45 mg/m^2/day, respectively. Two phase II studies for NSCLC showed response rates of 27.9% and 18.3%, while a phase II study for extensive-disease small cell lung cancer (ED-SCLC) had a response rate of 75.8% and a median survival time (MST) of 11.7 months. Based on these results, AMR seems to be active for both NSCLC and ED-SCLC.

CPT-11, a camptothecin derivative, is a semi-synthetic topo I inhibitor and is one of the most active drugs used in the treatment of NSCLC and SCLC (7, 8). Recently, the Japan Clinical Oncology Group (JCOG) indicated that the combination of cisplatin and CPT-11 allows for significantly better survival than the combination of cisplatin and etoposide for previously untreated ED-SCLC (9). Moreover, Kubota *et al.* recently reported the results of the Four Arm Cooperative Study (FACS), which showed that cisplatin plus CPT-11 had comparative activity to carboplatin plus paclitaxel, cisplatin plus gemcitabine and cisplatin plus vinorelbine for the treatment of advanced NSCLC(10). Therefore, in Japan, the combination of cisplatin and CPT-11 is considered to be one of the standard chemotherapy regimens for NSCLC and ED-SCLC.

With the aim of improving therapeutic effects, a phase I study of AMR and CPT-11, as a combined topo I/II-targeting chemotherapy regimen for advanced lung cancer, was conducted. The objectives of this phase I study were: (a) to determine the MTD of both drugs and the RD for phase II studies; (b) to evaluate the toxicity profile of this regimen; (c) to investigate the pharmacokinetics of CPT-11, SN-38, AMR and amrubicinol; and (d) to observe the antitumor activity.

Patients and Methods

Patient eligibility. Patients with histological or cytological confirmation of locally advanced or metastatic NSCLC or ED-SCLC, who had received either no prior chemotherapy or one previous chemotherapy regimen, were eligible. The eligibility criteria were as follows; (a) ≥20 but <75 years old; (b) Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1; (c) adequate organ function [white blood cell count (WBC) ≥4000 μl^{-1}, neutrophil count ≥2000 μl^{-1}, platelet count ≥100,000 μl^{-1}, hemoglobin concentration ≥9.5 gdl^{-1}, serum total bilirubin ≤1.5 mgdl^{-1}, serum transaminase ≤2.5 x upper normal limits, serum creatinine ≤ upper normal limits, PaO_2 ≥ 60 mmHg]. At least 4 weeks had to have passed after the completion of prior therapy and the patients had to have recovered from any toxic effects of such therapy. The exclusion criteria comprised pulmonary fibrosis or interstitial pneumonitis with symptoms or apparent abnormalities on chest X-ray, massive pleural effusion, pericardial effusion, or ascites, pregnancy, lactation, symptomatic brain metastases, active concurrent malignancies, severe drug allergies, severe heart disease, cerebrovascular disease, uncontrollable diabetes mellitus, severe infection or active peptic ulcer. This study was performed at the Kinki University School of Medicine, Japan, and was approved by the Institutional Review Board. Written informed consent was obtained from all patients. This study was conducted in accordance with the Declaration of Helsinki.

Table I. *Dose modification schemes.*

Dose	Amrubicin (mg/m^2)	Irinotecan (mg/m^2)	No. of patients (courses)
-2	30	50	3(8)
-1	30	60	5(14)
1	40	50	3(11)

Pretreatment and follow-up studies. Prior to entry, a full history and physical examination were completed, including age, height, weight, PS, histological diagnosis, tumor stage, nature of previous treatment and presence of a complication. The pretreatment laboratory examinations included a complete blood cell count, differential WBC count, hemoglobin, platelet count, serum electrolytes, total protein, albumin, total bilirubin, transaminase, alkaline phosphatase, lactate dehydrogenase, BUN, creatinine, blood gas analysis and electrocardiogram. After the initiation of therapy, a complete blood cell count with a differential WBC count was performed at least twice a week. Blood chemistry profiles and chest X-rays were obtained weekly. The lesion measurements were performed during every second course at least. Toxicities were evaluated according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2 and tumor responses were assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (11).

Drug administration and dose escalation. The treatment schedule included AMR, diluted with 20 ml of 5% glucose fluid, given *i.v.* over 5 min for 3 consecutive days, and CPT-11 with 500 ml of normal saline, given *i.v.* over 90 min after the completion of AMR infusion on days 1 and 8, every 3 weeks. All patients were allowed to receive antiemetics with dexamethasone and granisetron. Granulocyte colony-stimulating factor (G-CSF) prophylaxis was not administered. Doses of CPT-11 on day 8 were given if the WBC count was >2,500 μl^{-1}, the platelet count was >75,000 μl^{-1}, no episode of diarrhea had been experienced, pneumonitis incidents were less than grade 2 and the other non-hematological toxicities were less than grade 3. The subsequent courses were started if the WBC count was >3,000 μl^{-1}, the platelet count was >100,000 μl^{-1}, serum total bilirubin ≤1.5 mgdl^{-1}, serum transaminase ≤2.5 x upper normal limits, no episode of diarrhea had been experienced and pneumonitis incidents were less than grade 2. The doses of both drugs were decreased by one dose level if DLTs occurred. In the case of the initial dose level, the dose reduction was not permitted and this study was canceled.

The dose escalations were performed as listed in Table I. Intra-patient dose escalation was not allowed. At least three patients were treated at each dose level, and three additional patients were entered at the same dose level if DLT was observed in one or two of the first three patients. The MTD was defined as the dose level at which three out of three patients, or more than three out of six patients experienced DLT. The definition of DLT was: (a) grade 4 neutropenia for more than 4 days, (b) grade 3 febrile neutropenia, (c) thrombocytopenia <20,000 μl^{-1}, (d) grade 3 non-hematological toxicity except for nausea/vomiting, appetite loss and pneumonitis, (e) more than grade 2 pneumonitis, (f) delay of administration of CPT-11 on day 8 over a week, or delay of subsequent courses over 2

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.

