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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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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 $4.0-12.0\times10^3$ mm^{-3}, platelets $\geqslant100\times10^3$ mm^{-3}, haemoglobin $\geqslant9.0$ g dl^{-1}, and absolute granulocyte count $\geqslant2.0\times10^3$ mm^{-3}), hepatic function (bilirubin $\leqslant1.5\times$ upper limit of normal, aspartate/alanine transaminase (AST/ALT) $\leqslant2.5\times$ upper limit of normal, and serum albumin $\geqslant2.5$ g dl^{-1}), renal function (serum creatinine $\leqslant$ upper limit of normal and Cockcroft and Gault creatinine clearance $\geqslant60$ ml min^{-1}), and lung function (PaO2 $\geqslant60$ torr).

Prior chemotherapy or hormone therapy was allowed if it was carried out $\geqslant14$ days before study entry ($\geqslant35$ days for nitrosourea or mitomycin-C). Previous radiotherapy was also allowed, but only if $\leqslant25\%$ of marrow was irradiated and if it was completed $\geqslant21$ 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 $\geqslant38.0$°C), grade 4 leucopenia (<1000 mm^{-3}) or neutropenia (<500 mm^{-3}) lasting $\geqslant4$ days, thrombocytopenia ($<20\,000$ mm^{-3}), or thrombocytopenia ($\geqslant20\,000$ 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	4[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	4	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.

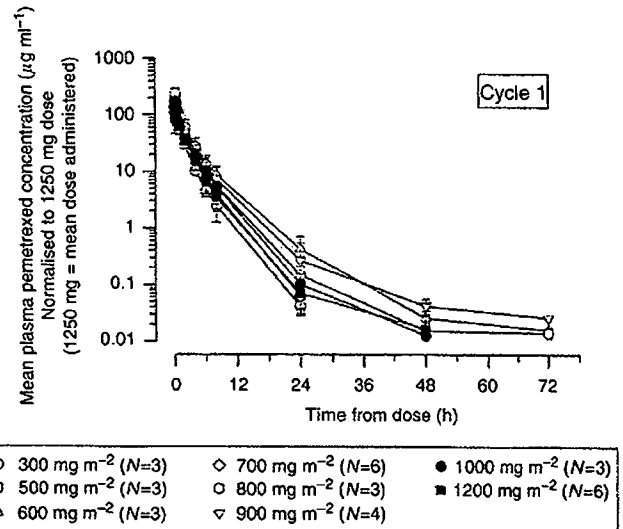

Figure 1 Mean dose-normalised pemetrexed plasma concentration–time profiles following single-dose administration in Japanese patients.

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}, ($\mu g\,ml^{-1}$)	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%)
$AUC_{0-\infty}$, ($\mu g\,h\,ml^{-1}$)	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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ORIGINAL ARTICLE

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Phase I study of weekly cisplatin, vinorelbine, and concurrent thoracic radiation therapy in patients with locally advanced non-small-cell lung cancer

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Abstract

Background. The combination of chemotherapy and thoracic radiation therapy (TRT) is considered as a standard treatment for locally advanced non-small-cell lung cancer (NSCLC). Although the frequent interaction of anticancer agents and irradiation may produce stronger radio-sensitizing effects, the daily administration of these agents is complicated. We therefore used weekly administration of these agents, and conducted a phase I study of weekly cisplatin, vinorelbine, and concurrent TRT. The purpose of this study was to identify the maximum tolerated dose (MTD), the dose-limiting toxicity (DLT), and the recommended dose of this treatment.

Methods. Patients with locally advanced NSCLC were enrolled in this study. Both cisplatin and vinorelbine were given intravenously on a weekly schedule for 6 weeks, starting on the first day of TRT, i.e., on days 1, 8, 15, 22, 29, and 36. The total dose of TRT was 60 Gy. The dose of cisplatin was fixed at 20 mg/m^2 per week. The starting dose of vinorelbine was 15 mg/m^2 per week (dose level 1).

Results. Nine patients were enrolled in this study. All three patients at dose level 1 experienced DLTs. We decreased the dose of vinorelbine to 10 mg/m^2 per week (dose level 0). Two of the six patients at dose level 0 experienced DLTs. Therefore, dose level 1 was considered as the MTD, and dose level 0 as the recommended dose. The DLTs of this treatment were esophagitis, fatigue, infection, and hyponatremia.

Conclusion. The recommended dose of cisplatin is 20 mg/m^2 per week and that of vinorelbine is 10 mg/m^2 per week with standard TRT. A phase II study of this treatment is warranted.

Key words Cisplatin · Vinorelbine · Chemoradiotherapy · Non-small-cell lung cancer

Introduction

Lung cancer is a leading cause of cancer mortality in Western industrialized countries.[1] Approximately 80% of lung cancer is of the non-small-cell histologic type, such as squamous cell carcinoma, adenocarcinoma, and large cell carcinoma. Surgery, if possible, is the mainstay of treatment for patients with non-small-cell lung cancer (NSCLC); however, the majority of NSCLC is considered as unresectable due to the local or systemic spread of the cancer. Approximately 30% of NSCLC is locally advanced, unresectable stage IIIA or IIIB disease. The American Society of Clinical Oncology (ASCO) published their guideline (update 2003) for the treatment of unresectable NSCLC.[2] This guideline recommends the following treatment for locally advanced NSCLC: chemotherapy in association with definitive thoracic irradiation is appropriate for selected patients with unresectable, locally advanced NSCLC; radiation therapy should be included as part of the treatment for selected patients with unresectable locally advanced NSCLC; and chemotherapy given to

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The results of this study were presented in part at the 43rd Annual Meeting of the Japan Lung Cancer Society in Fukuoka, Japan, November 21–22, 2002.

