Toxicities

The toxicities observed during this study are provided in Table 2. Hematological toxicities were the most common, but grade 3–4 toxicities, including neutropenia (37.5%), thrombocytopenia (5.0%), and anemia (2.5%) were relatively modest. There were only two cases of febrile neutropenia (5.0%). Grade 1 nausea, fatigue, alopecia, neuropathy, and angialgia occurred with a greater frequency than the non-hematologic toxicities. Grade 3–4 non-hematologic toxicities were not seen except in cases of pulmonary toxicity. Two patients (5.0%) developed interstitial pneumonitis (grade 3; one patient, grade 4; one patient), and were responsive to steroid therapy.

Efficacy of treatment

The median number of cycles administered per patient was 4, and the number of cycles ranged from 1 to 8. Twenty-two patients exhibited a partial response. The overall response rate was 55% (22/40) [95% confidence interval (CI): 38.2–71.8%]. Stable disease was achieved in 14 patients (35%), and 4 patients (10%) had progressive disease. All 40 patients were included in the survival analysis. The overall median survival time was 11.9 months (95% CI: 10.3–14 months). The 1-year survival rate was 47.5% (19/40). The median time to disease progression was 6.4 months. Thirty patients (75%) received chemotherapy, and 4 patients (10%) received thoracic irradiation as second-line treatment.

Discussion

Although a standard regimen of first-line chemotherapy for advanced NSCLC is being established, it is important to develop a more active and well-tolerated regimen. Several published randomized studies reported that non-platinum-based chemotherapy in advanced NSCLC was as effective and less toxic than platinum-based regimens [13, 15, 18, 29]. Georgoulias et al. [13] compared the combination of a cisplatin and docetaxel regimen with the GEM and docetaxel regimen. Objective response rates were similar in the two groups, with 32.4% in the former and 30.2% in the latter. The two groups did not differ in the overall survival or 1- or 2-year survival rates. They concluded that both drug combinations had comparable activity and the non-platinum-based regimen had the more favorable profile.

Generally, non-cisplatin-containing treatment does not require supplemental hydration as does standard cisplatin-based chemotherapy. This may be advantageous for elderly patients, patients with poor PS, and patients with renal or cardiac impairment. Recchia et al. [22] conducted a trial of PTX plus GEM in advanced NSCLC patients with a low PS. The chemotherapy regimen consisted of 200 mg/m^2 PTX on day 1 plus 1,000 mg/m^2 GEM on days 1 and 8, repeated every 3 weeks, for a maximum of eight cycles. They achieved a reasonable response rate of 41.3%. Median overall survival time was 13.6 months; the authors concluded that a satisfactory clinical benefit could be obtained with GEM plus PTX regimen in NSCLC patients with a poor PS.

Thus, non-platinum-based chemotherapy may be used as alternative to platinum-based regimens. We conducted a phase II trial was designed to examine the efficacy and tolerance of the non-platinum-based combination of weekly PTX and GEM for patients with untreated advanced NSCLC. Results including an overall response rate of 55%, a median survival time of 11.9 months, and a 1-year survival probability rate of 47.5% suggested that this regimen might have anti-tumor activity equal to that of platinum-based regimens.

Weekly chemotherapy for lung cancer has recently been carried out at several facilities, and favorable results were reported [9, 16, 26, 30]. Compared to standard chemotherapy with administration of drugs at intervals of 3–4 weeks, weekly chemotherapy appears acceptable for the reduction of a single dose level of anti-cancer drugs with fewer side effects. In addition, weekly dose level is more easily adjusted according to the general clinical condition of individual patients or if hematologic toxicity develops. Belani et al. [6] conducted a randomized phase II trial of a 3-week schedule of GEM plus PTX (ArmA) versus a weekly schedule of GEM plus PTX (ArmB) in the treatment of NSCLC. It was concluded that a weekly schedule resulted in improved survival and lower hematologic toxicity than the 3-week schedule.

The clinical outcomes of weekly PTX and GEM therapy found in the literature [3, 6, 7, 11, 12, 14, 19, 28] and in our results are summarized in Table 3. The response rate ranges were from 23.1 to 55%; overall median survival time was 4.9–11.9 months; and 1-year survival rates were 26–53%. Most adverse reactions were hematologic (such as leukope-

Table 2 Maximum toxicity over 40 patients

	CTCAE v 3.0 grade (no. of patients)		Grade 3 or 4 (%)
	Grade 3	Grade 4	
Leukopenia	11	1	12 (30)
Neutropenia	11	4	15 (37.5)
Febrile neutropenia	2	0	2 (5.0)
Anemia	1	0	1 (2.5)
Thrombocytopenia	2	0	2 (5.0)
Pneumonitis	1	1	2 (5.0)

CTCAE v 3.0: Common Terminology Criteria for Adverse Events version 3.0

Table 3 PG regimens used as first-line treatment of advanced NSCLC

First author (ref.)	No. of patients		Regimen and schedule	Response rate (%)	Survival median	One-year (%)
Belani et al. [6]	50	Arm A	P 200 mg/m^2 day 1 q3w G 1 g/m^2 days 1, 8 q3w	28.2	7.5	34
	50	Arm B	P 100 mg/m^2 days 1, 8 q 3w G 1 g/m^2 days 1, 8 q3w	26.8	9.6	42
Bhatia et al. [7]	39		P 110 mg/m^2 days 1, 8, 15 q 4w G 1 g/m^2 days 1, 8, 15 q4w	38.2	4.9	26
De Pas et al. [12]	54		P 100 mg/m^2 days 1, 8, 15, 22 q 4w G 1 g/m^2 days 1, 8, 15, 22 q4w	46	9.6	53
Akerley et al. [3]	39		P 85 mg/m^2 days 1, 8, 15, 22, 29, 36 q 8w G 1 g/m^2 days 1, 8, 15, 22, 29, 36 q8w	23.1	7.5	32
Gillenwater et al. [14]	39		P 100 mg/m^2 days 1, 8, 15, 21 q 4w G 1 g/m^2 days 1, 8, 15, 21 q4w	35	4.9	35
Kosmidis et al. [19]	225		P 200 mg/m^2 day 1 q 3w G 1 g/m^2 days 1, 8, q3w	31	9.3	42
Treat et al. [28]	312		P 200 mg/m^2 day 1 q 3w G 1 g/m^2 days 1, 8, q3w	43.6	8.4	33
Our study	40		P 100 mg/m^2 days 1, 8, q 3w G 1 g/m^2 days 1, 8 q3w	55	11.9	47.5

NSCLC non-small-cell lung cancer, *P* paclitaxel, *G* demcitabine

nia and neutropenia of grade 3 or greater occurrence) in 28–53%. Variable toxicities may be due to population-related pharmacogenomics [11]. Overall, the non-hematologic toxicity was mild, and there were few adverse reactions of grade 3 or greater. A few patients had pneumonitis which was not responsive to steroid therapy. The treatment in our current study was reasonably tolerated, especially in the area of non-hematologic toxicity. Nausea, vomiting, and fatigue, which are often seen in cisplatin-containing regimens, were relatively mild; no patients developed renal toxicity.

In conclusion, weekly chemotherapy with PTX and GEM is a well-tolerated and effective regimen for previously untreated patients with advanced NSCLC. Further studies are expected for the application of this regimen to the elderly, and patients with a poor PS or suspected vulnerability to platinum compound toxicity.

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Conflict of interest statement None.

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A Phase II Study of Cisplatin and Irinotecan as Induction Chemotherapy Followed by Accelerated Hyperfractionated Thoracic Radiotherapy with Daily Low-dose Carboplatin in Unresectable Stage III Non-small Cell Lung Cancer: JCOG 9510

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Objective: It is important to find optimal regimens of cisplatin (CDDP)-based third-generation chemotherapy and radiotherapy for patients with unresectable Stage III non-small cell lung cancer (NSCLC).
Methods: This Phase II study was designed to determine the toxicity and efficacy of two courses of chemotherapy (CDDP 80 mg/m^2 on day 1 and irinotecan 60 mg/m^2 on days 1 and 8) followed by accelerated hyperfractionated thoracic radiotherapy (60 Gy/40 fractions in 4 weeks) combined with daily carboplatin (CBDCA) administration. CBDCA was administered at a target area under the plasma level–time curve of 0.4 × (24 h creatinine clearance + 25), according to Calvert's formula.
Results: Twenty-six patients were enrolled in the study. The patients' median age was 63 years (range 40–74 years) and included 22 males and 4 females. Seven patients were Stage IIIA and 19 were Stage IIIB. Twenty had a performance status (PS) of 1 versus six with a PS of 0. There was one treatment-related death due to sepsis and pneumonia associated with Grade 4 neutropenia and diarrhea during chemotherapy. Grade 3 or 4 neutropenia and diarrhea were observed in 14 and 5 patients, respectively. Toxicity of the radiotherapy was mild. There were 0 complete response and 13 partial responses, giving a response rate of 50.0%. Median survival time and 2-year survival were 16.4 months and 21.5%, respectively. This study was designed with Simon's two-stage design, and the response rate did not meet the criteria to proceed to the second stage and the study was terminated early.
Conclusions: This regimen might be inactive for patients with unresectable Stage III NSCLC.

