (5 patients) and salvage surgical therapy (1 patient).

Table 1. Baseline patient demographics (intent-to-treat population)

Parameter	No. of patients	%
No. patients enrolled	60	100
Sex		
Male	33	55
Female	27	45
Age (years)		
Median	60	
Range	34–71	
Primary site		
Colon	33	55
Rectum	26	43
Colon/rectum	1	2
ECOG performance status		
0	42	70
1	17	28
2	1	2
Metastatic sites		
Liver	44	73
Lung	35	58
Lymph node	28	47
Other	10	17
Number of metastatic sites		
1	18	30
2	31	52
≥3	11	18
Resection		
Yes	54	90
No	6	10
Prior radiotherapy	1	2
Prior 5-FU or 5-FU analog-based adjuvant chemotherapy	10	17

The median dose per cycle was >75% of the planned dose up to 10 cycles.

EFFICACY

The objective response rate according to the IRC assessment was 35% (95% CI, 23–48%) (Table 2). Twenty-one patients had a partial response, and 31 (52%) had stable disease. Partial responses were observed in 11 out of 44 patients (25%) with liver metastases, 14 out of 35 patients (40%) with lung metastases and in 8 out of 28 patients (29%) with lymph nodes metastases. The median TTP was 5.5 months (95% CI, 4.2–6.7 months) (Fig. 1). Survival follow-up was performed at the cut-off date of October 2005. Thirty-five patients died of disease progression and there were no treatment-related deaths. The median overall survival was 20.2 months (95% CI, 16.6–27.8 months) and the 1-year survival rate was 70% (Fig. 1).

Table 2. Tumor responses (N = 60)

Response	No. of patients (%)	
	Assessed by investigators	Confirmed by Independent Review Committee
Complete response (CR)	0 (0)	0 (0)
Partial response (PR)	19 (32)	21 (35)
Stable disease (SD)	33 (55)	31 (52)
Progressive disease (PD)	7 (12)	8 (13)
Not evaluable	1 (2)	0 (0)
Overall response rate	32% (95% CI, 20–45%)	35% (95% CI, 23–48%)
Disease control (CR + PR + SD)	87% (95% CI, 75–94%)	87% (95% CI, 75–94%)

CI: confidence interval.

SAFETY

The common adverse drug reactions (all grades) were HFS (73%), pigmentation (38%), diarrhea (37%), anorexia (37%), nausea (37%) and stomatitis (37%) (Fig. 2). The most frequent grade 3/4 adverse drug reaction was HFS (13%), but it was managed relatively easily by treatment interruption or dose reduction. No grade 4 diarrhea was observed, and grade 3 diarrhea was seen in only one patient. Ileus occurred in one patient. As for grade 3/4 laboratory abnormalities, the common events were elevated total bilirubin (12%) and elevated AST (10%). One patient had grade 3 leucopenia, and 5 patients had grade 3 neutropenia. One patient had grade 4 hyperglycemia.

Treatment was interrupted due to adverse drug reactions in 48 patients (80%). The median time to the first interruption was 43 days. The major cause of treatment interruption was HFS (25 patients). Dose reduction was needed in 32 patients (53%), and 10 patients had the second dose reduction. The median time to the first dose reduction was 78 days, and to second dose reduction was 162 days. Nineteen patients had dose reductions due to HFS. Five patients discontinued treatment because of adverse events: ileus (grade 4, treatment related); hepatitis C (grade 3, not related, an accidental acute infection); liver function abnormality (grade 2, not related, due to the progression of liver metastasis); hydronephrosis (grade 4, not related) and HFS (grade 3, treatment related).

PHARMACOKINETICS

Plasma concentrations for capecitabine and its metabolites (5′-DFCR, 5′-DFUR, 5-FU and FBAL) are shown in Fig. 3. The pharmacokinetic parameters are summarized in Table 3. Peak plasma concentrations of capecitabine and its metabolites

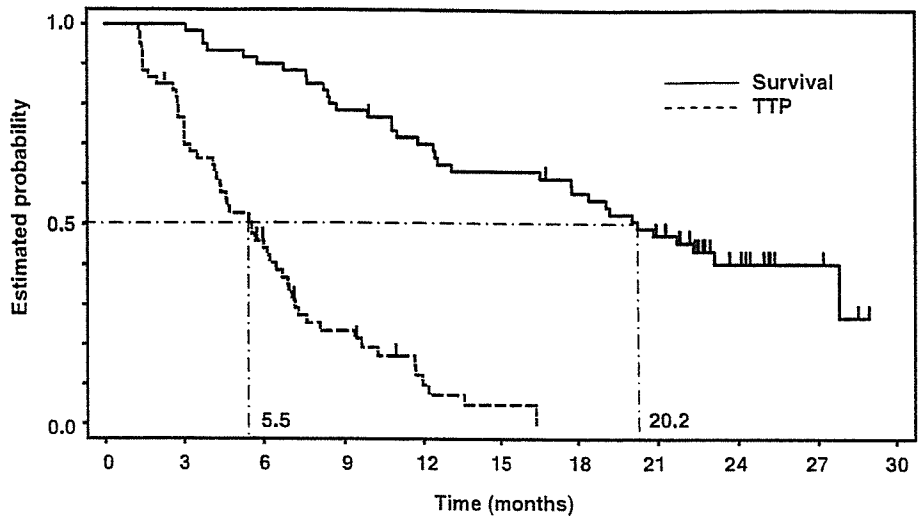

Figure 1. Time to disease progression (TTP) and overall survival.