NSCLC patients should be a platinum-based combination regimen.

The combination of cisplatin and vinorelbine is more effective than single-agent cisplatin, or cisplatin plus vindesine, for advanced NSCLC.[3,4] Furthermore, some randomized trials have shown that cisplatin plus vinorelbine is as effective as carboplatin plus paclitaxel, cisplatin plus gemcitabine, or cisplatin plus irinotecan.[5–7] Therefore, the cisplatin plus vinorelbine combination is considered as one of the standard platinum-based chemotherapy regimens.

There are two possible advantages of the combination of chemotherapy and radiation therapy. One is spatial cooperation (which means that radiation is effective against the loco-regional tumor, and chemotherapy eradicates micrometastases independently) and the other is the radiosensitizing effects.[8–10] Cisplatin is one of the anticancer agents whose radio-sensitizing effects have been studied extensively, and many preclinical studies have shown that cisplatin enhanced the cytotoxic effects of irradiation.[11] The European Organization for Research and Treatment of Cancer (EORTC) performed a randomized trial comparing the following three arms: thoracic radiation therapy (TRT) alone, TRT combined with weekly cisplatin, and TRT combined with daily cisplatin, for locally advanced NSCLC.[12] The survival rate was 54% at 1 year, 26% at 2 years, and 16% at 3 years for the TRT+daily-cisplatin group, as compared with 44%, 19%, and 13% for the TRT+weekly-cisplatin group, and 46%, 13%, and 2% for the TRT-alone group, respectively. The EORTC concluded that TRT+daily cisplatin had the greatest survival benefit of the three treatment arms and this benefit was due to the improvement of local control. On the other hand, some preclinical studies have shown that vinorelbine also had radio-sensitizing effects.[13–15] Vinorelbine is a potent inhibitor of mitotic microtubule polymerization, and this effect synchronizes cells at the G2/M phase of the cell cycle. This phase is considered as the most radio-sensitive phase: thus, vinorelbine can exhibit radio-sensitizing effects.

Although the frequent interaction of anticancer agents and irradiation may produce stronger radio-sensitizing effects, daily administration of these agents is complicated. Weekly administration is more convenient than daily administration. Therefore, we conducted a phase I study of weekly cisplatin, vinorelbine, and concurrent TRT for locally advanced NSCLC. The purpose of this study was to identify the maximum tolerated dose (MTD), the dose-limiting toxicity (DLT), and the recommended dose of this treatment.

Patients and methods

Eligibility criteria

Patients with histologically or cytologically confirmed locally advanced NSCLC were enrolled in this study. All patients were deemed suitable for definitive TRT by a radiation oncologist (T.T.). Other eligibility criteria included the following: age, 20 years or older; Eastern Cooperative Oncology Group (ECOG) performance status, 0 or 1; unresectable stage IIIA or IIIB; absence of malignant pleural or pericardial effusion; absence of involvement of contralateral hilar lymph nodes; no prior chemotherapy or TRT; adequate bone marrow function (leukocyte count ≥4000/μl, neutrophil count ≥2000/μl, hemoglobin level ≥10 g/dl, and platelet count ≥100000/μl), renal function (creatinine level ≤ upper limit of normal and creatinine clearance ≥50 ml/min), hepatic function (aspartate aminotransferase/alanine aminotransferase [AST/ALT] ≤ twice upper limit of normal and bilirubin level ≤ upper limit of normal), and pulmonary function (arterial partial pressure of oxygen [PaO_2] ≥70 mmHg); absence of interstitial pneumonitis or pulmonary fibrosis, or other serious illnesses; and no pregnancy or lactation. Written informed consent was obtained from all patients. This protocol was approved by the institutional review board of Osaka Prefectural Medical Center for Respiratory and Allergic Diseases. All patients received the protocol treatment at the same institution.

Chemotherapy

Both cisplatin and vinorelbine were given intravenously on a weekly schedule for 6 weeks, starting on the first day of TRT, i.e., on days 1, 8, 15, 22, 29, and 36 (Fig. 1). The doses of cisplatin and vinorelbine are described later. Cisplatin was administered as a 60-min infusion with adequate hydration (at least 1000 ml of fluid). Antiemetic drugs, such as 5-hydroxytryptamine type 3 (5-HT_3) receptor antagonists and dexamethasone 8 mg, were given intravenously before the administration of cisplatin. Vinorelbine was administered as a 5-min infusion. The minimum requirements for the administration of cisplatin and vinorelbine were as follows: leukocyte count 2000/μl or more, neutrophil count 1000/μl or more, platelet count 50000/μl or more, nonhematological toxicity grade 2 or less, and no suspension of TRT.