Key words: cisplatin – irinotecan – carboplatin – chemoradiotherapy – non-small cell lung cancer

INTRODUCTION

Over the past 2 decades, a great number of clinical trials have gradually proven the benefits of a chemotherapeutic approach for treatment of unresectable non-small cell lung cancer (NSCLC) (1,2). In unresectable Stage III NSCLC, in which the tumor is apparently confined to the chest but is surgically unresectable, several randomized trials have shown that combinations of chemotherapy and thoracic radiotherapy have improved survival compared with radiotherapy alone (3–6). It is important to find optimal regimens of combined chemotherapy and radiotherapy and to evaluate the feasibility and efficacy of those combinations.

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Irinotecan (CPT-11) is an antitumor agent which inhibits the nuclear enzyme topoisomerase I (7,8). CPT-11 has played a significant role in the development of chemotherapy for NSCLC since the initial reports of its efficacy as a single agent (9,10). Combination chemotherapy of CPT-11 and cisplatin (CDDP), which is also a commonly used agent for NSCLC, is a promising regimen for NSCLC, as its high antitumor activity and manageable toxicity have been reproducibly reported (11,12). One critical but uncommon toxicity of CPT-11 is reported to be pulmonary toxicity (10), and it is necessary to clarify how the chemotherapy regimen should be combined with thoracic radiotherapy in patients with Stage III NSCLC.

In addition to combined radio-chemotherapy, concomitant treatment with low doses of radiosensitizers has also been investigated in patients with Stage III NSCLC. Schaake-Koning et al. (13) reported that daily low-dose CDDP combined with thoracic radiation improved the local control of tumors in a randomized study. Furthermore, its favorable results were also confirmed in another Phase II study (14). Carboplatin (CBDCA) has also been investigated as a radiosensitizer (15). It has been suggested that CBDCA may be superior to CDDP in this role because it would provide a greater platinum concentration within cells at the time of irradiation (16). We have reported the concurrent daily CBDCA (25 mg/m^2) and accelerated hyperfractionated thoracic radiotherapy (AHRT) in locally advanced NSCLC (17). Of the 31 patients, the response rate was 84% (26/31) and the median survival time (MST) was 9.8 months. Major acute toxicity (Grade $\geq$3) included 55% with leukopenia, 16% with thrombocytopenia and 23% with esophagitis. Area under the plasma level–time curve (AUC) of CBDCA was significantly correlated with efficacy and leukopenia. In this setting, we concluded that daily CBDCA AUC of 0.4 plus concurrent AHRT was the most effective and safe treatment in locally advanced NSCLC.

On the other hand, the CDDP plus CPT-11 regimen is one of the standard platinum-based combination chemotherapies including a new agent in Stage IIIB/IV NSCLC in Japan (11). Therefore, in order to improve therapeutic outcome in patients with unresectable Stage III NSCLC, we have conducted a Phase II study of a regimen of two courses of CDDP plus CPT-11 as an induction chemotherapy, followed by AHRT with daily low-dose CBDCA administration.

PATIENTS AND METHODS

Patient Selection

Patients with histologically or cytologically confirmed unresectable Stage III NSCLC who had not received cancer therapy were enrolled in this study. Staging for entry criteria was performed according to the lung cancer staging system of the International Union against Cancer. Staging procedures included chest X-ray, computed tomography (CT) scan of the chest, CT scan or magnetic resonance imaging of the brain, CT scan or ultrasound of the abdomen and isotope bone scanning. N-status was mainly based on size criteria in chest CT scan. Patients with pleural or pericardial effusion were excluded from the study. Each patient was required to meet the following criteria: Eastern Cooperative Oncology Group performance status (PS) of 0 or 1; $<$75 years of age; predicted area of radiation field is less than half of one lung; adequate hematological, pulmonary, renal and hepatic function, i.e. white blood cell (WBC) count $\geq$4000/μL, hemoglobin level $\geq$10 g/dl, platelet count $\geq$130 000/μL, PaO_2 $\geq$70 torr, blood urea nitrogen and serum creatinine level no higher than the upper limit of normal, creatinine clearance (Ccr) $\geq$60 ml/min, serum total bilirubin level $\leq$1.5 mg/dl and serum glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) levels less than twice the upper limit of normal.

Patients with uncontrolled heart failure or infection, chronic pulmonary disease which restricts thoracic radiation, prolonged diarrhea, ileus, gastrointestinal bleeding or history of myocardial infarction in the last 3 months were excluded from the study. Female patients in pregnancy or lactation during chemotherapy were also excluded. All patients were required to give their own written informed consent.

Treatment Schedule

After enrollment in the study, the patients received chemotherapy consisting of intravenous infusion of 80 mg/m^2 of CDDP on day 1 and 60 mg/m^2 of CPT-11 on days 1 and 8. The chemotherapy was repeated 3–4 weeks after the start of the first course, as long as the patients had sufficiently recovered from toxicity. The chemotherapy was to be performed for two courses, unless unacceptable toxicity or disease progression occurred.

Four weeks after the start of the second course of chemotherapy, thoracic radiotherapy was started. The initial opposing anterior–posterior treatment fields encompassed the primary tumor, the bilateral mediastinal lymph nodes and the ipsilateral hilar nodes. The supraclavicular nodes were included within the field when there was clinical evidence of their involvement. A 1.5 cm tumor-free margin was required. The fraction size delivered was 1.5 Gy, given twice per day, 5 days per week. Thus, the total radiation dose was 60 Gy in 40 fractions over 4 weeks. The methods for spinal block and boost after the first 30 Gy delivery was left to the discretion of the treating radiation oncologist. On each day of thoracic radiotherapy, the patients also received intravenous CBDCA. CBDCA was dosed to a target AUC of 0.4 $\times$ (24 h Ccr + 25), according to Calvert's formula (18), and was administered intravenously over 15 min immediately before the first radiation of the day. The CBDCA AUC of 0.4 was determined based on our previous study (17).

CPT-11 on day 8 was skipped if the WBC count was $<$3000/μL, platelet count $<$75 000/μL or Grade 2 or higher diarrhea or abdominal pain was seen. During chemotherapy, if the WBC count fell $<$2000/μL or the neutrophil count

dropped $<1000/\mu L$, daily granulocyte colony-stimulating factor (G-CSF) was administered subcutaneously until the WBC count increased to $\geq 10\,000/\mu L$ or was no longer clinically indicated. Radiotherapy and concomitant use of G-CSF was contraindicated. When the second course of CDDP plus CPT-11 was started, each patient was required to meet the following criteria: WBC count $\geq 4000/\mu L$, neutrophil count $\geq 2000/\mu L$, platelet count $\geq 130\,000/\mu L$, serum creatinine level ≤ 1.5 mg/dl, serum GOT and GPT levels Grade 0 or 1, Ccr ≥ 30 ml/min, body temperature $<38.0°C$ and PS 0, 1 or 2. For patients receiving G-CSF, 3 days after discontinuation, patients were required to meet the aforementioned hematological toxicity criteria prior to starting the second course of CDDP plus CPT-11. If the second course was delayed 2 weeks or more due to toxicity, chemotherapy with CDDP plus CPT-11 and low-dose CBDCA was terminated and only radiotherapy was used. According to toxicities in the first course of chemotherapy, the dose of CDDP was reduced by 25% for Grade 4 leukopenia, Grade 4 neutropenia ≥ 7 days, Grade 3 thrombocytopenia, Grade 3 or 4 mucositis or Grade 2 or higher renal toxicity, and by 50% for Grade 4 thrombocytopenia. The dose of CPT-11 was reduced by 25% for Grade 3 or 4 diarrhea and administration of CPT-11 was terminated if Grade 2 or higher pulmonary toxicity was seen.

Criteria for starting AHRT with daily low dosage CBDCA administration were the same as mentioned above for the second course of CDDP plus CPT-11. Six weeks after initiation of the second course of chemotherapy, if the same criteria were not fulfilled, CBDCA administration was terminated. In that case, only radiotherapy was used.

During chemoradiation, if the WBC count fell $<2000/\mu L$, neutrophil count $<1000/\mu L$ or platelet count $<50\,000/\mu L$, daily use of CBDCA was suspended and only radiotherapy was continued. After recovery from neutropenia, administration of CBDCA was restarted. In case of Grade 4 hematological toxicities, chemoradiation was to be terminated. However, if any toxicity improved Grade 2 or lower, only radiotherapy could be used. If the PaO_2 level decreased by 10 torr or more compared with baseline value, chemoradiation was suspended and if it returned to baseline, treatment could be started again carefully. If Grade 3 or 4 radiation-related esophagitis was seen, chemoradiation was suspended but could be started again when this toxicity improved to Grade 2 or lower. If patients had a fever of 38°C or higher, chemoradiation was suspended until they were afebrile. Chemoradiation was also suspended when deterioration of PS to 3 or 4 occurred, and PS 0, 1 or 2 was necessary to restart the protocol treatment.

Treatment Evaluation

Tumor response and toxicity were evaluated according to World Health Organization response criteria (19) and Japan Clinical Oncology Group (JCOG) toxicity criteria (20), respectively. Complete response (CR), partial response (PR) and no change (NC) were reviewed and confirmed by central review with chest radiographs or CTs at the regular disease-group meeting. Complete blood cell count and routine blood chemistry were checked twice a week, and arterial blood gas and chest radiographs were checked at least once a week, until the patient had apparently recovered from all acute toxic effects after the completion of the treatment. In this trial, the methods to follow-up the patient after the protocol treatment were not clearly defined. In addition, not only late toxicities but also recurrence patterns after finishing protocol treatment were not routinely recorded in the case report form (CRF). Therefore, the interval of evaluation for late toxicities was left to the discretion of the treating physician. Consequently, the frequency of visiting the doctors and radiologic examinations was heterogeneous among the patients.