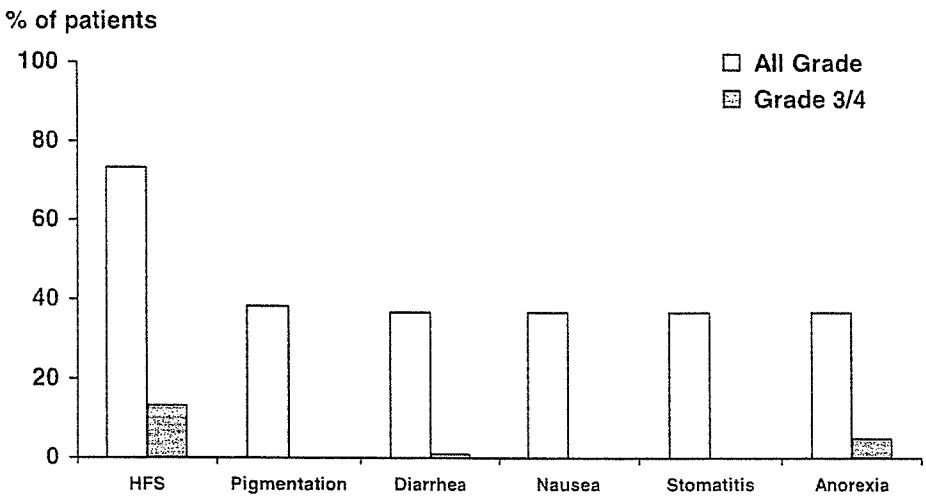

Figure 2. Common adverse drug reactions (≥20% of patients). HFS: hand-foot syndrome.

were reached rapidly at approximately 1.5–4 h after oral administration. Plasma concentrations of capecitabine, 5′-DFCR, 5′-DFUR and 5-FU were below the LLOQ at 8, 11, 8 and 8 h on day 1, respectively, and at 6, 11, 6 and 8 h on day 14, respectively. $T_{1/2}$ were generally short at <1 h, except for FBAL (around 2.5 h). After a single dose of capecitabine 1250 mg/m^2, the AUC for 5-FU was almost 30 times lower than its precursor 5′-DFUR on day 1. Comparing day 1 versus day 14, there was no significant accumulation of capecitabine and its metabolites except for 5-FU. The AUC for 5-FU on day 14 was 1.6 times higher than that on day 1.

The mean urinary excretion ratio of capecitabine and its metabolites are presented in Table 4. The mean proportions for the urinary recovery of capecitabine and its metabolites were 78% on day 1 and 80% on day 14. FBAL was the main urinary metabolite accounting for 50% on day 1 and 50% on day 14. The urinary excretion ratio of unmetabolized capecitabine was low at around 3%.

DISCUSSION

Two large randomized phase III studies have shown that capecitabine is more active than bolus 5-FU/LV in terms of tumor response (26 versus 17%), and equivalent to 5-FU/LV in terms of TTP and overall survival time in the first-line treatment of MCRC (11,13). Furthermore, a combined analysis of these randomized phase III studies revealed that capecitabine conferred a clinically meaningful advantage over 5-FU/LV in terms of safety (12). On the basis of these data, capecitabine was approved for the treatment of MCRC in Europe and in the US as an alternative to 5-FU/LV.

The results of the present study are similar to those observed in the pivotal phase III trials. The response rate in our study

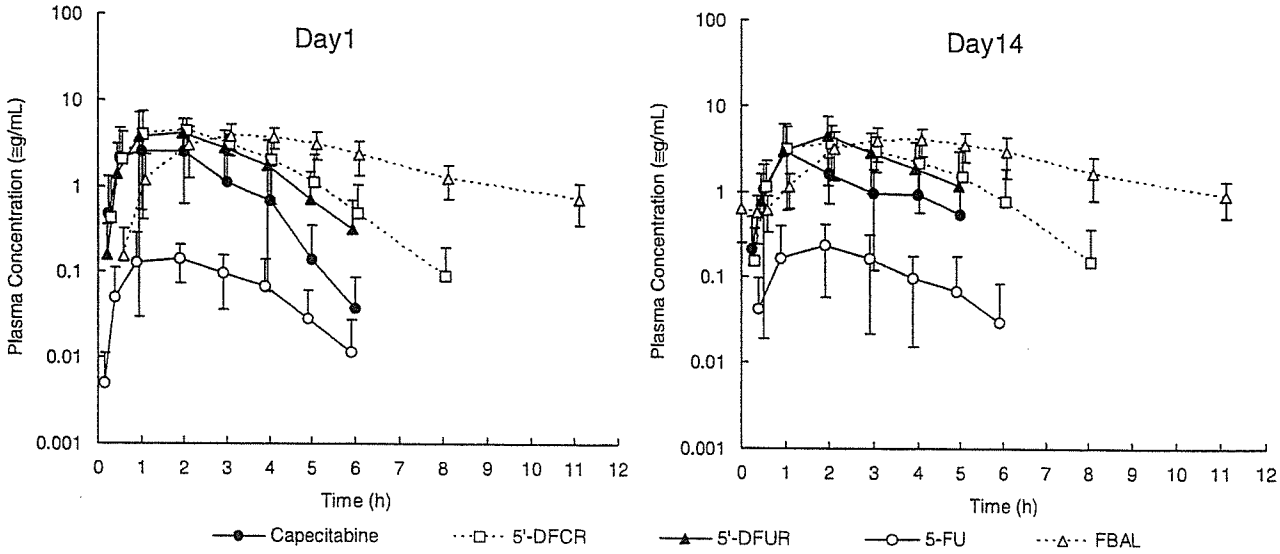

Figure 3. Plasma concentrations (mean ± standard deviation) for capecitabine and its metabolites 5′-deoxy-5-fluorocytidine (5′-DFCR), 5′-deoxy-5-fluorouridine (5′-DFUR) and α-fluoro-β-alanine (FBAL).