Subsequently, consolidation chemotherapy was given, starting 1 week after the completion of irradiation. If creatinine clearance was 60 ml/min or greater, cisplatin 80 mg/m^2 was given intravenously as a 60-min infusion on day 1 and vinorelbine 20 mg/m^2 was given intravenously as a 5-min infusion on days 1 and 8 of a 3-week cycle. Standard hydration and antiemetics were also given. If creatinine clearance was less than 60 ml/min, vinorelbine 25 mg/m^2 was given intravenously as a 5-min infusion on days 1, 8, and 15 of a 4-

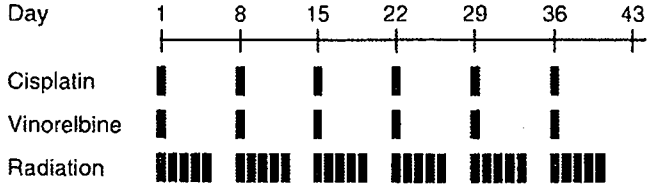

Fig. 1. Treatment schedule of weekly cisplatin, vinorelbine, and concurrent thoracic radiation therapy

week cycle. The minimum requirements for the initiation of consolidation chemotherapy were as follows: leukocyte count 4000/μl or more, neutrophil count 2000/μl or more, platelet count 100000/μl or more, and nonhematological toxicity grade 2 or less.

During the entire treatment period, granulocyte colony-stimulating factor (G-CSF) support was used if the leukocyte count was below 1000/μl, neutrophil count was below 500/μl, or febrile neutropenia (<1000/μl) was noted.

TRT

TRT was delivered concurrently with weekly chemotherapy, starting on day 1. The prescribed dose was 60 Gy in 30 fractions (2.0 Gy per fraction) over 6 weeks. Irradiation was performed with 10-MV photons from a linear accelerator. The radiation field was defined as the area that contained the primary tumor, a margin of 15 mm, the bilateral upper mediastinal lymph nodes, the subcarinal lymph nodes, and the enlarged regional lymph nodes. After initial irradiation at a dose of 40 Gy, off-cord (i.e., the spinal cord was outside the field) oblique boost fields were used. The boost field contained the same lymph nodes as the initial field. No correction for lung attenuation was made.

TRT was suspended if any of the following toxicities was noted: leukocyte count less than 1000/μl, neutrophil count less than 500/μl, febrile neutropenia (<1000/μl), platelet count less than 10000/μl, thrombopenia requiring platelet transfusion, esophagitis grade 3 or more, or pneumonitis grade 1 or more.

Toxicity and response evaluation

A complete medical history was obtained, and physical examination was performed. Staging procedures consisted of chest X-ray; computed tomographic (CT) scans of the chest, brain, and upper abdomen; bone scintigraphy; and bronchoscopy. The following laboratory tests were carried out: complete blood count (CBC) with differential count of leukocytes, blood biochemistry, tumor marker, arterial blood gas analysis, urinalysis, electrocardiogram, and pulmonary function test.

During the treatment, the following tests were performed: CBC, twice a week; blood biochemistry, arterial blood gas analysis (during TRT), urinalysis, and chest X-ray, once a week; and chest CT scan for response evaluation, once a month.

Toxicity was graded according to the National Cancer Institute-Common Toxicity Criteria version 2, published in 1998.[16] In this study, we defined DLTs as the following toxicities; leukocyte count less than 1000/μl, neutrophil count less than 500/μl, febrile neutropenia (<1000/μl), platelet count less than 10000/μl, thrombopenia requiring platelet transfusion, nonhematological toxicity of grade 3 or more (except for nausea and vomiting), or any toxicity that required treatment interruption lasting more than 2 weeks.

Response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST).[17] A complete response (CR) was defined as the disappearance of all target lesions. A partial response (PR) was defined as at least a 30% decrease in the sum of the longest diameters of target lesions for at least 4 weeks without the appearance of new lesions. Progressive disease (PD) was defined as at least a 20% increase in the sum of the longest diameters of target lesions, or the appearance of one or more new lesions. Stable disease (SD) was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

The survival curve was drawn using the Kaplan-Meier method.[18]

Table 1. Dose setting

Dose level	Cisplatin (mg/m^2 per week)	Vinorelbine (mg/m^2 per week)
0	20	10
1	20	15
2	20	20

Dose setting

Commonly, cisplatin is administered at 80 mg/m^2 every 3 or 4 weeks for advanced NSCLC, so the dose of cisplatin was fixed at 20 (= 80/4) mg/m^2 per week. We planned the dose escalation of vinorelbine, of which the starting dose was 15 mg/m^2 per week (dose level 1) with a 5 mg/m^2 per-week increment (Table 1). Three patients were treated initially at the starting dose level. If no patients experienced a DLT, the dose of vinorelbine was to be escalated. If one or two patients experienced a DLT, three additional patients were to be enrolled at the same dose level. If one or two of the six patients experienced a DLT, dose escalation was to be continued. If three or more patients experienced a DLT, that dose was to be considered as the MTD. The recommended dose was defined as the dose that immediately preceded the MTD. Although our plan was to carry out a dose-escalation study, as described above, the dose of vinorelbine was actually reduced, due to unacceptable toxicity. Details are described later.

For the patients who experienced a DLT, the dose of subsequent chemotherapy was reduced by one dose level or omitted if they had been given dose level 0.