Study Design and Statistical Methods

This trial was designed as a multicenter prospective single-arm Phase II study, and the study protocol was approved by the Clinical Trial Review Committee (protocol review committee) of JCOG (21) and the institutional review board of each participating institution before study activation. After pre-treatment staging and eligibility evaluation, patients were registered at the JCOG Data Center by telephone or fax. The study was performed by the JCOG Lung Cancer Study Group and all study data were managed by the JCOG Data Center.

The primary endpoints of this study were the overall response rate (ORR) and overall survival (OS). The ORR was defined as the proportion of the patients with CR or PR out of all eligible patients. The confidence intervals for the ORR were calculated based on the exact method. The OS was measured from the date of patient registration to the date of death due to any cause. If a patient was alive at the final follow-up survey, OS was censored at the last contact date. The estimates of survival distribution were calculated by the Kaplan–Meier method and confidence intervals were based on Greenwood's formula (22). And 2-year OS was expected to be ~40%. The progression-free survival was not measured in this study.

We set an expected level (P1) of response rate as 80%, threshold level (P0) as 60%, α-error level was 0.05 and β-error level was 0.10. We set the planned total sample size as 45 according to Simon's minimax two-stage design (23). If 15 or fewer patients out of 26 patients showed objective responses at the first stage, the study was to be terminated early. The OS was followed up to 20 months after the last enrollment.

RESULTS

Patient Characteristics

Between February 1996 and January 1999, 26 patients from 5 institutions were enrolled in this study and all received induction chemotherapy. The pace of enrollment was approximately one-fourth of the planned one in the protocol.

For the pre-specified first stage decision, the accrual was temporarily closed and the response rate was assessed. Characteristics of the 26 patients are listed in Table 1. The patients included 22 men and 4 women, with a median age of 63 (range, 40–74) years. The histologic classifications included adenocarcinoma in 14 patients and squamous cell carcinoma in 12. Seven patients were in Stage IIIA and 19 were in Stage IIIB. Six patients had ECOG PS of 0 and 20 had that of 1. All of the 26 patients were eligible and evaluable for both tumor response and toxicity.

Treatment Delivery and Protocol Compliance

Of the 26 patients enrolled in the study, 15 completed both of the scheduled chemotherapy and radiotherapy. Protocol compliance in the 26 patients is summarized in Tables 2 and 3. In six patients, treatment was terminated after the first course of chemotherapy. The reasons for the withdrawal were disease progression in three patients and toxicity in three. In three patients with disease progression after the first course of CDDP plus CPT-11, one patient could receive sequential chemoradiation. In one patient Cre >1.5 mg/dl persisted, whereas in another patient, Grade 4 diarrhea, Grade 2 neutropenia and Grade 2 fever caused deterioration of PS and resulted in termination of induction chemotherapy. That patient died of sepsis and pneumonia from Grade 4 neutropenia and diarrhea which we categorized as treatment-related death. One patient had disease progression after two courses of chemotherapy and could not receive radiotherapy. One patient experienced Grade 4 leukopenia and the dose of CDDP in the second course should have been reduced to 75% of the original dosage. However, this patient received only CPT-11 and CDDP was improperly omitted in the second course, which was judged as a protocol violation. Delay in the start of the second course occurred in three patients. CPT-11 administration on day 8 was skipped in four patients and three patients had dose reduction of CPT-11 in the second course. The reason for dose omission or dose reduction was diarrhea in five patients.

Twenty patients received thoracic radiotherapy according to the protocol but 3 of the 20 patients could not receive the whole 60 Gy of radiation with daily CBDCA because of hypoxemia, emesis or onset of herpes zoster in the radiation field in each patient, respectively. Radiotherapy could not be delivered for six patients. The reason for not receiving radiotherapy was disease progression in four patients and toxicity in two patients including treatment-related death in one patient. Of the 20 patients receiving radiotherapy, actual mean radiation dose and actual mean number of CBDCA infusion was 56.8 Gy and 17.5 times, respectively (Table 3).

Table 1. Patient characteristics

Characteristics		No.	%
Age (years)			
Median	63		
Range	40–74		
Sex			
Male		22	84.6
Female		4	15.4
Histology			
Adenocarcinoma		14	53.8
Squamous cell carcinoma		12	46.2
Others		0	0
Clinical Stage			
Stage IIIA		7	26.9
Stage IIIB		19	73.1
T-stage			
T1		4	15.4
T2		6	23.1
T3		5	19.2
T4		11	42.3
N-stage			
N0		2	7.7
N1		2	7.7
N2		11	42.3
N3		11	42.3
Performance status (ECOG)			
0		6	23.1
1		20	76.9

ECOG, Eastern Cooperative Oncology Group.

Table 2. Dose intensity of chemotherapy phase ($n = 26$)

	Planned DI	Actual DI	%[a]
CDDP	26.7	23	86
CPT-11	40	33.3	83

DI, dose intensity (mg/m^2/week); CDDP, cisplatin; CPT-11, irinotecan.
[a]Percentage of the drug dose actually delivered, vs. the planned dose, is presented.

Table 3. Chemoradiation delivery ($n = 20$)

	Planned delivery	Actual delivery, mean
AHRT	60 Gy	56.8 Gy
CBDCA infusion	20 times	17.5 times

AHRT, accelerated hyperfractionated thoracic radiotherapy; CBDCA, carboplatin.

Toxicity

There was one treatment-related death due to septic shock and pneumonia associated with Grade 4 neutropenia, Grade 4 thrombocytopenia and Grade 4 diarrhea. That patient had CDDP and CPT-11 administration on day 1 and CPT-11 on day 8 in the first course and suffered from serious toxicity. *Pseudomonous aeruginosa* was detected in the microbiological culture test from the stool of the patient. This patient died on day 35 from toxicities mentioned above. Toxicities in the 26 patients are listed in Table 4. Grade 3 or 4 neutropenia occurred in 54% of the patients. Grade 3 or 4 thrombocytopenia occurred in four patients and one patient required platelet transfusion.

The most frequent non-hematological toxicity was diarrhea, and Grade 2 or more occurred in 46% of the patients. Five patients had Grade 2 esophagitis during radiotherapy but it did not cause termination of the therapy. Pulmonary toxicity was not evident during the radiotherapy, as well as CPT-11 including chemotherapy. In one patient, radiotherapy was terminated due to a decrease in arterial oxygen pressure by 17 torr when compared with baseline but that patient also had disease progression during the therapy and it was difficult to evaluate the causal relationship to the protocol treatment. In this trial, late toxicities after finishing protocol treatment were not routinely recorded in CRF.

Table 4. Toxicity in 26 patients (JCOG grade)

	0	1	2	3	4
Leukopenia	4	5	10	7	0
Neutropenia	4	2	6	8	6
Anemia	2	4	13	7	—
Thrombocytopenia	16	5	1	3	1
Bilirubin	22	—	3	1	0
GOT	18	7	1	0	0
GPT	10	11	3	2	0
ALP	19	7	0	0	0
Creatinine	21	4	1	0	0
Arterial oxygen pressure	5	18	3	0	0
Hypo/hypernatremia	9	12	4	1	0
Hypo/hyperkalemia	23	1	1	1	0
Emesis	1	13	11	1	—
Cardiac dysfunction	24	1	0	0	1
Proteinuria	22	4	0	0	0
Hematuria	21	5	0	0	0
Diarrhea	3	11	7	3	2
Esophagitis	8	13	5	0	0
Fever	20	3	3	0	0
Weight loss	8	9	8	1	—

JCOG, Japan Clinical Oncology Group; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; ALP, alkaliphosphatase.

Response and Survival

Objective tumor response is summarized in Table 5. Among the 26 patients, there were 13 PRs and 0 CR, giving a response rate of 50% (95% confidence interval, 30–70%). In 10 patients, a PR was achieved before the start of radiotherapy. Disease progression occurred during chemotherapy in four patients, who had to terminate the protocol treatment. Tumor response could not be evaluated in the patient with treatment-related death. The response rate at the first stage did not meet the criteria to proceed to the second stage and the study was terminated early. Figure 1 shows the OS curve of all patients enrolled in the study. After follow-up for 20 months after the last enrollment, the MST was 16.4 months. The 1- and 2-year survival rates in the 26 patients were 65.4% and 21.5%, respectively.

DISCUSSION

The findings of the present study suggest several important points that should be applied in future studies of Stage III NSCLC, although the response rate of this combination therapy was not as high as expected. First, the protocol regimen may not be sufficiently optimized in order to keep high compliance. The inferior tumor response and the high frequency of disease progression during the induction chemotherapy with CPT-11 and CDDP appeared to be the major reason for the disappointing results, which led to the early termination of the present study. Only 10 out of the 26 patients showed >50% tumor reduction during chemotherapy. It appeared unsatisfactory when one considers

Table 5. Clinical response to the therapy in 26 patients

CR	PR	NC	PD	NE	% of CR + PR (95% confidence interval)
0	13	5	7	1	50.0 (29.9–70.1)

CR, complete response; PR, partial response; NC, no change; PD, progressive disease; NE, not evaluable.