Table 3. Pharmacokinetic parameters of capecitabine and its metabolites

	Parameter	Day 1		Day 14	
		N	Mean ± SD	*N*	Mean ± SD
Capecitabine	C_{max} (μg/ml)	20	4.80 ± 1.75	19	4.19 ± 2.55
	T_{max} (h)	20	1.68 ± 0.99	19	1.90 ± 1.40
	AUC (μg·h/ml)	18	7.06 ± 2.46	15	6.73 ± 1.71
	$t_{1/2}$ (h)	18	0.545 ± 0.245	15	0.478 ± 0.152
5′-DFCR	C_{max} (μg/ml)	20	5.95 ± 2.50	19	5.20 ± 1.90
	T_{max} (h)	20	2.00 ± 1.07	19	2.53 ± 1.27
	AUC (μg·h/ml)	20	15.2 ± 4.32	19	14.1 ± 4.60
	$t_{1/2}$ (h)	20	0.810 ± 0.112	19	0.855 ± 0.199
5′-DFUR	C_{max} (μg/ml)	20	6.02 ± 2.49	19	6.59 ± 2.83
	T_{max} (h)	20	2.25 ± 1.16	19	2.69 ± 1.21
	AUC (μg·h/ml)	19	13.1 ± 3.69	17	13.2 ± 3.40
	$t_{1/2}$ (h)	19	0.711 ± 0.140	17	0.689 ± 0.199
5-FU	C_{max} (μg/ml)	20	0.217 ± 0.121	19	0.376 ± 0.211
	T_{max} (h)	20	2.30 ± 1.25	19	2.74 ± 1.20
	AUC (μg·h/ml)	19	0.455 ± 0.180	17	0.719 ± 0.235
	$t_{1/2}$ (h)	19	0.732 ± 0.291	17	0.755 ± 0.258
FBAL	C_{max} (μg/ml)	20	4.50 ± 1.01	19	4.84 ± 1.20
	T_{max} (h)	20	3.35 ± 1.09	19	3.85 ± 1.31
	AUC (μg·h/ml)	20	24.5 ± 7.40	16	27.0 ± 7.84
	$t_{1/2}$ (h)	20	2.56 ± 0.690	16	2.72 ± 0.506

5′-DFCR, 5′-deoxy-5-fluorocytidine; 5′-DFUR, 5′-deoxy-5-fluorouridine; FBAL, α-fluoro-β-alanine.

was 35%, which compares favorably with the combined response rate reported in the phase III studies (26%) (11,13) and in a previous Japanese phase II study (27%) using the 4-week regimen (10). Comparing the patients' background, the number of patients who had more than 3 metastatic sites in this study was less than that in the phase III studies (18 versus 52%) (12), and our patients had better PS (PS 0, 70%). These better backgrounds might bring out slightly higher response rate in our study. The rate of stable disease was 52% in the current study and 38% with the 4-week regimen (10). Consequently, the disease control rate was superior in the present study than with the 4-week regimen (87 versus 64%). Moreover, the median TTP was similar to that reported in the phase III studies (5.5 months versus 4.6 months) using the same 3-week schedule, and was longer than that in the previous Japanese phase II study (2.2 months, unpublished data) using the 4-week regimen. Notwithstanding the limitations of comparing data between trials, these data strongly suggest that the capecitabine 3-week regimen is superior to the 4-week regimen. One of the reasons for these better results might be attributed to the higher dose intensity of the 3-week regimen than that of the 4-week regimen.

In terms of safety, most adverse events were reversible and manageable, and the tolerability of this regimen in a Japanese patient population seemed similar to that observed in Western patient populations. Compared with the randomized phase III studies (12), the rate of HFS, the most frequently reported adverse drug reaction, was higher in the present study (73 versus 54%), but grade 3 HFS appeared a little lower (13 versus 17%). However, HFS was controlled easily by interruption or dose reduction and it is not a life-threatening toxicity. Only one patient withdrew from the study due to this adverse reaction (2%), but none of the patients required hospitalization for the treatment of HFS. In the phase III studies (12), 2% of patients withdrew because of HFS, a rate that was similar to our study. The rate of diarrhea (all-grade and grade 3/4) was less frequent in the present study compared with that of the phase III data (all-grade 37 versus 48%; grade 3/4

Table 4. Urinary excretion of capecitabine and its metabolites

	Urinary excretion (% of dose)			
	Day 1		Day 14	
	N	Mean ± SD	*N*	Mean ± SD
Capecitabine	16	3.21 ± 2.04	19	3.42 ± 1.48
5′-DFCR	16	8.39 ± 3.73	19	8.42 ± 3.44
5′-DFUR	16	12.1 ± 4.34	19	14.6 ± 5.35
5-FU	16	0.691 ± 0.835	19	0.782 ± 0.642
FUPA	16	2.78 ± 0.808	19	2.98 ± 1.05
FBAL	16	50.3 ± 9.66	19	49.5 ± 11.3
Total	16	77.5 ± 14.8	19	79.6 ± 16.9

5′-DFCR, 5′-deoxy-5-fluorocytidine; 5′-DFUR, 5′-deoxy-5-fluorouridine; FUPA, α-fluoro-β-ureidopropionic acid; FBAL, α-fluoro-β-alanine.

2 versus 13%) (12). Though pigmentation, which was not reported more than 5% in the phase III trials, was frequently observed in this study (38%), all events of pigmentation were grade 1 and did not lead to interruption or reduction. The rate of other adverse drug reactions in our study was almost identical to that reported in the phase III trials (12). With regard to severe abnormalities in laboratory parameters, AST elevation was more frequently observed in the present study (10 versus 1%), although the rate of hyperbilirubinemia was similar to phase III observations (12 versus 23%) (12). Dose reduction was executed more frequently than the phase III trials (53 versus 34%), but the rate of dose reduction to second level was almost similar (17 versus 12%). Median time to reduction to the first level was similar to phase III trials (2.6 months versus 2.5 months), and median time to reduction to the second level was longer in our study (5.3 months versus 3.6 months). From these results, the current 3-week regimen seems quite feasible for the treatment of MCRC in Japan.