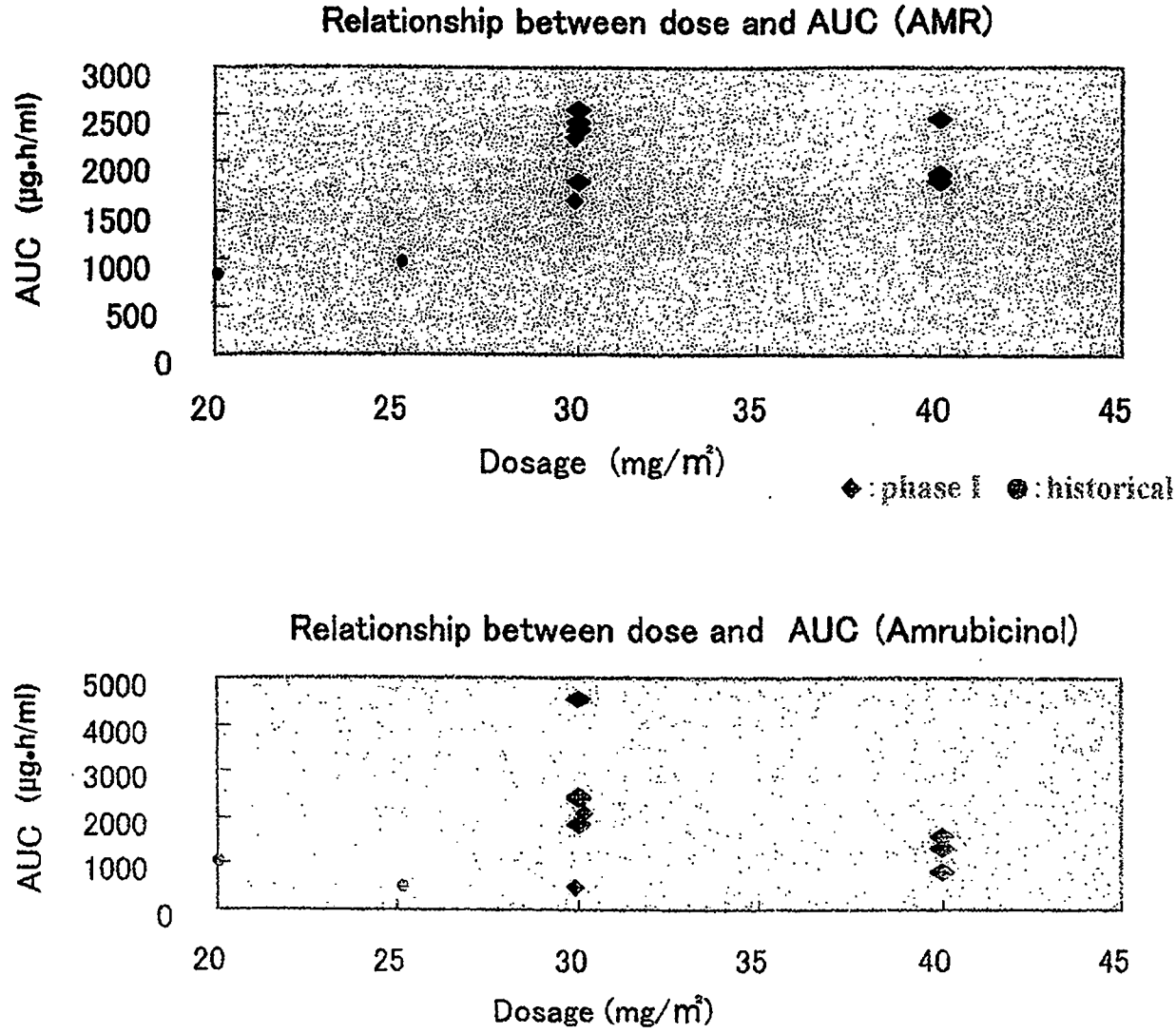

Figure 1. *Relationship between dose (mg/m²) and area under the concentration-time curve (AUC) (μg•h/ml) of (A) amrubicin; (B) amrubicinol.*