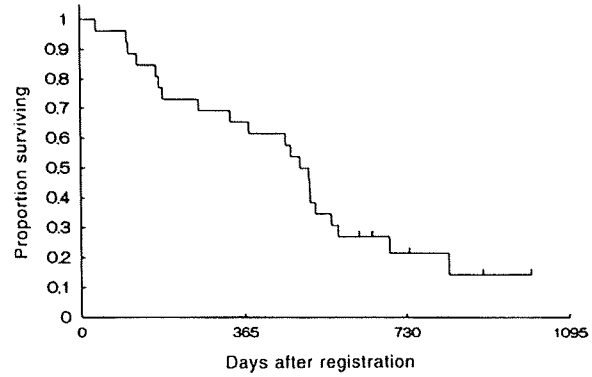

Figure 1. The overall survival curve of all patients enrolled in the study.

that only patients in Stage III were enrolled in the study. Another reason may be the fact that there were comparatively more Stage IIIB patients than Stage IIIA. Although the proportion of Stage IIIA cases was only 26.9% in this trial, in two recent studies, it was 43% and 49% (24,25). This case distribution might have contributed to the poor outcome of this study.

In the view of toxicity management, diarrhea is considered to be key toxicity to be managed carefully in combination chemotherapy using CPT-11. Relative dose intensity of CDDP, CPT-11 and radiotherapy was acceptable in this protocol; however, severe diarrhea caused lowering protocol compliance probably because high-dose loperamide therapy (26) even in the case of severe diarrhea was not used during initial period in this study. It might be possible that the anti-diarrhea agent was inadequate and protocol treatment could not be completed in some cases as a result. Had high-dose loperamide therapy been applied appropriately in all eligible cases, better response rate and survival might have been achieved in this study.

It is noteworthy that the strong association between CPT-11 delivery and antitumor response was seen in the present study. In fact, among the 12 patients who had two courses of induction chemotherapy without any delay, omission or dose reduction in CPT-11 administration, 7 showed >50% tumor reduction during the induction chemotherapy and 9 eventually achieved PR after the whole course of therapy (data not shown). This result suggests the possibility that the schedule of CPT-11 administration in this study (days 1 and 8) which was different from the more common regimen (days 1, 8 and 15) may explain the relatively low response rate and the large number of patients with disease progression. Six patients could not receive the protocol radiotherapy because of disease progression or toxicity of the induction chemotherapy. Planned omission of CPT-11 administration on day 15 was intended to reduce risk of pulmonary toxicity during radiotherapy but it might cause unsatisfactory tumor response in the chemotherapy.

Second, the timing of combination of thoracic radiation with chemotherapy may also not be optimized. The present study adopted sequential radiation following induction chemotherapy with CPT-11 and CDDP but suggests that inferior antitumor activity in the chemotherapy could cause failing to receive radiotherapy in some patients. It is difficult to find the best regimen using CPT-11 in the combined modality treatment for Stage III NSCLC.

Because late toxicities were not fully evaluated, the occurrence of both pneumonitis and delayed esophagitis might be possibly underestimated in this study. However, despite the high radiation dose, acute esophagitis were very mild contrary to our expectation, although we cannot clearly explain the reason. Most patients who could proceed to chemoradiotherapy could complete the scheduled radiation with acceptable toxicity. The MST of 16.4 months in the present study was almost as good as in other studies that showed high response rates and survival benefit in Stage III NSCLC. Although our study was prematurely closed after interim analysis because of low response rate, OS which was one of the primary endpoints was comparable with other literatures (24,25,27). In our opinion, AHRT with CBDCA still remains a chemoradiotherapeutic option and should be investigated further with combinations of other chemotherapy regimens.

In recent years, however, some articles have shown that addition of induction chemotherapy before concurrent chemoradiotherapy adds toxicity and provides no survival benefit (24,25). In addition, National Comprehensive Cancer Network (NCCN) practice guideline recommends CDDP plus etoposide or vinblastin with concurrent radiotherapy as preferred standard of cares (category 2A) for patients with unresectable NSCLC (28). Further studies to investigate the role of induction chemotherapy followed by chemoradiotherapy may be not necessary until appearance of more active anticancer agents.

In conclusion, we failed to demonstrate promising efficacy of this regimen, and the development of a brand-new treatment strategy for combining chemotherapy with radiotherapy is necessary for the improvement of the prognosis of the patients with unresectable Stage III NSCLC.

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Conflict of interest statement

None declared.

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Dose-escalating and Pharmacokinetic Study of a Weekly Combination of Paclitaxel and Carboplatin for Inoperable Non-small Cell Lung Cancer: JCOG 9910-DI

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Objective: Combined paclitaxel and carboplatin is a standard regimen for inoperable non-small cell lung cancer (NSCLC). Although an every-3-week schedule is common, weekly paclitaxel is clinically effective for various cancers. A Phase I clinical trial was conducted to determine maximum-tolerated doses (MTDs) for weekly combined paclitaxel and carboplatin, and to evaluate anti-tumor response, toxicity and pharmacokinetics of paclitaxel in patients with inoperable NSCLC.
Methods: Twenty patients with inoperable NSCLC received weekly carboplatin at area under the curve (AUC) = 2 mg/ml min and paclitaxel. Paclitaxel was escalated if MTD was not reached. Three patients each were entered at levels 1 and 2 (level 1, paclitaxel 50 mg/m^2 and carboplatin AUC = 2 mg/ml min; level 2, 60/2), six at level 3 (70/2), five at level 4 (80/2) and three at level 5 (90/2).
Results: One patient had grade 4 (G4) neutropenia at level 2, one had G3 hepatic toxicity at level 3 and one had G3 cardiac toxicity at level 4. MTD was not reached for all dose levels. Response rate (RR) was 35% (7/20) and median survival was 11.1 months. Severe neutropenia (G3 and G4) was seen in seven patients associated with greater AUC, peak concentration (C_{max}) and the duration of plasma concentration >50 ng/ml of paclitaxel.
Conclusions: Weekly combined paclitaxel (up to 90 mg/m^2) and carboplatin (AUC = 2 mg/ml min) was well tolerated. A higher dose intensity of paclitaxel can be given, and RR and survival are not less than the every-3-week protocol. The weekly regimen is an alternative for untreated inoperable NSCLC patients.

Key words: carboplatin – non-small cell lung cancer – paclitaxel – Phase I – weekly chemotherapy

INTRODUCTION

Lung cancer is the leading cause of cancer deaths in many countries, including Japan. Non-small cell lung cancer (NSCLC) comprises ~80% of all lung cancer cases. Nearly half of all patients with NSCLC are not candidates for curative surgery at the time of diagnosis (1). The prognosis for these inoperable NSCLC patients is still poor, even though new chemotherapy regimens are available.

Paclitaxel + carboplatin is one of the standard regimens for NSCLC. Paclitaxel, the first of the taxane anti-microtubule agents, showed overall response rates (RRs) of >30% in a Phase II study of NSCLC in Japan (2,3). The typical doses for the two drugs during a 3-week protocol are 200 mg/m^2 for paclitaxel and area under the curve (AUC) = 6 mg/ml min for carboplatin in Japan (4). However, the best administration method for paclitaxel is still under investigation.

In vitro experiments using lung, breast and ovarian cancer cell lines showed that prolonging the exposure to paclitaxel above a threshold concentration was more effective than a short-term exposure to a higher drug concentration (5,6). Thus, weekly administration of paclitaxel is worth investigating for possibly better effects and reduced toxicity. The clinical utility of weekly paclitaxel administration has been demonstrated for various cancers (7–9). Weekly carboplatin treatment is also effective in combination chemotherapy

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(10). Further, weekly administration of both paclitaxel and carboplatin is being investigated in NSCLC, ovarian cancers and other solid tumors (11,12). One purpose for weekly administrations of paclitaxel is to maintain the time of anti-tumor plasma concentrations as long as possible without increasing toxicity.

Hematological toxicity for paclitaxel was reported to be related to the duration of the time that the plasma paclitaxel concentration was $\geq$50–100 nM (13,14). However, there are no reports regarding hematological toxicity and plasma paclitaxel concentrations for the weekly administration of a combination treatment with carboplatin. In this study, we wanted to elucidate the relationship between the duration of plasma paclitaxel concentration >50 nM and hematological toxicity during weekly administrations of paclitaxel combined with carboplatin.

Therefore, we conducted a Phase I study to determine the maximum-tolerated dose (MTD) and recommended dose for weekly combinations of paclitaxel and carboplatin, and to evaluate the anti-tumor response, toxicity and the pharmacokinetics of paclitaxel in patients with inoperable NSCLC.

PATIENTS AND METHODS

Study Design

This trial was a single institution, prospective, single-arm Phase I study. This study was performed at Yokohama Municipal Citizen's Hospital. The protocol was approved by the institutional review board of Yokohama Municipal Citizen's Hospital and Japan Clinical Oncology Group (JCOG). Each patient gave written informed consent before enrollment.