The pharmacokinetic findings in the present study were basically similar to those reported in Caucasian patients (8,21). Pharmacokinetic analysis of plasma concentrations and urinary excretion showed rapid gastrointestinal absorption of capecitabine and efficient conversion to its metabolites. Peak concentrations of capecitabine and its metabolites, including 5-FU, were reached shortly after drug administration and declined exponentially with a half-life of approximately 1 h. Pharmacokinetic data obtained on days 1 and 14 showed no difference in pharmacokinetics over time and there was no clinically significant accumulation of capecitabine and its metabolites, except for 5-FU. The AUC of 5-FU on day 14 was 1.6 times higher than on day 1. A similar increase of 5-FU with multiple administration has been also reported in other clinical studies of capecitabine (7,8,21).

From these results, we conclude that the 3-week regimen of capecitabine is effective and well tolerated in Japanese patients with MCRC. Capecitabine has been reported to show good activity when combined with irinotecan (14,15) and oxaliplatin (16,17). Further investigation of this 3-week schedule is warranted in Japan.

Acknowledgments

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APPENDIX

List of participating centers: NHO Shikoku Cancer Center, National Cancer Center Hospital, National Cancer Center Hospital East, Cancer Institute Hospital, Aichi Cancer Center, Saitama Cancer Center, Kobe University Graduate School of Medicine, Kanagawa Cancer Center, Osaka Medical College, Kinki University, NHO Osaka National Hospital.

Randomized Phase II Study of Carboplatin/Gemcitabine versus Vinorelbine/Gemcitabine in Patients With Advanced Nonsmall Cell Lung Cancer

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BACKGROUND. Combined gemcitabine and carboplatin (GC) and combined gemcitabine and vinorelbine (GV) are active and well tolerated chemotherapeutic regimens for patients with advanced nonsmall cell lung cancer (NSCLC). The authors conducted a randomized Phase II study of GC versus GV to compare them in terms of efficacy and toxicity.

METHODS. One hundred twenty-eight patients with Stage IIIB or IV NSCLC were randomized to receive either carboplatin at an area under the curve of 5 on Day 1 combined with gemcitabine 1000 mg/m^2 on Days 1 and 8 ($n = 64$ patients) or vinorelbine 25 mg/m^2 combined with gemcitabine 1000 mg/m^2 on Days 1 and 8 ($n = 64$ patients) every 3 weeks.

RESULTS. Response rates were 20.3% for the GC patients and 21.0% for the GV patients. In the GC arm, the median survival was 432 days, and the a 1-year survival rate was 57.6%; in the GV arm, the median survival was 385 days, and the 1-year survival rate was 53.3% in the GV arm. The median progression-free survival was 165 days in the GC arm and 137 days in the GV arm. Severe hematologic toxicity (Grade 4) was significantly more frequent in the GC arm (45.3% vs. 25.8% in the GV arm; $P = .022$). Most notably, the incidence of Grade 3 or 4 thrombocytopenia was significantly higher in the GC arm (81.3% vs. 6.5% in the GV arm; $P < .001$). Conversely, severe nonhematologic toxicity (Grade 3 or 4) was more common in the GV arm (7.8% vs. 19.4% in the GC arm; $P = .057$).

CONCLUSIONS. Although the GV and GC regimens had different toxicity profiles, there was no significant difference in survival among patients with NSCLC in the current study. ***Cancer* 2006;107:599–605.** © *2006 American Cancer Society.*

KEYWORDS: gemcitabine, carboplatin, vinorelbine, nonsmall cell lung cancer.

Unfortunately, nonsmall cell lung cancer (NSCLC) belongs to a group of relatively chemoresistant neoplastic diseases. Recent meta-analyses have shown that cisplatin-based chemotherapy regimens improve survival,[1] and they now are considered standard treatment for patients with NSCLC. Most cisplatin-based regimens have substantial toxicities that require close monitoring and supportive care. Thus, active and less toxic chemotherapeutic regimens that include new, active compounds with novel mechanisms of action need to be developed. The recommendations recently presented in the American Society Clinical Oncology guidelines for chemotherapy in patients with Stage IV NSCLC stated that nonplatinum-containing chemotherapeutic regimens may be used as alternatives to platinum-based regimens as first-line treatment.[2,3]

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Carboplatin, which is an analog of cisplatin, administered either alone or in combination therapy, is associated with less emesis, nephrotoxicity, and neurotoxicity than cisplatin and has been proven to be as effective as cisplatin in NSCLC.[4,5] Several novel chemotherapeutic agents currently are being evaluated for the treatment of patients with advanced NSCLC. The combination of gemcitabine and carboplatin (GC) is a promising carboplatin-containing regimen and has been evaluated in several randomized trials. Mazzanti et al. conducted a randomized Phase II study of GC versus gemcitabine and cisplatin (GP) and observed no differences in activity between the 2 regimens, although there was less emesis, neuropathy, and renal toxicity with GC.[6] The same results were confirmed in a Phase III study of GC versus GP that was conducted by Zatloukal et al.[7] Moreover, GC reportedly prolonged survival significantly compared with single-agent carboplatin in a randomized Phase III study.[8]

The combination of gemcitabine and vinorelbine (GV) is among the representative nonplatinum regimens. GV has demonstrated promising activity and mild toxicity in some Phase II studies. We also conducted a Phase II trial of GV in patients with Stage IIIB and IV NSCLC and observed that toxicity was modest and was managed easily, and overall survival was promising (median survival, 13.9 months).[9] Several randomized Phase III trials have shown that this regimen conferred a comparable survival advantage and was less toxic than standard cisplatin-based chemotherapy.[10,11]

Thus, we can state reasonably that both GC and GV are attractive alternatives to cisplatin-based chemotherapy. However, we have neither survival data nor toxicity data for GC in Japanese patients with NSCLC. Therefore, we conducted a randomized Phase II trial of GC versus GV in patients with advanced NSCLC to compare the efficacy, feasibility, and toxicity profiles of the 2 regimens. The primary endpoint was the 1-year survival rate, and secondary endpoints were overall survival, the time to progression, and the response rate.