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

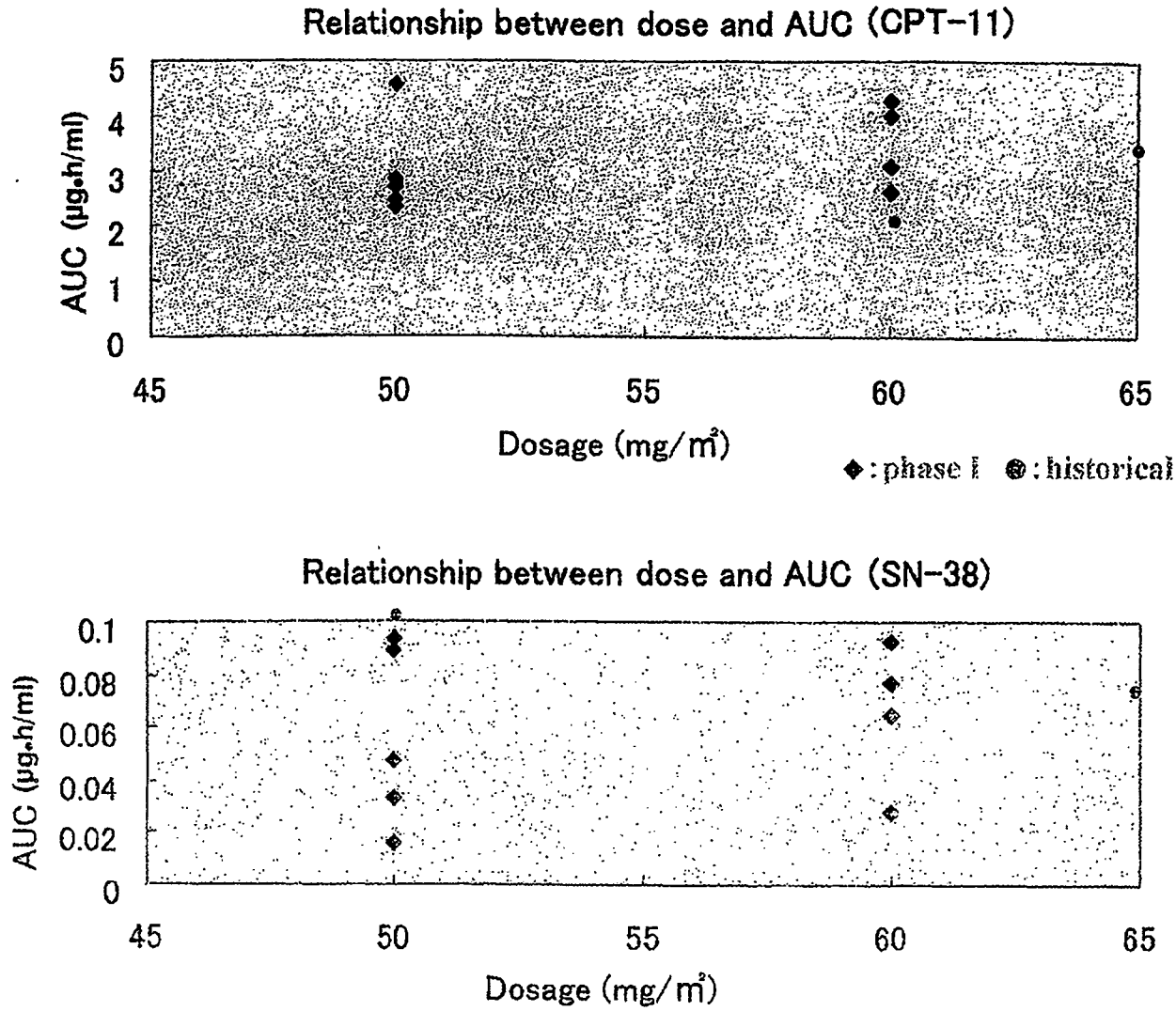

Figure 2. *Relationship between dose (mg/m²) and area under the concentration-time curve (AUC) (μg•h/ml) of (A) irinotecan; (B) SN-38.*

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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Full Paper

A phase I study of pemetrexed (LY231514) supplemented with folate and vitamin B_{12} in Japanese patients with solid tumours

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The purpose of this study was to determine the maximum tolerated dose (MTD) and recommended dose (RD) of pemetrexed with folate and vitamin B12 supplementation (FA/VB_{12}) in Japanese patients with solid tumours and to investigate the safety, efficacy, and pharmacokinetics of pemetrexed. Eligible patients had incurable solid tumours by standard treatments, a performance status 0–2, and adequate organ function. Pemetrexed from 300 to 1200 mg m^{-2} was administered as a 10-min infusion on day 1 of a 21-day cycle with FA/VB_{12}. Totally, 31 patients were treated. Dose-limiting toxicities were alanine aminotransferase (ALT) elevation at 700 mg m^{-2}, and infection and skin rash at 1200 mg m^{-2}. The MTD/RD were determined to be 1200/1000 mg m^{-2}, respectively. The most common grade 3/4 toxicities were neutropenia (grade (G) 3:29, G4:3%), leucopenia (G3:13, G4:3%), lympopenia (G3:13%) and ALT elevation (G3:13%). Pemetrexed pharmacokinetics in Japanese were not overtly different from those in western patients. Partial response was achieved for 5/23 evaluable patients (four with non-small cell lung cancer (NSCLC) and one with thymoma). The MTD/RD of pemetrexed were determined to be 1200/1000 mg m^{-2}, respectively, that is, a higher RD than without FA/VB_{12} (500 mg m^{-2}). Pemetrexed with FA/VB_{12} showed a tolerable toxicity profile and potent antitumour activity against NSCLC in this study.

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Keywords: antifolate; lung cancer; pemetrexed; pharmacokinetics; vitamin supplementation

Pemetrexed (LY231514, Alimta®, Eli Lilly and Company, IN, USA) is a novel antifolate (Taylor and Patel, 1992) that is approved in the United States and a number of European Union countries , for treatment of patients with malignant pleural mesothelioma (MPM) in combination with cisplatin, and non-small cell lung cancer (NSCLC) after prior chemotherapy as a single agent. *In vitro* experiments show that pemetrexed inhibits three enzymes in folate metabolism: thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT) (Shih *et al*, 1998). Given the schedule dependency observed preclinically, three regimens were explored in phase I studies: (1) 0.2–5.2 mg m^{-2} daily for 5 days every 3 weeks (McDonald *et al*, 1998); (2) 10–40 mg m^{-2} weekly for 4 weeks repeated every 6 weeks (Rinaldi *et al*, 1995); and (3) 50–700 mg m^{-2} every 3 weeks (Rinaldi *et al*, 1999).

The third regimen (one dose every 3 weeks) was chosen for subsequent phase II studies because of its convenient administration, ability to give repeated doses, and occurrence of objective responses. The original maximum tolerated dose (MTD) and the recommended dose (RD) was 600 mg m^{-2}, but was decreased to 500 mg m^{-2} owing to toxicities experienced early in phase II studies. The initial phase I and II studies showed that myelosuppression was the principle drug-related toxicity, with a frequency of grade 3/4 neutropenia of 50% and grade 3/4 thrombocytopenia of 15% (Hanauske *et al*, 2001). Less than 10% of patients experienced gastrointestinal toxicities such as diarrhoea or mucositis. Although the prevalence of gastrointestinal toxicities and severe hematologic toxicities was low, these toxicities were associated with a high risk of mortality.

Infrequent severe myelosuppression with gastrointestinal toxicity has been observed not only for pemetrexed, but for the class of antifolates, including the DHFR inhibitor methotrexate (Morgan *et al*, 1990), the TS inhibitor raltitrexed (Maughan *et al*, 1999), and the GARFT inhibitor lometrexol (Alati *et al*, 1996; Mendelsohn *et al*, 1996). Clinical experience and nonclinical studies with methotrexate and lometrexol indicated that severe toxicity may be associated with nutritional folate status (Morgan *et al*, 1990; Alati *et al*, 1996; Mendelsohn *et al*, 1996). In fact, in the study of lometrexol, a significant effect of folate supplementation on toxicity was observed (Laohavinij *et al*, 1996). Based on these experiences, Niyikiza *et al* (2002a) investigated relationships between toxicity and baseline patient characteristics for early pemetrexed studies. They found total plasma homocysteine and methylmalonic acid levels to predict severe neutropenia and

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thrombocytopenia, with or without grade 3/4 diarrhoea, mucositis, or infection. Homocysteine and methylmalonic acid are known as indicators of folate and vitamin B_{12} deficiencies (Rosenberg and Fenton, 1989; Savage *et al*, 1994). Thus, it was hypothesized that a patient's risk for severe toxicity could be reduced by decreasing the levels of homocysteine and methylmalonic acid with folate and vitamin B_{12} supplementation (FA/VB_{12}) (Niyikiza *et al*, 2002a).

FA/VB_{12} is now required for all patients participating in pemetrexed studies. Using this strategy, the pivotal phase III studies for MPM and NSCLC were successfully conducted with amelioration of severe drug-related toxicity (Niyikiza *et al*, 2002b; Vogelzang *et al*, 2003; Hanna *et al*, 2004).