Patient Selection

Patients eligibility requirements for entering into this study included the following criteria: histologically or cytologically confirmed NSCLC; measurable or assessable disease at stages IV and IIIB without curative radiotherapy; age 75 years or younger; no prior chemotherapy or radiotherapy; and Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1. Additional criteria were: expected survival $\geq$3 months; adequate organ functions; leukocyte count $\geq$4000/mm^3; neutrophil count $\geq$2000/mm^3; platelet count $\geq$100 000/mm^3; hemoglobin level $\geq$9.5 g/dl; total bilirubin within upper limit of normal range; AST/ALT $\leq$2 $\times$ upper limit of normal range; creatinine $\leq$1.5 $\times$ upper limit of normal range; 24 h creatinine clearance (CCR) $\geq$30 ml/min; and PaO_2 $\geq$70 mmHg. Exclusion criteria included other active malignancy, pleural effusion or pericardial effusion requiring medical treatment, symptomatic brain metastases, superior vena cava syndrome requiring radiotherapy, history of myocardial infarction within 3 months, serious medical illness, history of severe anaphylaxis, history of anaphylaxis to castor oil, pregnancy or lactation.

Staging procedures included chest x-ray, computed tomography (CT) scan of the chest, CT scan of the brain, CT scan or ultrasound of the abdomen and isotope bone scanning.

Treatment Plan

The trial was designed as a dose-escalation study of paclitaxel and carboplatin used in weekly combination therapy. The dose of carboplatin was fixed to target weekly AUC = 2 mg/ml min. The starting weekly dose of paclitaxel was 50 mg/m^2 given over 1 h. If treatment was well tolerated, then successive dose levels were increased at intervals of 10 mg/m^2 in groups of three patients to 60, 70, 80 and 90 mg/m^2. The initial dose level was determined to be nearly equivalent to, but not to exceed, the typical dosage of a 3-week regimen of carboplatin (AUC = 6 mg/ml min) + paclitaxel (200 mg/m^2). Dose-limiting toxicity (DLT) was defined as: (i) grade 4 (G4) ($\geq$4 days) leukopenia; (ii) G4 ($\geq$7 days) neutropenia; (iii) fever ($\geq$38°C) with G4 leukopenia or neutropenia; (iv) thrombocytopenia $\leq$25 000/mm^3 or requiring platelet transfusion; (v) any G3/4 non-hematological toxicities, except nausea, vomiting or hair loss; and (vi) a delay for the following cycle within 2 weeks. The National Cancer Institute (NCI) common toxicity scale was used to grade adverse events (15). If no patient experienced DLT, then subsequent patients entered the study at the next greater dose level. If one or two of the three patients experienced DLT, then subsequent patients entered at the same level, for a total of four to six patients. If more than three of the four to six patients had DLT at a specific dose level, this was defined as the MTD. If less than one of five or less than two of six patients had DLT, the next level will be entered. The recommended dose would be decided 1 level under the MTD, with special consideration for safety and efficacy. The MTD was determined according to the results following the first three administrations of the drugs. In the case of early discontinuation with three administrations, the MTD was determined at the time of discontinuation of the treatment.

Chemotherapy

Paclitaxel and carboplatin were administered on day 1 by intravenous (iv) infusion. Chemotherapy was repeated weekly for at least six cycles unless there was no progression of the disease. Patients who received at least six cycles were considered to have completed treatment. Treatment after protocol completion or disease progression was up to the responsible doctor. All patients received the following pre-medications 30 min before the paclitaxel infusion: dexamethasone 20 mg iv; diphenhydramine 50 mg po; and ranitidine 50 mg iv. Anti-emetics, such as granisetron, were also administered as pre-medications. Paclitaxel was administered over 1 h. Thirty minutes after the paclitaxel infusion, carboplatin at AUC = 2 mg/ml min according to the Calvert

formula (16) was delivered as an iv bolus infusion over 1 h. The carboplatin dose was based on the actual glomerular filtration rate (GFR) calculated by the measurement of CCR [dose = 2.0 × (GFR + 25)]. Subsequent courses of chemotherapy were initiated when the following criteria were met: leukocyte count $\geq$2000/mm^3, neutrophil count $\geq$1000/mm^3, platelet count $\geq$50 000/mm^3 within 24 h of the day of treatment; nephrotoxicities $\leq$G2; hepatic toxicities $\leq$G1; fever < 38°C or PS $\leq$ 2; neurological toxicities $\leq$G1; and stomatitis $\leq$G1. If the above criteria were not satisfied by the first day of the next course, treatment was withheld until recovery. If more than 3 weeks passed from day 1 of the last course, the patient was taken out of the study. Treatment was discontinued if the disease progressed, the patient withdrew or experienced septic shock, if there was G3 neurological toxicity or G4 non-hematological toxicity, if there was a treatment delay of more than 3 weeks, repeated toxicity after dose modification, or by a decision of the clinician. Dose modifications were made after the first administration based on toxicity. Patients had their paclitaxel dose reduced by 25% if they experienced G4 leukopenia $\geq$4 days, G4 neutropenia $\geq$7 days, fever ($\geq$38°C) with G4 leukopenia or neutropenia, G3 hepatic toxicity, G3 neurological toxicity or G3 stomatitis. Patients had their carboplatin dose reduced by 25% if they experience fever ($\geq$38°C) with G4 leukopenia or neutropenia, thrombocytopenia $\leq$25 000/mm^3 or requiring platelet transfusion, G3 hepatic toxicity or G3 stomatitis. In case of nephrotoxicity grade $\geq$2, CCR would be measured and the carboplatin dose adjusted according to this result.

Evaluation

Toxicities were evaluated according to the NCI common toxicity scale (15). Tumor responses were evaluated according to World Health Organization criteria (17). Response was determined at the end of the treatment if the protocol was completed. If the treatment was stopped earlier, response was determined at the time of protocol discontinuation. Overall survival (OS) was determined from the time of registration to death or the last follow-up evaluation.

Statistics

This trial was a single institution, prospective, single-arm Phase I study. The primary endpoint was toxicity, and the secondary endpoints were anti-tumor effect (RR and survival) and pharmacokinetics of paclitaxel. Analysis of the trial was based on the intention-to-treat principle. OS were calculated using the method of Kaplan and Meier.

Pharmacokinetics

For the pharmacokinetic study of paclitaxel, each patient gave written informed consent for this study separately from the treatment protocol. During the first course of the treatment, a 2 ml blood sample was withdrawn from patients at 0, 0.5, 1.5, 3, 6, 10, 24, 48, 72 and 96 h after paclitaxel treatment (total of 20 ml). The time for blood sampling was according to previous reports during the first 10 h (18,19), and after this, they were determined every 24 h. Heparin was added to the blood and stored at 4°C. Plasma was separated by centrifugation and stored at −20°C. Plasma paclitaxel concentrations were measured using an HPLC method.

RESULTS

Patient Characteristics

Between March 2000 and November 2003, 20 patients were registered and all received chemotherapy (Table 1). The median age was 67 years, 85% were male, 70% had adenocarcinoma and 70% were stage IV.

Toxicities of Therapy

One of 3 patients experienced G4 neutropenia at level 2, but none of the other 19 patients had G4 hematological toxicities (Table 2). None had febrile neutropenia. Seven of 20 patients (35%) had G3/4 neutropenia, and 1 of 20 patients (5%) had G3/4 thrombocytopenia. With regard to non-hematological

Table 1. Patient characteristics

Characteristic	No. of patients
Total no. of patients	20
Age (years)	
Range	51–75
Median	67
Sex	
Male	17
Female	3
Histology	
Adenocarcinoma	14
Squamous cell carcinoma	4
Large cell carcinoma	2
Stage	
IIIB	6
IV	14
Performance status	
0	3
1	17
Prior treatment	
Yes[a]	10[a]
No	10

[a]Surgical resection, 6; brain radiotherapy, 1; pleural drainage, 4.

Table 2. Hematological toxicity

Level	1 ($n=3$)			2 ($n=3$)			3 ($n=6$)			4 ($n=5$)			5 ($n=3$)		
Grade	1/2	3	4	1/2	3	4	1/2	3	4	1/2	3	4	1/2	3	4
Leukopenia	2	0	0	1	1	0	4	1	0	2	2	0	2	1	0
Neutropenia	2	0	0	1	1	1[a]	3	2	0	2	2	0	2	1	0
Anemia	3	0	0	3	0	0	5	0	0	5	0	0	3	0	0
Thrombocytopenia	0	1	0	3	0	0	2	0	0	0	0	0	2	0	0

[a]For 2 days, not febrile.

Table 3. Non-hematological toxicity

Level	1 ($n=3$)			2 ($n=3$)			3 ($n=6$)			4 ($n=5$)			5 ($n=3$)		
Grade	1/2	3	4	1/2	3	4	1/2	3	4	1/2	3	4	1/2	3	4
Emesis	1	0	0	2	0	0	4	0	0	2	0	0	1	0	0
Neurological	2	0	0	2	0	0	1	0	0	2	0	0	1	0	0
Skin	1	0	0	2	0	0	5	0	0	2	0	0	1	0	0
Stomatitis	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
Fever	0	0	0	1	0	0	3	0	0	1	0	0	0	0	0
Hepatic	1	0	0	2	0	0	3	1[a]	0	1	0	0	0	0	0
Renal	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cardiac	0	0	0	0	0	0	0	0	0	0	1[a]	0	0	0	0
Lung	1	0	0	0	0	0	1	0	0	1	1[b]	0	0	0	0

[a]DLT.
[b]Pneumonia after 3 course.

toxicities, one of six patients had G3 hepatic toxicity at level 3, and one of five patients had G3 cardiac toxicity (angina) at level 4 (Table 3). Only these two cases had DLT. There were no treatment-related deaths. One case (5%) had an allergic reaction, but none had G3/4 neurological toxicity. MTD was not reached for all dose levels (Table 4).