MATERIALS AND METHODS

Patient Selection

The patients who were enrolled in this trial had histologically or cytologically confirmed Stage IIIB or IV NSCLC. Patients with Stage IIIB disease who were not candidates for thoracic radiation and patients with Stage IV disease were eligible if they had not received previous chemotherapy, had measurable disease, and had a life expectancy $\geq$3 months. Patients who had received previous radiotherapy were included if they had assessable disease outside of the radiation field. Patients with who had postoperative recurrences also were allowed. Additional entry criteria were age between 20 years and 74 years, a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) scale, and adequate bone marrow function (leukocyte count $\geq$3500/μL, neutrophil count $\geq$2000/μL, hemoglobin concentration $\geq$10.0 g/dL, platelet count $\geq$ 100,000/μL), kidney function (creatinine $\leq$1.2 mg/dL), liver function (aspartate aminotransferase [AST] and alanine aminotransferase [ALT] levels $\leq$2.5 times the upper limit of normal; and total bilirubin $\leq$1.5 mg/dL), and pulmonary function (partial pressure of alveolar oxygen $\geq$60 torr). Patients were excluded if they had any active concomitant malignancies, symptomatic brain metastases, prior radiotherapy to the sole site of measurable disease, past history of severe allergic reactions to drugs, interstitial pneumonia identified by chest X-ray, cirrhosis, superior vena cava syndrome, or other serious complications, such as uncontrolled angina pectoris, myocardial infarction within 3 months, heart failure, uncontrolled diabetes mellitus or hypertension, and uncontrolled massive pleural effusion or ascites. All patients gave written informed consent, and the Institutional Review Board for Human Experimentation approved the protocol.

Randomization and Treatment Plan

Patients were assigned randomly to receive the GC regimen or the GV regimen and were stratified by disease stage (Stage IIIB vs. Stage IV), prior treatment (yes vs. no), and institution. On the GC regimen, gemcitabine was given at a dose of 1000 mg/m^2 in 100 mL of normal saline solution as a 30-minute intravenous infusion on Days 1 and 8. Carboplatin was administered at area under the curve (AUC) of 5 in 500 mL of normal saline solution as a 60-minute intravenous infusion on Day 1 only. We used the Calvert formula[12] to determine the dose of carboplatin as follows: dose in mg = target AUC $\times$ (creatinine clearance + 25). The glomerular filtration rate was estimated by using the formula described by Gault et al.[13]

The GV regimen consisted of gemcitabine 1000 mg/m^2 in 100 mL of normal saline solution as a 30-minute intravenous infusion and vinorelbine 25 mg/m^2 in 20 mL of normal saline solution as a 5-minute intravenous infusion on Days 1 and 8. The scheduled Day-8 treatment was delayed until recovery (no longer than 1 week) if patients had a leukocyte count <2000/μL, platelet count <75,000/μL, interstitial pneumonia Grade $\geq$1, constipation Grade $\geq$3, and/or other nonhematologic toxicities Grade $\geq$2. If these parameters did not improve sufficiently, then the Day-8 gemcitabine and vinorelbine doses were omitted.

Both regimens were repeated every 3 weeks. The subsequent course of chemotherapy was begun if patients had a leukocyte count $\geq$3000/μL, neutrophil count $\geq$1500/μL, platelet count $\geq$100,000/μL, creatinine $\leq$1.5 mg/dL, AST and ALT levels $\leq$2.5 times the upper limit of normal, and total bilirubin $\leq$1.5 times the upper limit of normal. A 2-week delay in initiating the subsequent course was allowed. Otherwise, the patient was withdrawn from the study. We planned for patients to receive at least 3 cycles, up to a maximum 6 cycles, of chemotherapy unless there was evidence of disease progression, intolerable toxicity, or patient refusal.

For dose modification in the subsequent cycle in both arms, if, during the previous course, Grade 4 leukopenia, chemotherapy-induced neutropenic fever >38°C, thrombocytopenia (< 20,000/μL), nonhemotologic toxicity Grade $\geq$3, or cancellation of Day-8 treatment had occurred, then the doses of gemcitabine, vinorelbine, and carboplatin were reduced by 200 mg/m^2, 5 mg/m^2, and AUC 1, respectively. Treatment was discontinued in patients who could not tolerate either gemcitabine 800 mg/m^2 and carboplatin AUC 4 or gemcitabine 800 mg/m^2 and vinorelbine 20 mg/m^2.

It was acceptable to administer a 5-hydroxytriptamine receptor antagonist and/or dexamethasone intravenously before the start of chemotherapy to prevent nausea and emesis. The use of granulocyte-colony stimulating factors was not allowed during treatment except in patients who had Grade 4 leukopenia, Grade 4 neutropenia, or febrile neutropenia, according to the investigator's decision. Transfusions of red blood cells and platelets were allowed in patients who had Grade $\geq$3 anemia and in patients who had platelet counts $\leq$20,000/μL and/or a tendency for bleeding.

Treatment Evaluation

Before enrollment in the study, all patients provided a complete medical history and underwent physical examination. We obtained a complete blood count, blood chemistry, blood gas analysis, chest X-ray, electrocardiography, computed tomographic (CT) scans of the brain and chest, a CT scan or ultrasound examination of the abdomen, and a bone scintigram. Patients were monitored weekly throughout treatment by physical examination, recording of toxic effects, complete blood cell counts, and blood chemistry. Studies of drug-related toxicities were evaluated according to National Cancer Institute Common Toxicity Criteria (version 2.0, revised 1994).