One may expect that pemetrexed administration with supplementation would be more tolerable for patients and permit significant dose escalation above the current RD of 500 mg m^{-2}. Therefore, we conducted a phase I study to determine the MTD of pemetrexed with FA/VB_{12} for Japanese patients with solid tumours and to identify the RD for subsequent Japanese phase II studies. Our secondary objectives were to investigate the safety, antitumour effect, and pharmacokinetics of pemetrexed with supplementation in Japanese patients. A similar phase I study has been conducted outside Japan, but only preliminary data are available at this time (Hammond *et al*, 2003).

PATIENTS AND METHODS

Patient selection

Eligible patients had histologic or cytologic diagnosis of solid cancer that was incurable by standard treatments. Patients also must have been between 20 and 75 years of age, have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and have an estimated life expectancy of at least 3 months. Adequate organ function was required, which included bone marrow reserve (white blood cell count $4.0-12.0 \times 10^3$ mm^{-3}, platelets $\geqslant 100 \times 10^3$ mm^{-3}, haemoglobin $\geqslant 9.0$ g dl^{-1}, and absolute granulocyte count $\geqslant 2.0 \times 10^3$ mm^{-3}), hepatic function (bilirubin $\leqslant 1.5 \times$ upper limit of normal, aspartate/alanine transaminase (AST/ALT) $\leqslant 2.5 \times$ upper limit of normal, and serum albumin $\geqslant 2.5$ g dl^{-1}), renal function (serum creatinine $\leqslant$ upper limit of normal and Cockcroft and Gault creatinine clearance $\geqslant 60$ ml min^{-1}), and lung function (PaO2 $\geqslant 60$ torr).

Prior chemotherapy or hormone therapy was allowed if it was carried out $\geqslant 14$ days before study entry ($\geqslant 35$ days for nitrosourea or mitomycin-C). Previous radiotherapy was also allowed, but only if $\leqslant 25\%$ of marrow was irradiated and if it was completed $\geqslant 21$ days before study entry. Pretreated patients must have recovered from all toxicities before study entry. Prior surgery was allowed if patients recovered from the effect of the operation. Patients were excluded from this study for active infection, symptomatic brain metastasis, interstitial pneumonitis, or pulmonary fibrosis diagnosed by chest X-ray, serious concomitant systemic disorders incompatible with the study, clinically significant effusions, or the inability to discontinue aspirin and other nonsteroidal anti-inflammatory agents during the study.

This study was conducted in compliance with the guidelines of good clinical practice and the Declaration of Helsinki Principles, and it was approved by the local institutional review boards. All patients gave written informed consent before study entry.

Treatment

Pemetrexed was administered as a 10-min infusion on day 1 of a 21-day cycle. Patients remained on study unless they were discontinued because of disease progression, unacceptable adverse events, inadvertent enrollment, use of excluded concomitant therapy, cycle delay >42 days, or patient refusal.

Patients were instructed to take a daily 1 g multivitamin with 500 μg of folate beginning 1 week before day 1 of cycle 1 until study discontinuation. Vitamin B_{12} (1000 μg) was intramuscularly injected, starting 1 week before day 1 of cycle 1 and repeated every 9 weeks until study discontinuation.

Patients enrolled in pemetrexed clinical studies have received dexamethasone prophylactically to avoid pemetrexed-induced rash. As this was the first study of pemetrexed in Japanese patients and the incidence of the drug-induced rash in Japanese patients was unknown, the steroid was not to be administered prophylactically.

Dose escalation

In this study, 10 dose levels of pemetrexed, 300, 500, 600, 700, 800, 900, 1000, 1200, 1450, and 1750 mg m^{-2}, were to be examined with a starting dose of 300 mg m^{-2}. At dose levels from 300 to 1000 mg m^{-2}, three patients were to be treated initially. If no dose-limiting toxicities (DLTs) occurred during cycle 1, escalation proceeded to the next dose level. If 1 DLT occurred, three patients were added. If no additional DLTs were observed, escalation proceeded to the next dose level. At dose levels from 1200 to 1750 mg m^{-2}, six patients were to be treated at once. If two or more patients had DLTs at any dose level, dose escalation stopped, and this dose level was considered the MTD. The RD was then established by discussion with principal investigators, and the Efficacy and Safety Evaluation Committee.

A DLT was defined as the occurrence of one of the following toxicities during cycle 1: any grade 3/4 nonhematologic toxicity (except grade 3 nausea/vomiting and AST, ALT, or alkaline phosphatase elevation $< 10 \times$ upper limit of normal that returns to grade 0–1 by the beginning of cycle 2), grade 3/4 febrile neutropenia (<1000 mm^{-3} with $\geqslant 38.0$°C), grade 4 leucopenia (<1000 mm^{-3}) or neutropenia (<500 mm^{-3}) lasting $\geqslant 4$ days, thrombocytopenia ($<20\,000$ mm^{-3}), or thrombocytopenia ($\geqslant 20\,000$ mm^{-3}) requiring platelet transfusion. A failure to start the second cycle by day 42 owing to toxicity was also considered a DLT. All toxicities were assessed according to National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 2.

Treatment assessments

Tumour response was assessed by the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Evaluable patients were subjected to CT or MRI measurement to determine the size of tumours at anytime at the discretion of investigators.

Pharmacokinetic analysis

Blood and urine were collected from each patient over a period of 72 h following administration in cycle 1. Blood samples were taken just before administration, at the end of infusion, and approximately 5, 15, 30 min and 1, 2, 4, 6, 8, 24, 48 and 72 h after the start of infusion. Urine was collected over the following time intervals: 0–4, 4–8, 8–12, 12–24, 24–36, 36–48, 48–60, and 60–72 h. Plasma and urine samples were analysed for pemetrexed at Taylor Technology Inc., Princeton, NJ, USA. Plasma samples were analysed using a validated liquid chromatography/electrospray ionisation-tandem mass spectrometry method that generated a linear response over the concentration ranges of 10–2000 ng/ml and 1000–200 000 ng/ml (Latz *et al*, 2006). Urine samples were analysed using a similar analytical technique (Chaudhary *et al*, 1999).