Results

Patient characteristics

From March 2001 to April 2002, nine patients were enrolled in this study. Patient characteristics are listed in Table 2. The study population consisted of eight men and one woman with a median age of 59 years. The majority had a performance status of one. There were four patients with stage IIIA disease and five with stage IIIB. The histologic

Table 2. Patient characteristics

Characteristic	No. (%) [$n = 9$]
Sex	
Male	8 (89)
Female	1 (11)
Age, years	
Median	59
Range	48–68
Weight loss, %	
≤10	8 (89)
>10	1 (11)
Performance status (ECOG)	
0	1 (11)
1	8 (89)
Stage	
IIIA	4 (44)
IIIB	5 (56)
Histology	
Adenocarcinoma	3 (33)
Squamous cell carcinoma	6 (67)

Table 3. Toxicity profile

Toxicity	Dose level 1 ($n = 3$)				Dose level 0 ($n = 6$)			
	Grade				Grade			
	1	2	3	4	1	2	3	4
Hematological								
Leukocytes	1	1	0	0	0	3	3	0
Neutrophils	0	1	0	0	1	3	2	0
Hemoglobin	2	1	0	0	4	2	0	0
Platelets	1	0	0	0	0	0	0	0
Nonhematological								
Esophagitis	0	0	3	0	3	2	0	0
Fatigue	1	2	0	0	1	0	2	0
Infection	0	0	0	0	0	0	2	0
Febrile neutropenia	0	0	0	0	0	0	0	0
Hyponatremia	2	0	0	0	0	0	2	0
Pneumonitis (acute)	0	0	0	0	1	0	0	0
Pneumonitis (late)	0	1	0	0	1	3	0	0
AST/ALT	1	1	0	0	2	0	0	0
Creatinine	0	0	0	0	0	0	0	0
Nausea	1	0	1	0	0	2	2	0
Vomiting	0	0	1	0	0	0	0	0

type was adenocarcinoma in three patients, and squamous cell carcinoma in six. The weight loss of all but one patient was less than 10%.

Toxicity

First, we treated three patients at dose level 1, and all of them experienced grade 3 esophagitis. Therefore we decreased the dose of vinorelbine to dose level 0. One of the three patients at dose level 0 experienced grade 3 fatigue, infection, and hyponatremia. Three additional patients were enrolled at the same dose level. One of the three additional patients also experienced grade 3 fatigue, infection, and hyponatremia. Esophagitis, fatigue, infection, and hyponatremia were considered as the DLTs. All three patients at dose level 1 and two of the six patients at dose level 0 experienced DLTs. Therefore, dose level 1 was considered as the MTD, and dose level 0 as the recommended dose. Other nonhematological toxicities, such as pneumonitis, hepatic dysfunction, and nausea and vomiting, were mild to moderate. Hematological toxicity was not severe in any patients. No treatment-related death occurred. The toxicity profile is summarized in Table 3.

Treatment delivery

In the four patients without DLT and one with DLT, weekly chemotherapy and TRT were administered according to the planned dosing schedule. In four patients with DLT, dose reduction or omission of chemotherapy was necessary. In three patients with DLT, TRT was completed with an interruption of 10 to 13 days. In one patient with DLT, TRT was discontinued at 54 Gy.

Consolidation chemotherapy was administered in seven patients. All received the combination of cisplatin and vinorelbine. In six of the seven patients, the initiation of consolidation chemotherapy was delayed due to esophagitis, leukopenia, or neutropenia.

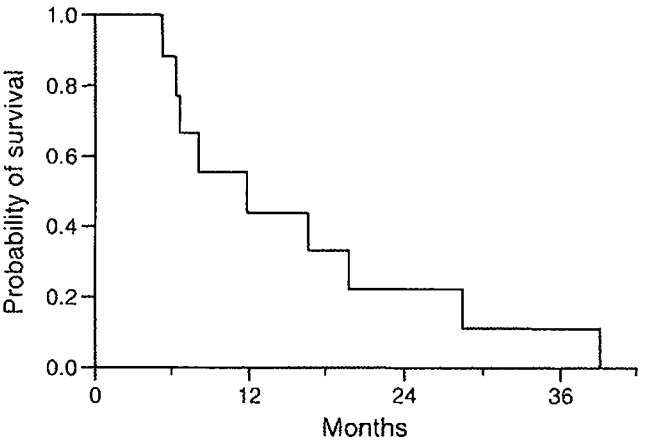

Fig. 2. Overall survival

Response and survival

There were five PRs and no CRs, with a response rate of 56% (95% confidence interval, 21% to 86%). All three patients at dose level 1 and two of the six patients at dose level 0 responded.

All patients were followed up to death. The median overall survival was 11.9 months, with a 1-year survival rate of 44% (Fig. 2). The median time to progression was 7.8 months. The initial relapse site was local progression in six patients and distant metastasis in three.

Discussion

Some randomized trials and meta-analyses have shown that the combination of chemotherapy and TRT has survival benefits compared with TRT alone for locally advanced NSCLC.[12,19–26] However, long-term survival was rare, with a median survival of 12 to 13.7 months and a 5-year survival rate of only 8% to 17%.

The West Japan Lung Cancer Group conducted a phase III study to compare concurrent chemoradiotherapy with sequential therapy.[27] The chemotherapy consisted of cisplatin, vindesine, and mitomycin, and TRT delivered a total of 56 Gy. The median survival in the concurrent arm was significantly longer than that in the sequential arm (16.5 versus 13.3 months). The Radiation Therapy Oncology Group (RTOG) and a Czech group conducted similar randomized trials and confirmed the superiority of the concurrent therapy over the sequential therapy.[28,29] Furthermore, Choy et al.[30] conducted a randomized phase II study of three regimens: sequential chemoradiotherapy versus induction chemotherapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy followed by consolidation chemotherapy: this was the so-called locally advanced multimodality protocol (LAMP) study. They used the combination of paclitaxel, carboplatin, and TRT. The median survival was 12.5 months for the sequential arm, 11 months for the induction/concurrent arm, and 16.1 months for the concurrent/consolidation arm. These results suggested that concurrent chemoradiotherapy, or possibly concurrent chemoradiotherapy followed by consolidation chemotherapy, was the most effective treatment in patients with locally advanced NSCLC. However, it is undetermined what regimen or what schedule is optimal for chemoradiotherapy.