A weekly combination of paclitaxel and carboplatin was well tolerated, and a higher dose intensity of paclitaxel could be given to patients compared with the standard every-3-week regimen of paclitaxel (Table 5).

Therapeutic Response and OS

The RR was 35% (7/20; Table 4), and the median survival time (MST) was 337 days (11.1 months).

Pharmacokinetics

The pharmacokinetics of paclitaxel was examined in all 20 patients (Tables 6 and 7). The AUC, peak plasma concentration (C_{max}) and the duration of plasma concentration

Table 4. Dose level, emergence of DLT and response

Level	PTX (mg/m^2)	CBDCA (AUC)	No. of patients	DLT	Response
1	50	2	3	0	1 PR
2	60	2	3	0	2 PR
3	70	2	6	1	2 PR
4	80	2	5	1	2 PR
5	90	2	3	0	0 PR

PTX, paclitaxel; CBDCA, carboplatin; AUC, area under the curve; DLT, dose-limiting toxicity; PR; partial response.

Table 5. Protocol compliance

	Level 1 ($n=3$)	Level 2 ($n=3$)	Level 3 ($n=6$)	Level 4 ($n=5$)	Level 5 ($n=3$)
Protocol completed	2	3	3	1	2
Number of course (median)	6	9	5.5	7	6
Withdrawal by toxicity	1[a]	0	1[b]	3[c]	0
Withdrawal by PD	0	0	2	1	1
Treatment delay	1	2	5	4	2

PD, progressive disease.
[a]Allergic reaction.
[b]Hepatic toxicity (DLT).
[c]Angina (DLT), neutropenia, pneumonia.

>50 ng/ml (duration of $C > 50$ ng/ml) were increased in proportion to the increase in paclitaxel dose level (Table 6).

Severe neutropenia (grades 3 and 4) was observed in seven patients and was associated with a greater AUC, C_{max} and the duration of $C > 50$ ng/ml (Table 7). Pharmacological responses had the tendency of association with increased pharmacokinetic parameters of paclitaxel (Fig. 1).

DISCUSSION

This is a Phase I clinical trial for a weekly combination of paclitaxel and carboplatin that was conducted to determine the MTD and to evaluate toxicity, anti-tumor response and the pharmacokinetics in patients with inoperable NSCLC. In this study, a weekly combination of paclitaxel and carboplatin was well tolerated, and a higher dose intensity of paclitaxel could be given to patients compared with a standard, every-3-week regimen of paclitaxel.

The combination of paclitaxel (225 mg/m^2) and carboplatin (AUC = 6 mg/ml min) administered every 3 weeks is the most commonly used chemotherapy regimen in the USA for the treatment of advanced and metastatic NSCLC. The RR with this regimen ranges from 17% to 25%, with MST ranging from 8 to 10 months (20–23). In this study, the RR was 35% and the MST was 337 days (11.1 months). In a randomized Phase II trial comparing three different regimens of

Table 6. Pharmacokinetic parameters of paclitaxel

	Level 1 ($n = 3$)	Level 2 ($n = 3$)	Level 3 ($n = 6$)	Level 4 ($n = 5$)	Level 5 ($n = 3$)
AUC (ng/ml h)	2874 ± 590	3351 ± 590	4442 ± 1294	4696 ± 839	10 726 ± 7307
C_{max} (ng/ml)	1517 ± 230	1603 ± 552	1913 ± 686	2002 ± 614	3857 ± 1656
Duration of $C > 50$ ng/ml (h)	6.9 ± 2.3	11.4 ± 2.0	18.1 ± 6.5	19.6 ± 8.9	33.7 ± 14.8

Values are given as mean ± SD.

Table 7. Pharmacokinetic parameters of paclitaxel and neutropenia

	Neutropenia	
	Grade 0–2 ($n = 13$)	Grade 3–4 ($n = 7$)
AUC (ng/ml h)	4899 ± 4238	5327 ± 2058
C_{max} (ng/ml)	1854 ± 661	2617 ± 1497
Duration of $C > 50$ ng/ml (h)	16.3 ± 11.4	21.5 ± 9.5

Values are given as mean ± SD.

weekly paclitaxel and carboplatin, Belani et al. (24) showed that the most favorable regimen was paclitaxel (100 mg/m^2) weekly for 3 of 4 weeks with carboplatin (AUC = 6 mg/ml min) on day 1 every 4 weeks. This showed an RR of 32% and an MST of 49 weeks, comparable to our results. They also showed 5% with G3/4 neuropathy, 2% with G3/4 febrile neutropenia and 22% with G3/4 neutropenia for that treatment, compared with 0%, 0% and 35% in our study. Even though the sample size was smaller in our study, the toxicities appear to be comparable and tolerable.

In spite of the initial promising report of a weekly regimen (24), a Phase III trial that compared a weekly regimen with a standard every 3 weeks with carboplatin and paclitaxel failed to show a survival or response benefit for the weekly approach (25). In contrast, Socinski et al. (26) reported that RR and survival outcomes were similar in a Phase II trial comparing every-3-week carboplatin and paclitaxel with every-3-week carboplatin and weekly paclitaxel. However, the toxicity profiles were different between the two regimens, suggesting that the weekly regimen is a feasible and acceptable alternative for certain patients such as the elderly and/or poor PS patients. In many trials with weekly paclitaxel, carboplatin is often combined with monthly or tri-/bi-weekly administration. Weekly administrations of both drugs were done in two Phase II trials and one Phase III trial (11,24,27). Although the original Belani et al.'s (24) trial showed that monthly carboplatin was the most favorable therapeutic index compared with other weekly carboplatin regimens, a recent Phase III trial showed comparable results with both weekly paclitaxel and carboplatin compared with a standard 3-week regimen (27). Schuette et al. (27) used weekly paclitaxel (100 mg/m^2) and carboplatin (AUC = 2 mg/ml min). This showed an RR of 38% and an MST of 8.9 months, compared with an RR of 33% and an MST of 9.5 months for every-3-week paclitaxel (200 mg/m^2) and carboplatin (AUC = 6 mg/ml min), and less frequent ≥G3 neuropathy in the weekly regimen (4.4% vs. 9.1%). A small Phase II study with weekly administration of both paclitaxel and carboplatin (100 mg/m^2 for paclitaxel and AUC = 2 mg/ml min for carboplatin; weekly for 3 of 4 weeks; $n = 30$) reported a 43.5% RR and 10.8 months MST (11). Regarding toxicities, only 1 of 30 patients (4%) suffered from G3 neurotoxicity. Our results also suggest that the toxicities were acceptable. In fact, a subanalysis of the Phase II and III studies showed comparable efficacy and a favorable tolerability profile for a weekly regimen in elderly patients (28,29). Several Phase II results also showed reasonable activity and acceptable toxicities in the elderly and/or unfit NSCLC patients (12,30,31). Along with these results, our study suggests the feasibility of weekly carboplatin/paclitaxel trials for the treatment of NSCLC patients with modest activity, and that this regimen may be especially suitable for elderly and/or unfit patients.

In Japan, results from several Phase I and I/II studies were reported (32–34). In a Phase I trial of advanced NSCLC (32), a recommended dose level of paclitaxel was 70 mg/m^2 on days 1, 8 and 15 in combination with carboplatin (AUC = 6 mg/ml min) on day 1 of a 4-week cycle. In a Phase I study with the same treatment schedule (carboplatin: AUC = 6 mg/ml min with weekly paclitaxel in a 4-week cycle), Kikuchi et al. (34) reported a recommended dose level of paclitaxel of 100 mg/m^2. Although carboplatin was delivered weekly in our trial, the recommended dose of paclitaxel was >90 mg/m^2, comparable to the report by Kikuchi et al. (34). This relatively higher MTD dose in our trial and another Phase I trial (34) compared with that of Hirabayashi et al. (33) may be due to differences in background patient PS (0–1 vs. 1–2). In Japan, the usual doses in a 3-week protocol are 200 mg/m^2 for paclitaxel and AUC = 6 mg/ml min for carboplatin (4). In the Phase III study (4), the RR was 32% and the MST was 12.3 months. Although we cannot draw any definitive conclusions from the comparison between the Phase III trial and our Phase I trial, the RR was comparable and the higher dose of paclitaxel delivery can be achieved by our weekly paclitaxel schedule with an MTD of ≥90 mg/m^2.