Pharmacokinetics were evaluated using noncompartmental methods (WinNonlin Professional Version 3.1; Pharsight Corporation, Cary NC, USA). Pharmacokinetic parameters determined

based on plasma concentration *vs* time data were maximum plasma concentration (C_{max}), elimination half-life ($t_{1/2}$), area under the plasma concentration *vs* time curve (AUC) from time 0 to infinity ($AUC_{0-\infty}$), volume of distribution at steady-state (V_{ss}) and plasma clearance (CL_p) (Rowland and Tozer, 1995). The fraction of drug excreted unchanged in urine (f_e) was calculated by dividing the cumulative amount of pemetrexed excreted unchanged in urine within 72 h (Ae_{0-72}) by the administered dose (Rowland and Tozer, 1995).

RESULTS

Patient disposition and characteristics

From October 2001 to September 2004, a total of 35 Japanese patients were enrolled and 31 were treated at four centres in Japan. Four patients were not treated owing to protocol criteria not met ($n = 3$) and investigator decision ($n = 1$). The majority of patients were male (65%), had an ECOG performance status of 1 (84%), were diagnosed with NSCLC (61%), and received prior chemotherapy (94%) (Table 1).

Table 1 Baseline patient characteristics

Parameter	N = 31
Sex, n (%)	
Male	20 (65)
Female	11 (35)
Age, years	
Median (range)	59 (31–74)
Mean (s.d.)	57 (11)
ECOG performance status, n (%)	
0	4 (13)
1	26 (84)
2	1 (3)
Diagnosis, n (%)	
Non-small cell lung cancer	19 (61)
Malignant pleural mesothelioma	7 (23)
Thymoma	2 (7)
Alveolar soft part sarcoma	1 (3)
Rectal cancer	1 (3)
Unknown primary cancer	1 (3)
Prior therapy, n (%)	
Surgery	14 (45)
Radiation	9 (29)
Chemotherapy	29 (94)

ECOG = Eastern Cooperative Oncology Group; s.d. = standard deviation.

Table 2 Dose escalation and DLTs

Dose ($mg\,m^{-2}$)	Number of patients	DLTs (*n*)
300	3	None
500	3	None
600	3	None
700	6	G3 ALT elevation (1)
800	3	None
900	1[a]	None
1000	3	None
1200	6	G3 infection (1); G3 rash (1)

ALT = alanine transaminase; DLT = dose-limiting toxicity; G3 = grade 3. [a]One patient was excluded for DLT analysis because of grade 3 hyperglycemia at the beginning of the study.

Dose escalation and dose-limiting toxicities

Three or six patients were enrolled at each dose level from 300 to 1200 $mg\,m^{-2}$, except the 900 $mg\,m^{-2}$ dose level (Table 2). At this dose level, one additional patient was enrolled because a patient was excluded from the DLT analysis. Before the dose initiation, this patient had grade 3 fasting hyperglycemia that was aggravated after the start of dosing. Therefore, this patient was rated as inappropriate for evaluation.

The first DLT was observed at the 700 $mg\,m^{-2}$ dose level. This 66-year-old woman with NSCLC experienced grade 3 ALT elevation. After an additional three patients were enrolled, no other DLTs were observed.

The next DLTs were observed at the 1200 $mg\,m^{-2}$ dose level, which enrolled six patients at once. One patient, a 72-year-old woman with MPM, had grade 3 infection at day 6 of cycle 1. Neutropenia was not simultaneously observed in this cycle. After 12 days, the event was resolved with antibiotics. This patient continued in study with dose reduction to 1000 $mg\,m^{-2}$. The other patient, a 68-year-old man with NSCLC, had grade 2 rash at day 5 of cycle 1. The severity of the event reached grade 3 at day 7. After 9 days from the occurrence, rash was resolved with dexamethasone and H_1-antihistamine. This patient continued in study without dose reduction. As two DLTs were observed, the 1200 $mg\,m^{-2}$ dose level was considered as the MTD. The RD for subsequent phase II studies was then evaluated to be pemetrexed 1000 $mg\,m^{-2}$. Both events were considered as drug-related events by investigators.

Safety

The safety evaluation was completed from data obtained from cycle 1–6 for all dose levels except 1200 $mg\,m^{-2}$ (cycle 1–3). These data were collected and analysed to evaluate safety when the MTD and RD were determined. The major toxicities observed in >50% of patients during all cycles evaluated for this report included rash, nausea, anorexia, fatigue, ALT elevation, AST elevation, lactate dehydrogenase elevation, leucopenia, neutropenia, lymphopenia, hematocrit decreased, haemoglobin decreased and erythropenia (Table 3). The most commonly reported grade 3/4 toxicity was neutropenia: nine patients (29%) had grade 3 neutropenia, and one patient (3%) had grade 4 neutropenia. Other grade 3/4 hematologic toxicities were grade 3 leucopenia in four patients (13%), grade 4 leucopenia in one patient (3%), grade 3 lymphopenia in four patients (13%), and grade 3 haemoglobin decreased in two patients (6%). The most commonly reported grade 3 nonhematologic toxicity was ALT elevation (four patients (13%)). Other grade 3 toxicities included AST elevation in one patient (3%), anorexia in one patient (3%), infection in one patient (3%), malaise in one patient (3%), and rash in one patient (3%) were observed. No grade 4 nonhematologic toxicities were reported.

The only serious adverse event was observed at the 900 $mg\,m^{-2}$ level. This 71-year-old man with NSCLC experienced grade 1 pyrexia at day 18 of cycle 3 and was hospitalized; however, the event was resolved the next day. The investigator did not consider it as a drug-related event. One patient at 900 $mg\,m^{-2}$ level discontinued treatment owing to adverse events (neutropenia, anorexia, and pyrexia). No deaths were observed during the study period or for 31 days after the last dose.