Tumor responses were classified according to the Response Evaluation Criteria in Solid Tumors.[14] In target lesions, a complete response (CR) was defined as the complete disappearance of all target lesions for a minimum of 4 weeks, during which no new lesions appeared. A partial response (PR) was defined as a decrease $\geq$30% in the sum of the greatest dimensions of target lesions for a minimum of 4 weeks. Progressive disease (PD) was defined as an increase $\geq$20% in the sum of the greatest dimensions of target lesions or the appearance of $\geq$1 new lesion(s). Stable disease (SD) was defined as neither sufficient shrinkage to qualify for a PR nor a sufficient increase to qualify for PD for a minimum of 6 weeks. Response duration in patients who achieved a CR or PR was measured from the start of treatment to the date of disease progression.

In nontarget lesions, a CR was defined as the disappearance of all nontarget lesions. An incomplete response/SD was defined as the persistence of $\geq$1 nontarget lesion(s). PD was defined as the appearance of $\geq$1 new nontarget lesion(s) and/or unequivocal progression of existing nontarget lesions. An extramural review was conducted to validate staging and responses during a regular meeting of the West Japan Thoracic Oncology Group.

Statistical Methods

The main objective of this study was to test whether either of the 2 regimens had promise in terms of increasing survival. Each arm was to be analyzed separately. One or both of the regimens would be considered promising if the true 1-year survival rates were $\geq$55%, or the regimens would be of no additional interest if the true 1-year survival rates were $\leq$32%. The study was designed to accrue 57 patients to each arm over 12 months followed by 1 additional year of follow-up to confer a power of 0.80 for a 1-sided .05 level for a 1-year survival rate of 32% versus 55%.

We compared Kaplan–Meier curves for overall survival and progression-free survival by using the standard log-rank test. Overall survival was defined as the interval from the date of random treatment assignment to the date of death or last follow-up information for patients who remained alive. Progression-free survival was defined as the interval from the date of random treatment assignment to the date of progression or death, whichever occurred first, or last follow-up information for patients who remained alive and for patients whose disease did not progress.

Patient characteristics except for age, response rates, dose reduction rate in each cycle, and toxicity incidence, were compared by using Pearson chi-square contingency table analysis. Age and the number of treatment cycles were compared by using the Wilcoxon test.

TABLE 1
Baseline Patient Characteristics

Characteristic	No. of patients GC	GV	P
Total no. of patients	64	64	
Gender			.851
Male/female	43/21	42/22	
Age, y			
Median	60	62	.929
Range	30–74	36–74	
PS			
0/1	25/39	24/40	.855
Smoking history			
Yes/no	18/46	27/37	.095
Histology			
Adenocarcinoma	36	45	.128
Squamous cell carcinoma	21	16	
Others	7	3	
Disease stage			
Stage IIIB/IV	16/48	16/48	1.000
Prior treatment			
Yes/no	15/49	14/50	.832

GC indicates gemcitabine and carboplatin; GV, gemcitabine and vinorelbine; PS, performance status.

RESULTS

Patient Characteristics

From June 2001 to October 2002, 128 patients were assigned to receive GC ($n = 64$ patients) or GV ($n = 64$ patients). All enrolled patients were eligible. Baseline patient characteristics according to treatment arm are shown in Table 1. Patients essentially were divided equally between the 2 treatment arms in terms of gender, age, performance status, disease stage, and histologic subtypes. Patients with Stage IIIB disease accounted for 27% of the study population, and patients with adenocarcinoma accounted for 63% of the study population. In the GV arm, 2 patients did not receive trial therapy because of deterioration in their condition. These 2 patients were excluded from the analysis of toxicity, response, and progression-free survival.

Treatment Delivery

Median numbers of 3 cycles and 4 cycles were administered in the GC and GV arms, respectively. Three or more cycles were delivered to 76.6% and 72.6% of patients, and 6 cycles were delivered to 7.8% and 32.3% of patients in the GC and GV arms, respectively. Differences between arms in the number of chemotherapy courses administered were not statistically significant ($P = .161$) (Table 2).

Chemotherapy was omitted on Day 8 for 6.4% of patients in the GC arm and for 3.8% of patients in the GV arm. Dose reductions in the second cycle were more frequent in the GC arm than in the GV arm (49.2% vs. 14.8%, respectively; $P < .001$). The dose reduction rates after the second cycle did not differ between the 2 arms (Table 2). Most dose reductions in the GC arm were because of hematologic toxicity, especially thrombocytopenia. Reasons for stopping treatment also differed between the 2 arms; Treatment was stopped before 3 cycles for disease-related causes (progression or death) in 46.7% and 58.8% of patients and because of toxicity or refusal in 40.0% and 29.4% of patients in the GC and GV arms, respectively.

TABLE 2
Treatment Delivery and Dose Reduction Rate

No. of cycles	Gemcitabine and carboplatin: No. of patients (%)	No. of patients who required dose reduction (%)	Gemcitabine and vinorelbine: No. of patients (%)	No. of patients requiring dose reduction (%)
2	61 (95.3)	30 (49.2)	54 (87.1)	8 (14.8)
3	49 (76.6)	6 (12.2)	47 (75.8)	6 (13.3)
4	29 (45.3)	2 (6.7)	34 (54.8)	2 (5.9)
5	9 (14.1)	2 (22.2)	24 (38.7)	1 (4.2)
6	5 (7.8)	0	20 (32.2)	0

Treatment Response and Survival

In the GC arm, there was 1 CR and 12 PRs for an overall response rate of 20.3%. In addition, 34 patients (53.1%) had SD, and 17 patients (26.6%) had PD. In the GV arm, there were 2 CRs and 11 PRs for an overall response rate of 21.0%. There were 29 patients (46.8%) with SD and 17 patients (27.4%) with PD. The difference in the overall response rate between the 2 arms was not significant ($P = .60$).