We stopped our dose of paclitaxel at 90 mg/m^2 because this dose is thought to be reasonably comparable to the dose of a regular 3-week regimen (200–225 mg/m^2). Although we could not reach an MTD, for comparisons with other

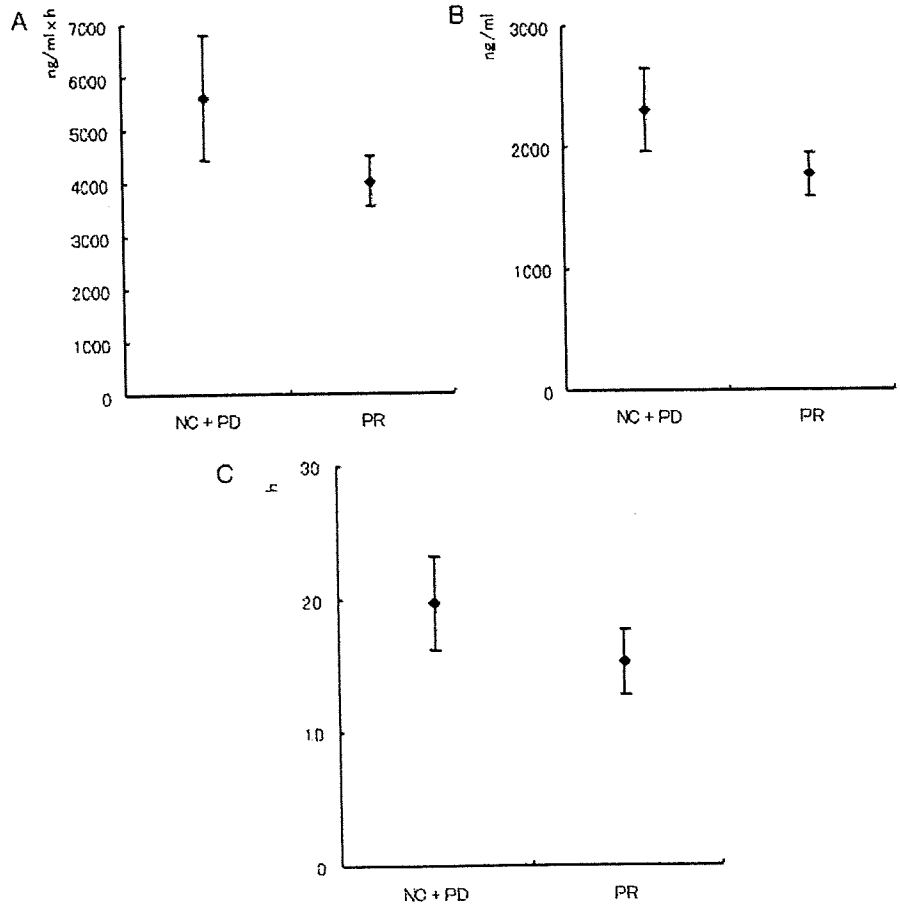

Figure 1. Pharmacokinetic parameters of paclitaxel and response. (a) AUC of paclitaxel and response (mean ± SEM). (b) Peak plasma concentration (C_{max}) of paclitaxel and response (mean ± SEM). (c) The duration of paclitaxel plasma concentration >50 ng/ml and response (mean ± SEM). AUC, area under the curve.

weekly regimens, paclitaxel with 90 mg/m^2 every week is a reasonably high dose. We may try increasing dosage, but based upon feasibility and the modest activity, the dose levels used here will be suitable for regular practical settings.

The severity of neutropenia in this weekly regimen with paclitaxel and carboplatin was consistent with that observed in patients treated with every-3-week schedules. Belani et al. (13) examined the pharmacokinetics of a combination treatment with paclitaxel and carboplatin (every 3 weeks) in a Phase I trial with metastatic NSCLC. They showed a pharmacodynamic relationship between the duration of the time that plasma paclitaxel concentration was at or above 0.05 μM and relative neutropenia, which is consistent with our study with weekly settings. They also showed that patients who had received carboplatin in combination with paclitaxel experienced less thrombocytopenia than would be expected from carboplatin alone. We did not thoroughly examine this issue, but only 1 of 20 patients (5%) had G3 thrombocytopenia, and none had G4 thrombocytopenia in this trial. It may also be possible in the weekly combination scenario that thrombocytopenia will be limited, although this issue may require further evaluation.

In conclusion, although the every-3-week protocol of paclitaxel and carboplatin is considered to be the standard treatment, the weekly regimen can be an alternative for untreated, inoperable NSCLC patients. A Phase II study is warranted with this treatment protocol, i.e. recommended dose of weekly paclitaxel (90 mg/m^2) and carboplatin (AUC = 2 mg/ml min).

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Conflict of interest statement

None declared.

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Phase I/II trial of gemcitabine plus oral TS-1 in elderly patients with advanced non-small cell lung cancer: Thoracic oncology research group study 0502

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ABSTRACT

A phase I/II trial of TS-1 combined with gemcitabine was designed to determine the maximum tolerated dose (MTD) and recommended dose (RD) and to evaluate the efficacy and toxicity in elderly patients with advanced non-small cell lung cancer (NSCLC). Patients older than 70 years of age received TS-1 orally b.i.d. on days 1–14 and gemcitabine intravenously on days 8 and 15 every 4 weeks. In phase I ($n=22$), each cohort received escalating doses of TS-1 (30–40 mg/m^2 b.i.d.) and gemcitabine (800–1000 mg/m^2); MTD was 40 mg/m^2 b.i.d. TS-1 and 1000 mg/m^2 gemcitabine; RD was 30 mg/m^2 b.i.d. TS-1 and 1000 mg/m^2 gemcitabine. Dose-limiting toxicities included a grade 3 infection, skin toxicity, and stomatitis. In phase II ($n=37$), the overall response rate was 27% (90% confidence interval (CI): 15–42%) and the median time to progression and overall survival were 4.2 months (90% CI: 3.2–5.7) and 12.9 months (90% CI: 10.4–14.7), respectively. The most common grade 3 or higher toxicity was neutropenia (45.9%), and thrombocytopenia was observed in 13.5% of patients. Two cases each of grade 3 pneumonitis and skin toxicity were observed, but nonhematological toxicities occurred at generally low frequencies. TS-1 with gemcitabine is a promising doublet regimen in elderly patients with advanced NSCLC with acceptable toxicities.

1. Introduction

Non-small cell lung cancer (NSCLC) is a leading cause of cancer death. Most patients with NSCLC have metastatic disease or malignant pleural effusion at the time of diagnosis and require systemic treatment. The number of elderly patients with NSCLC is increasing yearly [1] and the current standard treatment for those patients is single-agent chemotherapy with either vinorelbine, gemcitabine, or docetaxel [2–4]. The choice of these treatments is based largely on the results of a randomized phase III study from Italy comparing vinorelbine or gemcitabine monotherapy to a combination of vinorelbine plus gemcitabine for patients 70 years or older [3]. Although this study failed to show survival benefit for combination chemotherapy over monotherapy, the 1-year survival rate with these single-agents remains 30–40% at most. Therefore, the development of effective combination chemotherapy with a low incidence of toxicity is strongly warranted.

Tegafur-uracil (UFT) is an oral agent composed of a 1:4 molar ratio of tegafur, a prodrug that is converted to fluorouracil (5-FU), and uracil, which elevates serum levels of 5-FU by inhibiting its enzymatic degradation [5]. Previous studies have extensively suggested a potential synergistic effect between 5-FU and gemcitabine [6–8] in both *in vitro* and clinical studies. We conducted phase I and II studies of combination chemotherapy with daily administration of UFT for 2 weeks and a bolus injection of gemcitabine on days 8 and 15 as a first-line treatment for advanced NSCLC [9,10]. The phase II study in 44 patients demonstrated a promising objective response rate (ORR) of 41% and a median survival time of 13.2

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months with an incidence of grade 3 or higher nonhematological adverse events of less than 5% and tolerable myelosuppression. The regimen also showed a high antitumor activity in a subset of 21 patients 75 years or older (ORR = 38%) [9].

TS-1 (Taiho Pharmaceutical Co., Tokyo, Japan) is a new oral anticancer agent that is composed of tegafur, 5-chloro-2, 4-dihydroxypyridine (CDHP), and potassium oxonate in a molar ratio of 1:0.4:1. The 5-FU concentrations in blood and tumors achieved by TS-1 are much higher and longer-lasting than those by UFT [11]. In a phase II trial of TS-1 monotherapy in previously untreated patients with advanced NSCLC, the ORR was 22% and the median survival time was 10.2 months [12]. A phase I/II trial of TS-1 plus gemcitabine was conducted to further enhance the efficacy of the combination of UFT plus gemcitabine, while maintaining a mild level of toxicity in the treatment of elderly patients.

2. Patients and methods

2.1. Patient eligibility

Patients were registered at the central data center when the following eligibility criteria were confirmed: cytologically or histologically confirmed NSCLC; stage IIIB disease without any indications for radiotherapy or stage IV disease; no prior treatment; age 70 years of age or older; and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1. The criteria for organ function included: neutrophil count $\geq$2000/μL; platelet count $\geq$100,000/μL; hemoglobin level $\geq$9.5 g/dL; serum bilirubin concentration $\leq$1.5 mg/dL; serum aspartate aminotransferase and alanine aminotransferase concentrations $\leq$100 IU/L; creatinine level $\leq$1.3 mg/dL; creatinine clearance rate $\geq$30 mL/min ($\geq$60 mL/min for the phase II portion); and arterial oxygen saturation $\geq$90%.

Patients were excluded from the study if they had either interstitial pneumonia or pulmonary fibrosis on chest X-ray films, any severe concomitant disease (severe cardiac disease, uncontrolled diabetes mellitus, severe infection), concomitant malignancy, pleural effusion necessitating treatment, or symptomatic cerebral involvement. Written informed consent was required from all patients. The protocol was approved by the institutional review committee of each of the participating institutions.