At the 900 $mg\,m^{-2}$ and higher dose levels, all patients had either grade 1/2 or grade 3/4 rash. At cycle 1, 25 patients experienced rash. Of these, 20 patients received corticosteroid. At or after cycle 2, corticosteroid treatment was given only for nine rash events, whereas rash events were observed in 20 cycles in cumulative total among patients. In addition, the severity of rash quickly improved or disappeared after administration of corticosteroid. Although the protocol allowed corticosteroid use for prevention of rash from cycle 2, only seven patients actually received the preventive treatment. Among those who did not receive the prophylactic

Table 3 Incidence of clinically relevant toxicities

	Dose (mg m^{-2}) (*n*)															
	Grade															
	300 (3)		500 (3)		600 (3)		700 (6)		800 (3)		900 (4)		1000 (3)		1200 (6)	
Toxicity	1/2	3/4	1/2	3/4	1/2	3/4	1/2	3/4	1/2	3/4	1/2	3/4	1/2	3/4	1/2	3/4
Hematologic																
Erythropenia	1	0	1	0	3	0	4	0	2	0	2	0	2	0	5	0
Hematocrit decreased	1	0	1	0	3	0	4	0	3	0	2	0	2	0	5	0
Haemoglobin decreased	2	0	2	0	2	0	3	0	2	0	1	1	2	0	4	1
Leucopenia	1	0	3	0	2	1	3	1	1	1	1	1	1	0	5	1
Lymphopenia	0	0	2	1	0	1	3	0	1	0	1	1	3	0	4	1
Neutropenia	1	0	1	2	1	2	3	2	0	2	1	1	2	0	2	1
Thrombocytopenia	0	0	2	0	1	0	2	0	2	0	2	0	1	0	2	0
Nonhematologic																
ALT elevation	0	0	2	0	2	0	2	3	3	0	1	1	1	0	5	0
AST elevation	0	0	3	0	2	0	4	1	3	0	3	0	2	0	5	0
Blood bilirubin increased	0	0	1	0	0	0	2	0	0	0	0	0	0	0	1	0
LDH elevation	0	0	3	0	3	0	5	0	3	0	2	0	1	0	4	0
Alopecia	0	0	0	0	2	0	2	0	1	0	2	0	0	0	0	0
Anorexia	0	0	1	0	3	0	5	0	3	0	0	1	3	0	4	0
Constipation	1	0	1	0	0	0	1	0	0	0	0	0	2	0	1	0
Diarrhoea	0	0	2	0	1	0	1	0	1	0	1	0	1	0	2	0
Fatigue	1	0	2	0	2	0	2	0	3	0	1	0	2	0	3	0
Infection	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	1
Nausea	2	0	3	0	3	0	5	0	3	0	2	0	2	0	5	0
Malaise	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0
Pruritus	0	0	0	0	2	0	2	0	1	0	0	0	1	0	2	0
Rash	3	0	2	0	3	0	5	0	2	0	1	0	3	0	5	1
Vomiting	2	0	3	0	2	0	3	0	1	0	1	0	1	0	0	0

ALT = alanine transaminase; AST = aspartate transaminase; LDH = lactate dehydrogenase.

corticosteroid, the incidence of a rash observed at, or after, cycle 2 was about one-third of the incidence observed in cycle 1.

Pharmacokinetic analysis

Mean dose-normalised pemetrexed plasma concentration *vs* time profiles following single doses of 300–1200 mg m^{-2} pemetrexed are provided in Figure 1. This body surface area (BSA)-normalized dose range represents absolute doses of 414–2018 mg in Japanese patients with a mean BSA of 1.64 m^2 (range, 1.36–1.97 m^2).

Pharmacokinetic parameters for each dose group are summarised in Table 4. Lack of a monotonic trend in CL_p and V_{ss} between cohorts indicated that pemetrexed pharmacokinetics are consistent across dose groups. Consistency of pemetrexed pharmacokinetics across dose groups is also illustrated by the lack of systematic pattern across dose groups in the dose-normalised plasma concentration *vs* time profiles (Figure 1). The overall mean $t_{1/2}$ is approximately 2.74 h and was essentially similar across all dose groups (range, 2.28–3.62 h).

In this study, pemetrexed was primarily excreted unchanged in urine, which is consistent with its known elimination pathway (i.e., renal excretion). The F_e averaged 0.752 (range, 0.645–0.827). Mean F_e values were consistent across dosing cohorts.

Tumour response

In this study, 23 of the 31 patients were evaluable for response by RECIST criteria (Table 5). Partial responses (PRs) were observed in four patients with NSCLC (one patient each at 500, 700, 800, and 1200 mg m^{-2}) and one patient with thymoma at 500 mg m^{-2}. In addition, one patient with NSCLC at 500 mg m^{-2} had a PR by the World Health Organization criteria, but was not evaluable via RECIST.

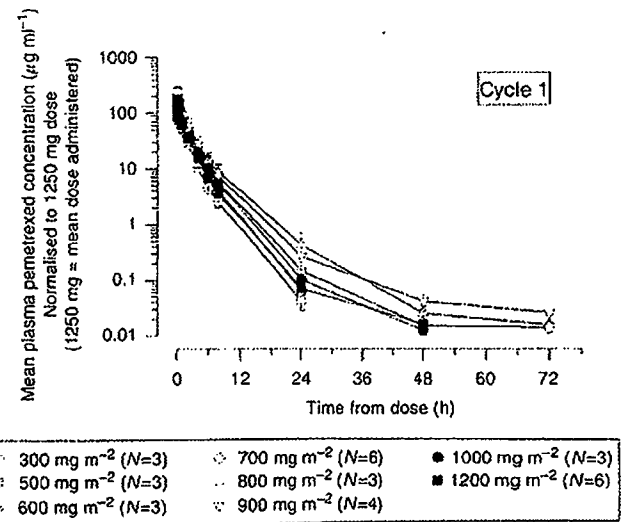

Figure 1 Mean dose-normalised pemetrexed plasma concentration–time profiles following single-dose administration in Japanese patients.

DISCUSSION

This is the first phase I study of pemetrexed in Japanese patients. The MTD for pemetrexed administered with FA/VB$_{12}$ was 1200 mg m^{-2} and determined the RD for subsequent phase II studies was 1000 mg m^{-2}.