Several schedules and doses of cisplatin, vinorelbine, and concurrent TRT have been reported. Masters et al.[31] recommended that cisplatin should be administered at 80 mg/m^2 on day 1 and vinorelbine at 15 mg/m^2 on days 1 and 8 every 3 weeks with standard TRT. After that, the Cancer and Leukemia Group B (CALGB) performed a randomized phase II study of cisplatin with gemcitabine or paclitaxel or vinorelbine as induction chemotherapy followed by concomitant chemoradiotherapy.[32] In the cisplatin-vinorelbine arm, the doses reported by Masters et al.[31] were used, and the CALGB concluded that induction chemotherapy followed by concomitant chemoradiotherapy was feasible, with the observed survival rates exceeding those of previous CALGB trials for all treatment arms. Sekine et al.[33] conducted a phase I study and reported that the recommended dose of cisplatin was 80 mg/m^2 on day 1 and that of vinorelbine was 20 mg/m^2 on days 1 and 8 every 4 weeks with TRT including a 4-day interval. The Czech group[29] used the following schedule and dose: cisplatin 80 mg/m^2 on day 1 and vinorelbine 12.5 mg/m^2 on days 1, 8, and 15 every 4 weeks with standard TRT starting on day 4.

Although the frequent interaction of anticancer agents and irradiation may produce stronger radio-sensitizing effects, there has been no report of a weekly schedule to date. Therefore we conducted a phase I study of weekly cisplatin and vinorelbine with standard TRT. The studies described above[29,31–33] reported that esophagitis and neutropenia were the major toxicities. The present study showed that the DLTs of our regimen were esophagitis, fatigue, infection, and hyponatremia. All patients at dose level 1 experienced grade 3 esophagitis, so this dose was considered an overdose. The strong radio-sensitizing effects may have resulted in the severe esophagitis. On the other hand, no severe neutropenia was observed. The recommended dose of cisplatin is 20 mg/m^2 per week and that of vinorelbine is 10 mg/m^2 per week in the present study.

The response rate and the median overall survival in this study were 56% and 11.9 months, respectively. Some concurrent chemoradiotherapy studies have reported better results, with response rates of 63% to 85% and median overall survivals of 11 to 18.3 months.[12,27–30,32] As our study had a very small sample size, of only nine patients, we cannot draw conclusions on the efficacy of this treatment from our present results.

In conclusion, our phase I study of weekly cisplatin, vinorelbine, and concurrent TRT showed that the DLTs of this treatment were esophagitis, fatigue, infection, and hyponatremia. The recommended dose of cisplatin is 20 mg/m^2 per week and that of vinorelbine is 10 mg/m^2 per week, i.e., on days 1, 8, 15, 22, 29, and 36, with standard TRT. We believe a phase II study of this treatment is warranted.

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ORIGINAL ARTICLE

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Phase I/II study of weekly docetaxel dose escalation in combination with fixed weekly cisplatin and concurrent thoracic radiotherapy in locally advanced non-small cell lung cancer

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Abstract *Purpose*: We conducted a phase I study to determine the maximum-tolerated dose (MTD) and dose-limiting toxicities (DLT) of weekly docetaxel and cisplatin (DOC/CDDP) with concurrent thoracic radiotherapy (TRT) in patients with unresectable stage III non-small-cell lung cancer (NSCLC). *Materials and methods*: The DOC/CDDP administration schedules consisted of a split schedule (SS) with administration in 3 out of every 4 weeks, and a continuous schedule (CS) with administration every week. TRT was given to a total dose of 60 Gy at 2 Gy per fraction over 6 weeks. *Results*: Twenty-one patients entered the study. The patient characteristics were: PS 0/1/2, 6/13/2; Sq/Ad, 16/5; stage IIIA/IIIB, 4/17. The principal DLT was grade3 esophagitis. The MTD of DOC on the SS and CS in combination with CDDP (25 mg/m2/week) was 25 and 20 mg/m^2/week, respectively. We determined the RD and schedule of DOC/CDDP on the SS to be 20/25 mg/m^2/week. The serum α-1-acid glycoprotein (AAG) concentration values were found to be negatively correlated with the grade of esophagitis. The median survival time was 23.1 months. *Conclusion*: The chemoradiation regimen tested in this study has promising activity and manageable toxicity. The continuous schedule could not be recommended due to excessive toxicity. The main DLT was esophagitis, and it significantly correlated with the plasma AAG concentration.

Keywords Docetaxel · Cisplatin · Chemoradiation · AAG

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Introduction

Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancers, and although surgery offers the best chance of cure and long-term survival, only a small percentage of patients present with resectable disease. In fact, 25–30% of patients with NSCLC present with locally or regionally advanced unresectable tumors. Chest irradiation with modern megavoltage equipment plays a critical role in the treatment of these patients, since it assures good local control of the tumor in most patients. However, the development of distant metastases also affects their prognosis, and the addition of chemotherapy to thoracic radiation therapy (TRT) has been proposed in an attempt to reduce the risk of distant metastases.