Overall and progression-free survival curves for the 2 treatment arms are shown in Figures 1 and 2. The 1-year survival rate was 57.6% (95% confidence interval, 45.5–69.8%) in the GC arm versus 53.3% (95% confidence interval, 40.8–65.7%) in the GV arm. Respective median survival, 2-year survival rates, and median progression-free survival were 432 days, 38.3%, and 165 days in the GC arm and 385 days, 22.4%, and 137 days in the GV arm. No significant differences were noted between groups in progression-free survival ($P = .676$) or overall survival ($P = .298$), although there were trends toward higher 1-year and 2-year survival rates in the GC arm.

After primary chemotherapy, 94 patients (73.4%) received other chemotherapeutic agents with no difference between the 2 arms (47 patients in the GC arm and 47 patients in the GV arm received other chemotherapeutic agents). In the GC arm, 27 patients

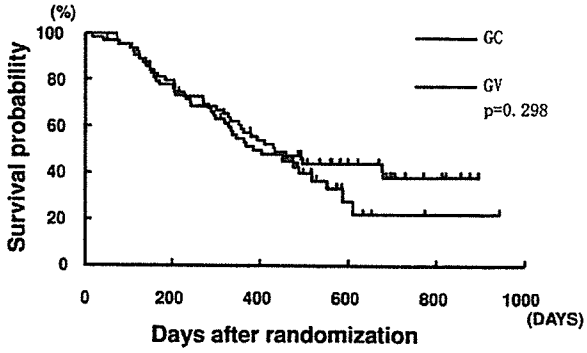

FIGURE 1. Overall survival is illustrated for the 2 treatment arms. GC indicates gemcitabine and carboplatin; GV, gemcitabine and vinorelbine.

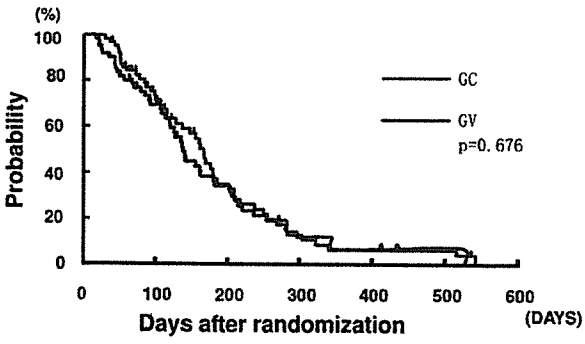

FIGURE 2. Progression-free survival is illustrated for the 2 treatment arms. GC indicates gemcitabine and carboplatin; GV, gemcitabine and vinorelbine.

received a single anticancer agent (docetaxel, 17 patients; vinorelbine, 4 patients; gemcitabine, 3 patients; other agents, 3 patients). Platinum doublets were given to 12 patients (carboplatin and paclitaxel, 3 patients; cisplatin and docetaxel, 3 patients; carboplatin and docetaxel, 2 patients; other doublets, 4 patients). In the GV arm, 21 patients received platinum doublets (carboplatin and paclitaxel, 14 patients; carboplatin and docetaxel, 3 patients; other doublets, 4 patients). A single cytotoxic agent was given to 9 patients (docetaxel, 6 patients; vinorelbine, 1 patient; gemcitabine, 1 patient; other agents, 3 patients). There was a tendency for more patients to receive single-agent chemotherapy, whereas fewer patients received platinum doublets, in the GC arm. The number of patients who received gefitinib treatment apparently did not differ between the 2 arms (31 patients in the GC arm and 27 in the GV arm received gefitinib).

Toxicity

Severe hematologic toxicity (Grade 4) was significantly more frequent in the GC arm (45.3% vs. 25.8% in the GV arm; $P = .022$). Conversely, severe nonhematologic toxicity (Grade 3 or 4) occurred more often in the GV arm (7.8% vs. 19.4% in the GC arm; $P = .057$). There were no treatment-related deaths.

TABLE 3
Hematologic Toxicity: Maximum Toxicity Grade in Any Course*

Toxicity	No. of patients (%) GC	GV	P
Leukopenia			
Grade ≥3	34 (53.1)	26 (41.9)	.208
Grade 4	1 (1.6)	1 (1.6)	.981
Neutropenia			
Grade ≥3	51 (79.7)	40 (64.5)	.057
Grade 4	22 (34.4)	16 (25.8)	.294
Anemia			
Grade ≥3	32 (50.0)	3 (4.8)	<.001
Grade 4	9 (14.1)	0	.002
Thrombocytopenia			
Grade ≥3	52 (81.3)	4 (6.5)	<.001
Grade 4	6 (9.4)	0	.013
Platelet transfusion			
Yes	29 (45.3)	0	<.001
Febrile neutropenia	20		
Yes	5 (7.8)	7 (11.3)	.506

GC indicates gemcitabine and carboplatin; GV, gemcitabine and vinorelbine.
* Studies of drug-related toxicities were evaluated according to National Cancer Institute Common Toxicity Criteria (version 2.0, revised 1994).

Hematologic and nonhematologic toxicities are listed in Tables 3 and 4. Hematologic toxicity was prominent. In particular, the incidence of Grade 3 or 4 thrombocytopenia was significantly higher in the GC arm (81.3% vs. 6.5% in the GV arm; $P < .001$). However, most patients who had thrombocytopenia in the GC arm did not experience bleeding. Two patients had Grade 3 bleeding in the GC arm. Patients in the GC arm required more platelet transfusions (45.3% vs. 0.0% in the GV arm; $P < .001$). Grade 3 or 4 neutropenia and anemia also occurred in a significantly higher percentage of patients in the GC arm (neutropenia, 79.7% vs. 62.5% in the GV arm; $P < .031$; anemia, 50.0% vs. 4.7% in the GV arm; $P < .001$). The difference in febrile neutropenia incidence was not significant. ($P = .264$).