In contrast with the previously determined MTD (600 mg m^{-2}) without vitamin supplementation (Rinaldi *et al*, 1999), our MTD

Table 4 Summary of pemetrexed pharmacokinetic parameters by dosing cohort arithmetic mean (CV%)

	Dose (mg m^{-2}) (*n*)							
Parameter	**300 (3)**	**500 (3)**	**600 (3)**	**700 (6)**	**800 (3)**	**900 (4)**	**1000 (3)**	**1200 (6)**
Dose (mg)	459 (12.4%)	783 (7.56%)	919 (8.28%)	1180 (8.06%)	1280 (16.5%)	1550 (5.47%)	1820 (7.04%)	1910 (6.71%)
C_{max} (μg ml^{-1})	58.2 (7.15%)	115 (19.1%)	178 (15.7%)	172 (9.30%)	240 (14.5%)	217 (7.05%)	269 (17.8%)	212 (13.2%)
$AUC_{0-\infty}$ (μg h ml^{-1})	70.1 (7.04%)	158 (21.6%)	290 (12.5%)	250 (23.5%)	361 (17.0%)	388 (19.6%)	382 (6.55%)	337 (24.6%)
CL_p (ml min^{-1})	109 (5.89%)	86.5 (32.5%)	53.0 (3.95%)	83.4 (27.7%)	61.4 (35.2%)	68.5 (20.0%)	79.3 (2.57%)	99.7 (24.7%)
V_{ss} (l)	13.5 (22.2%)	12.1 (20.1%)	11.5 (25.5%)	11.7 (20.0%)	10.6 (33.6%)	13.9 (31.7%)	14.4 (7.40%)	14.8 (9.41%)
$t_{1/2}$ (h)	2.28 (25.2%)	2.62 (3.29%)	3.62 (28.7%)	2.51 (3.91%)	2.93 (14.6%)	3.02 (17.8%)	2.67 (1.90%)	2.55 (10.9%)
F_e	0.659 (8.78%)	0.645 (8.34%)	0.788 (3.76%)	0.807 (10.1%)	0.705 (34.9%)	0.797[a] (5.11%)	0.648[a] (12.5%)	0.827[a] (7.58%)

CV% = coefficient of variation expressed as a percentage; C_{max} = maximum observed drug concentration; $AUC_{0-\infty}$ = area under the concentration versus time curve from zero to infinity; CL = total body clearance of drug after intravenous administration; V_{ss} = volume of distribution at steady state; $t_{1/2}$ = half-life associated with the terminal rate constant; F_e = fraction of dose eliminated unchanged in urine. [a]The numbers of patients in 900, 1000, and 1200 mg m^{-2} were three, two, and five, respectively, owing to incompletion of urine collections for patients 209, 210, and 306.

Table 5 Antitumour activity by dose (RECIST)

		Evaluable (*n* = 23)				
Dose (mg m^{-2})	**Number of patients**	**CR**	**PR[a]**	**s.d.**	**PD**	**NE**
300	3	0	0	2	0	1
500	3	0	2	0	0	0
600	3	0	0	1	0	0
700	6	0	1	3	1	0
800	3	0	1	0	1	1
900	4	0	0	2	0	1
1000	3	0	0	1	1	0
1200	6	0	1	2	1	0
Total	31	0	5	11	4	3

NSCLC = non-small cell lung cancer; CR = complete response; NE = not evaluated; PD = progressive disease; PR = partial response; s.d. = stable disease. [a]In addition, one NSCLC patient at 500 mg m^{-2} had PR via WHO criteria.

increased by a factor of 2 whereas maintaining a tolerable safety profile. Niyikiza *et al* (2002a, b) conducted a multivariate analysis on 246 patients in phase II pemetrexed studies without vitamin supplementation, and the incidence of grade 4 neutropenia was 32% and grade 4 thrombocytopenia was 8% . Also 6% of patients had grade 3/4 diarrhoea, 5% had grade 3/4 mucositis, and a 5% incidence of drug-related death occurred. In contrast, our study had grade 4 neutropenia of only 3% (one patient) and no grade 4 thrombocytopenia. In addition, no grade 3/4 diarrhoea or mucositis, and no drug-related deaths were observed.

In the pivotal phase III study of NSCLC patients, those who received pemetrexed (500 mg m^{-2}) plus vitamin supplementation had a lower incidence of severe toxicities compared to those who received docetaxel (75 mg m^{-2}), including grade 3/4 neutropenia (5.3 *vs* 40.2%) and grade 3/4 diarrhoea (0.4 *vs* 2.5%) (Hanna *et al*, 2004).

Dose-dependency for toxicity of pemetrexed plus supplementation was further investigated to understand the effect of supplementation on safety. The patients in this study were divided into three groups by doses: low dose (300–600 mg m^{-2} ($n = 9$)), middle dose (700–900 mg m^{-2} ($n = 13$)), and high dose (1000 and 1200 mg m^{-2} ($n = 9$)). Grade 1/2 toxicity such as erythropenia, lymphopenia, hematocrit decreased, ALT and AST elevation, and anorexia increased dose dependently from approximately 20–50% to approximately 75%. However, there was no obvious correlation between grade 3/4 toxicity and dose group. Therefore, high dose levels of pemetrexed with FA/VB_{12} is expected to be tolerable enough for patients.

In this study, severe rash was rarely observed even without the prophylactic corticosteroid. Although this result suggests that the steroid premedication for prevention of severe rash is no longer necessary for patients with pemetrexed treatment if the FA/VB_{12} is concomitantly conducted, it would be too early to conclude it as the data of patients untreated with the premedication are limited at this moment.

The pharmacokinetic results in our study were consistent with a phase I study of pemetrexed without vitamin supplementation in western patients by Rinaldi *et al* (1999) In that study, pemetrexed $t_{1/2}$ was 3.1 h; and CL was 85 ml/min (Rinaldi *et al*, 1999 and unpublished results). In our study, the $t_{1/2}$ of pemetrexed was about 2.7 h; and CL was 81.9 ml/min. Additionally, the F_e of pemetrexed was similar for Japanese patients (75% in our study) and western patients (78% in the Rinaldi study (Rinaldi *et al*, 1999)). These results indicate that pharmacokinetics of pemetrexed in Japanese patients are similar to those in western patients.

Although our study is the first phase I study to evaluate pemetrexed with FA/VB_{12} in Japanese patients, a similar phase I study has been conducted in western patients. In the preliminary results of that study, heavily pretreated patients had a MTD of 925 mg m^{-2}, and lightly pretreated patients had a MTD of 1050 mg m^{-2} (Hammond *et al*, 2003). The comparison of these two studies suggests that the improved tolerability experienced by Japanese patients when pemetrexed is administered with FA/VB_{12} is not attributable to ethnic differences; rather, it is attributable to the vitamin supplementation.

In our phase I study, four NSCLC patients and one thymoma patient had PRs. Except for one, all of the patients with PR had $\geqslant 3$ prior chemotherapy regimens. The NSCLC patients with PRs received doses of pemetrexed higher than 500 mg m^{-2}, which is the approved dose for NSCLC treatment in a number of countries. Therefore, subsequent phase II studies using our RD of 1000 mg m^{-2} with vitamin supplementation could show more prominent antitumour activity for cancer patients. To examine this hypothesis, a Japanese phase II study is being conducted, examining pemetrexed 500 or 1000 mg m^{-2} every 3 weeks with full supplementation for patients with locally advanced or metastatic NSCLC. Clinical trials for other tumours, including MPM, are also ongoing. For the prophylactic corticosteroid, as severe rash was not frequently observed in this study, the steroid is not to be administered prophylactically in both currently on-going studies.