Recent studies support the benefit of combined modality therapy in stage III NSCLC. The results of randomized studies that used sequential or concomitant chemotherapy for unresectable non-small cell lung cancer have shown significant differences in survival, local control rates, and distant metastasis rates for chemoradiotherapy over radiotherapy alone [1–5], and a recent meta-analysis of all randomized trials that compared TRT alone with the combined approach showed an unequivocal, although modest, survival advantage when cisplatin-based chemotherapy was added to TRT [6]. Concomitant chemoradiotherapy offers the potential advantage of synergistic interactions for local control

and the added possibility of direct antitumor activity [4, 5]. More recently, there has been accumulating phase III evidence that concomitant chemoradiotherapy probably yields higher response rates and survival in patients with stage III disease [7, 8].

Several novel agents with remarkable radiosensitizing properties have recently been introduced in clinical practice. In preclinical studies the taxanes were found to be potent radiation-enhancers by virtue of their ability to cause cell cycle arrest in the radiosensitive G2/M phase [9, 10]. Preclinical studies further illustrated the taxanes' radiosensitizing effect in tumor-cell lines, with docetaxel exhibiting an effect ten times that of paclitaxel at equimolar concentrations [11]. Four phase I trials of docetaxel and concurrent radiation have been reported [12–15]. Mauer et al. [12] and Koukourakis et al. [14] conducted phase I trials of weekly docetaxel with concurrent thoracic radiotherapy and determined that the maximum-tolerated dose (MTD) of weekly docetaxel was 20–30 mg/m^2 with thoracic radiation. The dose-limiting toxicities (DLTs) were esophagitis and neutropenia. The phase II studies of docetaxel [16, 17] and thoracic radiotherapy have shown an encouraging, high response, but an increased incidence of esophagitis and asthenia was observed.

The use of low daily doses of cisplatin concomitantly with RT seems to be of particular interest, since clear synergism has been demonstrated in vitro [18]. In a European Organization for Research and Treatment of Cancer (EORTC) study, daily administration of cisplatin proved to be more effective than a weekly schedule in potentiating the local tumor control achievable with RT alone, although the difference between the two schedules were not statistically significant [4].

In view of these considerations, we planned this phase I study. The objectives of this study were to determine the MTD, recommended dose (RD) and DLT of cisplatin and docetaxel when given weekly concomitantly with conventional TRT, and evaluate the efficacy of this regimen.

Moreover, since it has reported that serum α-1-acid glycoprotein (AAG) combined with docetaxel extensively [19] and that the AAG levels were significantly associated with time to progression in NSCLC patients and febrile neutropenia [20]. The AAG levels were significantly associated with the toxicity of docetaxel because AAG strongly binds docetaxel in serum. Thus, we examined the relationship between serum AAG level and major toxicities in this regimen.

Patients and methods

Patient eligibility

Previously untreated patients with histologically or cytologically documented inoperable stage IIIA or IIIB NSCLC were eligible for this study. Patients with malignant pleural effusion or any disease that required irradiation of more than half of the hemithorax were ineligible. Other eligibility criteria included: (1) age less than 75, (2) Eastern Cooperative Oncology Group performance status equal to or less than 2, (3) evaluable or measurable disease, (4) no prior therapy, (5) adequate bone marrow function (leukocyte count ≥4,000/mm^3, platelet count ≥100,000/mm^3, hemoglobin ≥9.5 g/dl), renal function (serum creatinine ≤ 2.0 mg/dl), hepatic function (AST/ALT ≤ 2.5 times upper limit of normal, serum bilirubin ≤ 1.5 mg/dl), and pulmonary function (arterial blood gases PaO2 ≥70 mmHg), (6) absence of active infection, heart failure, or acute myocardial infarction within 3 months before study entry, no serious medical or psychiatric illness. All patients signed an informed consent form that was approved by each of the institutional review boards. Before entry into the study, all patients underwent an evaluation that consisted of a complete history and physical examination, chest X-ray, chest and upper abdomen (to include the liver and adrenals) computed tomography (CT) scan, brain CT or MRI, and a bone scan.

Chemotherapy

The treatment regimens are outlined in Fig. 1. The study was designed to fix the cisplatin dose at 25 mg/m^2/week and escalate docetaxel dose. The docetaxel and cisplatin administration schedules were: split schedule (SS), 3 out of every 4 weeks (day 1, 8, 15, 29, 36, and 43), continuous schedule (CS), weekly (day 1, 8, 15, 22, 29, 36). Docetaxel was administered as an intravenous (IV) infusion over 30 min and followed by cisplatin given as an IV infusion over 30 min. The participating investigators at each institution were allowed to decide the volume of fluid replacement and the antiemetic therapy to be administered, but adequate amounts of parenteral fluid and diuretics were given in order to prevent the renal toxicity of cisplatin. The patients did not receive steroids due to prevention of a hypersensitivity reaction. The starting dose of docetaxel was 20 mg/m^2/week, and the docetaxel dose was increased by 5 mg/m^2/week. There was no dose escalation in individual patients, and administration of cisplatin and docetaxel was cancelled if the leukocyte count fell below 2,000/mm^3 or any DLTs occurred.