2.2. Evaluation for enrollment

All patients were required to undergo a computed tomography (CT) scan of the thorax and the upper abdomen, either CT or magnetic resonance imaging (MRI) of the brain and a radioisotopic bone scan for stage assessment. A complete blood cell count and a blood chemistry panel were also obtained at enrollment. After protocol treatment was started, the blood examinations and chest radiography were performed at least once per week. CT or MRI examinations were repeated every 6 weeks to evaluate the target lesions. The tumor response was assessed with the Response Evaluation Criteria in Solid Tumors, and toxicity was assessed with the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

2.3. Phase I portion

The primary endpoint for the phase I trial was to determine the maximum tolerable dose (MTD) and dose-limiting toxicity (DLT). The doses were escalated in each successive cohort of 3 or more new patients. TS-1 was administered orally twice daily after meals on days 1–4. Gemcitabine was administered intravenously in 30 min or less on days 8 and 15. The schedule was repeated every 4 weeks for more than 3 cycles, unless disease progression or unacceptable toxicity occurred. Satisfaction of the entry eligibility criteria regarding the organ function was required before the next cycle could be started.

Three dose levels were evaluated with the following doses: level 1, 30 mg/m^2 (60 mg/m^2/day) of TS-1 and 800 mg/m^2 of gemcitabine; level 2, 30 mg/m^2 of TS-1 and 1000 mg/m^2 of gemcitabine; and level 3, 40 mg/m^2 (80 mg/m^2/day) of TS-1 and 1000 mg/m^2 of gemcitabine. Gemcitabine was administered when the leukocyte count was $\geq$2000/μL, the thrombocyte count was $\geq$75,000/μL, and nonhematological toxicities were no greater than grade 1.

The dose level was escalated on the basis of the toxicity during the first cycle of chemotherapy and was not escalated for each individual. A DLT was defined as any of the following: (i) grade 4 neutropenia; (ii) grade 3 febrile neutropenia; (iii) grade 4 thrombocytopenia; (iv) grade 3 nonhematological adverse events (except anorexia and fatigue); (v) a delay of gemcitabine infusion on day 15 for more than 7 days; and (vi) a delay of administration of the next course for more than 2 weeks. If DLT occurred in 1 or 2 of the 3 initial patients at a particular dose level, then 3 additional patients were treated at the same dose level. If DLT developed in all 3 patients or in 3 of 6 patients, then enrollment was stopped at this dose level, which was defined as the MTD. The preceding dose level was designated as the recommended dose (RD) for the phase II portion.

2.4. Phase II portion

The primary endpoint for the phase II study was the ORR. The patients were enrolled until the number of those treated with RD, including the patients who received the RD in the phase I portion, reached the predetermined sample size. The treatment schedule used in phase I was also followed in the phase II portion.

2.5. Statistical analysis

The phase II portion was designed to detect the difference between the ORRs of 0.10 and 0.30 with more than 90% power (exact binomial test for one sample proportion, 1-sided $\alpha = 0.05$). The new regimen was to be considered worthy of further investigation if >7 responses were observed in a 37-patient cohort treated at the RD. The Kaplan–Meier method was used to estimate the median values of time-to-event variables, such as overall survival (OS) and progression-free survival (PFS), and their confidence intervals (CIs) were calculated with the Brookmeyer and Crowley method [13]. All analyses were performed with the SAS software package, version 9.1 (SAS Institute, Cary, NC).

3. Results

Forty-nine patients were enrolled from May 2005 through December 2006. The phase I portion had 22 patients. Thirty-seven patients, including 10 patients from the phase I portion who were treated with the RD level, were enrolled in phase II. The median age of all patients in the study was 77 years (range, 70–85 years). Thirty-two (65%) patients had an ECOG PS of 1, 28 (57%) patients had adenocarcinoma, and 32 (65%) patients had stage IV disease (Table 1).

3.1. MTD and DLT in the phase I portion

The phase I portion included 22 patients. At level 1, 1 of 6 patients had a DLT (grade 3 infection). Then, the dose was escalated to level 2 where 6 patients were enrolled and treated. However, 3 of them were not evaluable with regard to the DLT of TS-1/gemcitabine combination; 1 patient experienced sudden death which was unrelated to TS-1 on day 2 of the first cycle, and 2

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Table 1
Patients characteristics.

	Phase I	Phase II	Total
Number of patients	22	37	49
Age (years)			
Median	76	77	77
Range	70–85	70–85	70–85
Sex			
Male	18 (82%)	27 (73%)	37 (76%)
Female	4 (18%)	10 (27%)	12 (24%)
ECOG PS			
0	7 (32%)	14 (38%)	17 (35%)
1	15 (68%)	23 (62%)	32 (65%)
Histologic type			
Adenocarcinoma	13 (59%)	21 (57%)	28 (57%)
Other	9 (41%)	16 (43%)	21 (43%)
Stage			
IIIB	8 (36%)	12 (32%)	17 (35%)
IV	14 (64%)	25 (68%)	32 (65%)

ECOG PS, Eastern Cooperative Oncology Group Performance Status.

patients stopped the chemotherapy before the first infusion of gemcitabine (1 refused the protocol treatment, and 1 had grade 3 allergic dermatitis). The Independent Data Monitoring Committee (IDMC) reviewed the reports from investigators on these results and requested the enrollment of 3 additional patients at the level 2 cohort for the evaluation of MTD. However, in enrolling the ninth patient at the level 2, the data center had two simultaneous new registrations from two different hospitals. Therefore, a total of 10 patients were enrolled into the level 2 cohort. Seven of these patients received at least the first gemcitabine infusion and were used in the evaluation; 2 patients at this level had DLTs (1 case of grade 3 infection, 1 case of grade 3 stomatitis, and 1 case of grade 3 skin toxicity). On the basis of these results, the IDMC permitted the dose escalation to level 3. At level 3, 3 of 6 patients had DLTs (2 cases of grade 4 neutropenia, 1 case of grade 3 leukocytopenia, 1 case of grade 3 febrile neutropenia, 1 case of grade 3 infection, 2 cases of grade 3 nausea, 2 cases of grade 3 diarrhea, 2 cases of grade 3 skin toxicity, and 1 case of grade 3 dyspnea). The MTD and RD were then determined to be level 3 and level 2, respectively. Table 2 lists all adverse events observed during the phase I portion.

The eligibility criterion for the creatinine clearance rate was modified to be ≥60 mL/min in the phase II rather than the rate of ≥30 mL/min in the phase I portion because skin toxicities were more often observed in patients with a creatinine clearance rate of less than 60 mL/min.

3.2. Treatment cycle for patients treated at the RD

Of 37 patients treated at the RD level (TS-1, 60 mg/m^2/day, and gemcitabine, 1000 mg/m^2), 19 (51%) received more than 3 cycles, and 6 (16%) continued for more than 6 cycles. The median number of treatment cycles received was 3. The gemcitabine dose was reduced to 800 mg/m^2 in 5 patients.

3.3. Tumor response and overall survival in patients treated at RD

None of the 37 patients treated at the RD had a complete response (CR) and 10 had a partial response (PR). Therefore, the ORR was 27% (90% exact CI, 15–42%), and the null hypothesis for the phase II portion of the study was rejected. Fourteen patients had stable disease (SD), and 9 patients had progressive disease (PD). Four patients were not evaluable for tumor response. The median PFS time was 4.2 months (90% CI, 3.2–5.7 months). The median survival time was 12.9 months (90% CI, 10.4–14.7 months), and the 1-year survival rate was 51% (90% CI, 36–64%; Fig. 1). All patients had PD and 28 death events were observed at 2 years follow-up after the end of patient enrollment.

Table 2
All adverse events in the phase I portion[a].

Grade	Level 1 (n = 6)					Level 2 (n = 10)					Level 3 (n = 6)				
	1	2	3	4	3–4	1	2	3	4	3–4	1	2	3	4	3–4
Neutropenia	1	5	1		1	1	3	1		1		1	1	2	3
Leukopenia	2	1	1		1	3		1		1	1	2	1	1	2
Anemia		2	1		1	2	1				1	1			
Thrombocytopenia	1	1				1	1	1		1	1	2	2		2
Febril neutropenia													1		1
Infection			1		1			1		1			1		1
Billirubin	1	1				2	1				1	1			
AST/ALT	2/3					3/0	0/2				1/1				
Blood urea nitrogen	1														
Creatinine															
Na/K	1/0					1/1									
Ca	3										1				
Fever	1					1					1				
Fatigue	1					2	1						1		1
Anorexia	2					2		1		1	1	2			
Vomiting	2						1				1				
Nausea	2												2		2
Diarrhea	2										1		2		2
Constipation						2									
Skin		1					4	1		1			2		2
Stomatitis								1		1		1			
Edema	1					2									
Dyspnea	1										1		1		1
Cough	1					1	1								
Pain	1														
Allergic dermatitis								1		1					
Dose-limiting toxicity	Infection					Infection, skin, stomatitis					Neutropenia, leukocytepenia, febrile neutropenia, infection, nausea, diarrhea, skin, dyspnea				

[a] The worst grade during the first cycle was summarized. At the level 2 dose, one patient experienced death which was not drug-related.

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