In conclusion, pemetrexed with FA/VB_{12} resulted in a tolerable toxicity profile. The MTD was 1200 mg m^{-2}. The RD was 1000 mg m^{-2}.

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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_{last}/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_{last}). 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

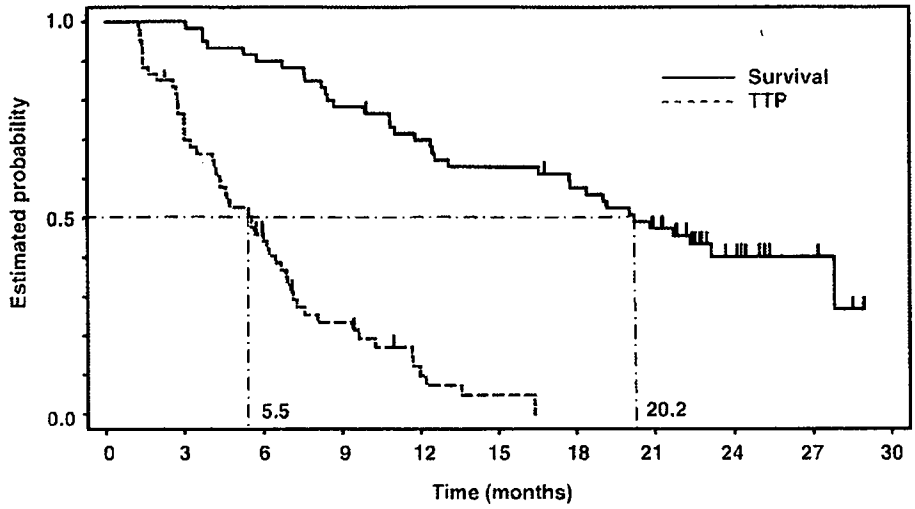

Figure 1. Time to disease progression (TTP) and overall survival.

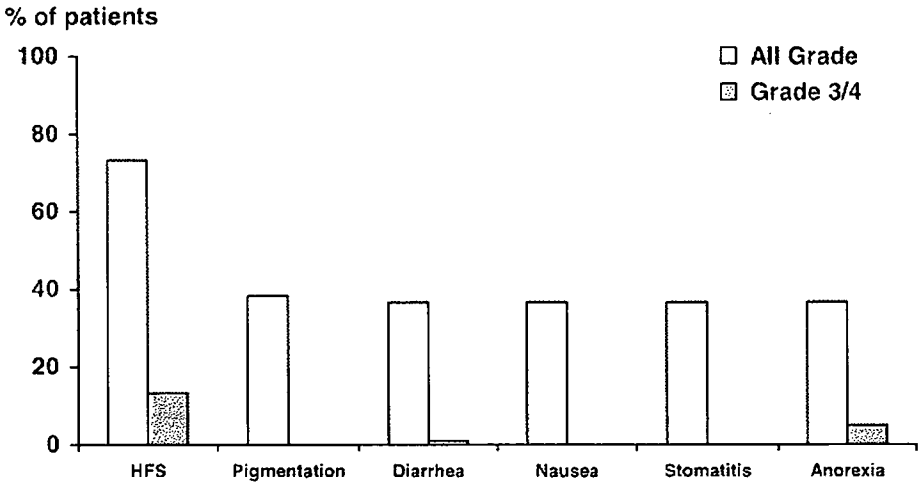

Figure 2. Common adverse drug reactions (≥20% of patients). HFS: hand-foot syndrome.

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

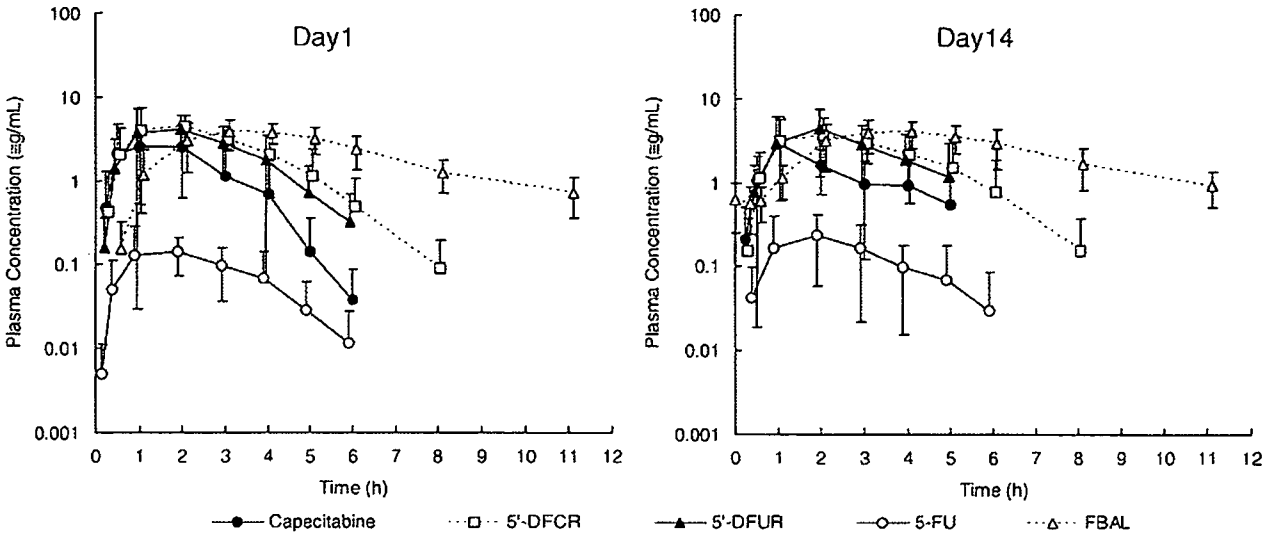

Figure 3. Plasma concentrations (mean ± standard deviation) for capecitabine and its metabolites 5′-deoxy-5-fluorocytidine (5′-DFCR), 5′-deoxy-5-fluorouridine (5′-DFUR) and α-fluoro-β-alanine (FBAL).

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.

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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.