At first, we planed only sequential schedule. However, as we thought that continuous schedule had a stronger radiosensitizing effect compared with sequential schedule, we amended protocol and added continuous schedule. After the MTD and RD of SS had been determined, we treated with CS using the RD of SS.

Thoracic radiation

Thoracic radiation therapy of 60 Gy in 2.0 Gy fractions was given concurrently with weekly docetaxel and

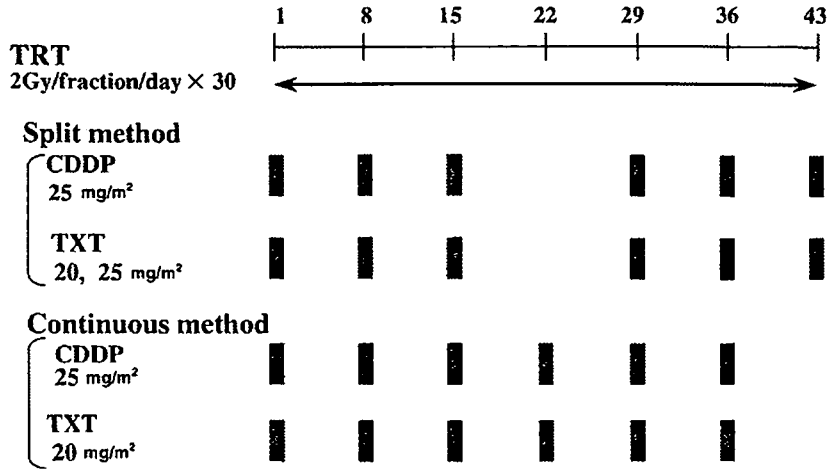

Fig. 1 Treatment regimens for weekly docetaxel and cisplatin concomitant with TRT

cisplatin infusion for 6 weeks. A 6- or 10-MV linear accelerator was used. Two-dimensional treatment planning of TRT was performed by conventional X-ray simulators. Inhomogeneity correction for lung tissues was not done. The initial planning target volume (PTV) consisted of the primary tumor, ipsilateral hilar nodes, and superior mediastinal nodes with 1–1.5 cm margin. If metastasis to supraclavicular nodes were found, they were also included in the initial PTV. This initial large field was treated by parallel-opposed anterior and posterior fields to 40 Gy in 20 fractions. The widths and lengths of the initial fields with appropriate trimming ranged from 10.5 to 16 cm (median; 14 cm) and 10.5–20 cm (median; 16 cm), respectively. After 40 Gy, oblique parallel-opposed fields were used to exclude the spinal cord. The angles of the oblique fields ranged from 15° to 45° with a median of 40°. In the boost fields, the primary tumors and the involved nodes were included with a margin of 0.5–1.5 cm. The total dose to the boost field was 60 Gy in 30 fractions. In the present study, patients were excluded if the initial radiation field exceeded half of the ipsilateral lung. However, no dose constraints on the normal tissues including the percentage of pulmonary volume irradiated to > 20 Gy (V20) or esophageal length was determined, as three-dimensional treatment planning using a CT-simulator was not available.

If grade 4 hematologic toxicity occurred during the course of TRT, it was suspended and restarted after recovery to grade 3 or less. If grade 3 or greater esophagitis occurred and the physician decided that the TRT could not be continued, it was suspended and restarted after recovery to grade 2 or less. If PaO_2 fell to 10 torr and a patient had a fever of 38°C or higher, both TRT and chemotherapy were suspended and restarted immediately after recovery.

Definition of MTD, RD and DLT

Maximum-tolerated dose was defined as the dose level at which DLT occurs in more than 50% of the patients treated, and the preceding dose level was defined as RD. At least six patients were entered at each dose level. DLT was defined as grade 4 leukopenia or neutropenia lasting 3 days or more, a platelet count of ≤ 20,000/mm^3, febrile neutropenia and grade 3 or greater non-hematologic toxicities other than nausea and vomiting. Suspension of docetaxel and cisplatin two or more times was also considered as a DLT.

Response evaluation and survival analysis

The criteria for assessing the response to treatment were as follows. Complete response (CR) was defined as total disappearance of all clinically detectable lesions for at least 4 weeks. Partial response (PR) was defined as a reduction of 50% or more in the sum of the products of the cross-sectional diameters of all measurable lesions for at least 4 weeks, without the development of new lesions. Stable disease (SD) was defined as a reduction of less than 50% or an increase of less than 25% in the sum of the products of the cross-sectional diameters of all measurable lesions, with no clear evidence of either regression or progression for at least 6 weeks. Progressive disease (PD) was defined as an increase of 25% or more 25% in the sum of the products of the cross-sectional diameters of all measurable lesions, together with an increase of assessable disease or the appearance of new lesions. Survival time was defined as the interval between the date of the start of treatment and the date of death due to any cause or the most recent follow-up evaluation. The survival curves were estimated by the Kaplan–Meier method.

Statistical analysis

The *T*-test was used to examine the relationship between serum AAG values and the categorical endpoints of major toxicities, such as grade of esophagitis. A *P*-value of 0.05 or less was considered statistically significant.

Results

Patient characteristics

Between April 1999 and April 2000, 21 patients were enrolled in the study, and their characteristics are listed in Table 1. All patients were eligible for evaluation of efficacy, but one who enrolled at a docetaxel dose of 20 mg/m^2/week in SS was excluded from the evaluation of toxicity because chemotherapy was suspended due to exacerbation of a gastric ulcer. That patient experienced no DLT. The 19 men and 2 women enrolled in the study had a median age of 65 (range: 51–75). Most patients had squamous cell carcinoma (n=16: 76%) and stage IIIB disease (n=17: 81%). Median performance status was 1 (range: 0–2), while only two patients had a performance status of 2.