Nonhematologic toxicity was mild. Grade ≥2 nausea occurred significantly more often in the GC arm than in the GV arm (21.0% vs. 42.2%; $P = .010$). Conversely, Grade ≥2 phlebitis (29.0% vs. 0%; $P < .001$) and hepatic toxicity (elevation of AST or ALT, 43.5% vs. 25.0%; $P = .028$) were significantly more common in the GV arm than in the GC arm. Other nonhematologic toxicities occurred with similar frequency in the 2 treatment arms.

There was 1 treatment-related death in the GV arm, which was caused by pneumonitis. No treatment-related deaths occurred in the GC arm.

TABLE 4
Nonhematologic Toxicity: Maximum Toxicity Grade in Any Course*

Toxicity	No. of patients (%) GC	GV	P
Nausea			
Grade ≥2	27 (42.2)	13 (21.0)	.010
Grade 3	5 (7.8)	0	-
Emesis			
Grade ≥2	8 (12.5)	5 (8.1)	.413
Grade 3	0	0	-
Fatigue			
Grade ≥2	9 (14.1)	15 (24.2)	.147
Grade 3	2 (3.1)	2 (3.2)†	-
Diarrhea			
Grade ≥2	0	2 (3.2)	.147
Grade 3	0	1 (1.6)	-
Constipation			
Grade ≥2	28 (43.8)	19 (30.6)	.128
Grade 3	3 (4.7)	1 (1.6)	-
Rash			
Grade ≥2	11 (17.2)	11 (17.7)	.934
Grade 3	2 (3.1)	1 (1.6)	-
Phlebitis			
Grade ≥2	0	18 (29.0)	<.001
Grade 3	0	0	-
Pneumonitis			
Grade ≥2	0	3 (4.8)	.074
Grade 3	0	2 (3.2)‡	-
ALT/AST			
Grade ≥2	16 (25.0)	27 (43.5)	.028
Grade 3	5 (7.8)	12 (19.4)	.057
Creatinine			
Grade ≥2	0	1 (1.6)	.307
Grade 3	0	1 (1.6)	-

GC indicates gemcitabine and carboplatin; GV, gemcitabine and vinorelbine; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

* Studies of drug-related toxicities were evaluated according to National Cancer Institute Common Toxicity Criteria (version 2.0, revised 1994).

† One patient had Grade 3 fatigue, and 1 patient had Grade 4 fatigue.

‡ One patient had Grade 3 pneumonitis, and 1 patient had Grade 5 pneumonitis.

DISCUSSION

This study, the first cooperative group trial to our knowledge of the GC regimen, demonstrated the feasibility of the GC regimen compared with the GV regimen. The GC regimen was identified as a promising regimen for patients with advanced NSCLC. Sederholm et al. of the Swedish Lung Cancer Group demonstrated that GC conferred a significant survival advantage compared with gemcitabine alone.[8] Other Phase III trials demonstrated that the GC regimen was tolerated better; conferred a survival advantage over the combination of mitomycin, ifosfamide, and cisplatin;[15] and resulted in a comparable survival advantage and less nausea and emesis compared with GC.[7]

Based on a large body of Phase II data, including those from our study,[9] and Phase III data, the GV regimen apparently produces less hematologic and nonhematologic toxicity, when it is compared indirectly with more standard combinations. In recent Phase III studies, GV was compared with cisplatin-based regimens. Overall, there was no significant difference in survival, but toxicity was less pronounced.[10,11,16]

GC and GV have comparable efficacy and less toxicity than platinum doublets, as discussed above. However, we do not know which regimen, GC or GV, is more feasible or more effective. Thus, we conducted a randomized study to compare the 2 regimens.

This randomized Phase II study showed that GC and GV are tolerated well and have comparable activity in patients with advanced NSCLC. However, there were marked differences in hematologic toxicity and moderate differences in nonhematologic toxicity. GC resulted in higher incidences of Grade 3 or 4 neutropenia, anemia, and thrombocytopenia. Conversely, hepatic toxicity and phlebitis were increased in patients who received GV.

GC was associated with more thrombocytopenia. The difference in the incidence of severe thrombocytopenia between our study and European or American studies may be attributable to blood counts that were obtained more often in Japan (more than once or twice per week) or to ethnic differences. It is unknown whether there are any the ethnic differences between Japanese and European or American patients concerning thrombocytopenia on the GC regimen. However, a report described severe hematologic toxicity with the combination of paclitaxel and carboplatin that may have been caused by an ethnic difference. Gandara et al. performed a comparative analysis of paclitaxel and carboplatin from cooperative group studies in Japan and the United States. Their analysis showed that the incidence of Grade 4 neutropenia (69% vs. 26%) and Grade 3 or 4 febrile neutropenia (16% vs. 3%) was significantly higher in Japanese patients despite the lower paclitaxel dose.[17]

Overall efficacy was comparable between the GC and GV arms in the current study. There was a trend toward inferior overall survival in the GV arm, but the differences were small numerically, and the study did not have adequate power to detect survival differences. Survival in the current study was better than that reported in other studies of patients with advanced NSCLC. The median progression-free survival in the GC arm in our study was 165 days and was almost equal to that of GC reported by Rudd et al. (5.3 months)[15]; however, overall survival in our study was much longer (432 days vs. 10 months, respectively). Moreover, the proportion of patients who received second-line therapies

in our study was higher (73% vs. 8%).[15] Thus, we believe that better survival in the current study was because a higher proportion of our patients received second-line therapies.

In conclusion, the current results demonstrated that the GC and GV regimens both were active and well tolerated. Although Grade 3 and 4 thrombocytopenia was more frequent in the GC arm, the low incidence of bleeding indicated that thrombocytopenia was not major clinical problem. Thus, we believe that both the GC regimen and the GV regimen are reasonable treatment options for patients with advanced NSCLC.

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