Dose escalation

The DLTs encountered at each dose level are listed in Table 2. On the SS, six and seven patients were evaluable for toxicity at docetaxel doses of 20 and 25 mg/m^2/week, respectively. Two of the six patients at the 20 mg/m^2/week dose experienced DLTs consisting of grade 3 esophagitis in one patient and cancellation of chemotherapy twice because of grade 3 leukopenia in the other. At the 25 mg/m^2/week dose, four of the seven patients developed DLTs consisting of grade 3 esophagitis in two patients, grade 3 fatigue in one, and febrile neutropenia in one. Accordingly, the MTD and RD on the SS were concluded to be a dose of docetaxel 25 and 20 mg/m^2/week, respectively. The next cohort of patients was treated with a docetaxel dose of 20 mg/m^2/week in CS. However, four of the seven patients developed DLTs, consisting of grade 3 esophagitis in two patients, grade 3 fatigue in one patient, and cancellation of chemotherapy twice because of grade 3 neutropenia in one patient. Finally, we concluded that the dose level 1 in SS was the recommended dose for further study of this therapy.

Table 1 Patient characteristics

Characteristic	Number of patients
Total number of patients	21
Assessable for toxicity	20
Assessable for survival and response	21
Age, years	
Median (range)	65 (51–75)
Sex	
Male	19
Female	2
Performance status	
0	6
1	13
2	2
Histology	
Squamous cell carcinoma	16
Adenocarcinoma	5
Stage	
IIIA	4
IIIB	17

Toxicity

Hematologic and non-hematologic toxicities are summarized in Table. 3 and 4. Twenty patients could be assessed for toxicities. The hematologic toxicities were mild, and there were no grade 4 hematologic toxicities. Grade 3 neutropenia, decrease in hemoglobin, and thrombocytopenia were observed in 6 patients (30%), 6 patients (30%), and 1 patient (5%), respectively. Febrile neutropenia developed in only one patient, and it occurred at the 25 mg/m^2/week dose of docetaxel.

The principal toxicity on this regimen was esophagitis. Grade 2 or higher esophagitis occurred in 12 of the 20 (60%) patients enrolled, and in 5 cases (25%) it was of grade 3 and caused suspension of treatment in 2 patients and permanent discontinuation of treatment in one patient at 52 Gy. Another dose-limiting non-hematologic toxicity was grade 3 fatigue which occurred in one patient each at 25 mg/m^2/week dose of docetaxel on the SS and at the 20 mg/m^2/week dose of docetaxel on the CS. Other non-hematologic toxicities were mild and never greater than grade 2. Grade 2 nausea and pneumonitis occurred in five patients and two patients, respectively. No hypersensitivity reactions occurred. There were no treatment related deaths.

Treatment delivery

A total of 110 chemotherapy cycles were administered to 20 patients at three dose levels. Ten (9%) of the planned doses were omitted. The ratio of actual dose intensity to planned dose intensity of docetaxel and cisplatin at 20 and 25 mg/m^2/week docetaxel dose levels on the SS and at the 20 mg/m^2/week docetaxel dose level on the CS was 0.95, 0.93, and 0.88, respectively. A TRT dose of 60 Gy was administered to 18 of 20 (90 %) patients. TRT at the 25 mg/m^2/week dose of docetaxel on the SS and the 20 mg/m^2/week of docetaxel on the CS each one patient was discontinued at 58 and 52 Gy, respectively, because of grade 3 esophagitis.

Response and survival

Table 5 shows the responses observed at each dose level. All 21 patients enrolled were evaluable for response. CR was observed in 5 of the 21 (24%) patients, PR in 14 (67%) and SD in 1 (5%). The overall response rate was 90% (95% confidence interval: 69.6–98.8%). No significant differences in response were observed between the three dose levels of docetaxel.

Table 2 Dose limiting toxicity

Dose of docetaxel	Assessable patients	Dose limiting toxicitiy
Split schedule		
20 mg/m^2	6	2 1: Grade 3 esophagitis1: 2 times cancellation of chemotherapy due to grade 3 leukopenia
25 mg/m^2	7	4 2: Grade 3 esophagitis1: Grade 3 fatigue1: Febrile neutropenia
Continuous schedule		
20 mg/m^2	7	4 2: Grade 3 esophagitis1: Grade 3 fatigue1: 2 times cancellation of chemotherapy due to grade 3 neutropenia

Table 3 Hematologic toxicity

Dose level of docetaxel	No. of patients	ANC		Febrile neutropenia	Hb		Platelet	
		Grade			Grade		Grade	
		3	4		2	3	2	3
Split schedule								
20 mg/m^2	6	0	0	0	1	2	0	0
25 mg/m^2	7	2	0	1	3	2	1	1
Continuous schedule								
20 mg/m^2	7	4	0	0	2	2	0	0

ANC absolute neutrophil count, *Hb* hemoglobin

Figure 2 shows the overall survival for all 21 patients enrolled in the study; 16 patients (76%) had died at the time of the analysis. All survivors had a follow-up time of 30 months. Based on the Kaplan–Meier method, the 1-, 2-, and 3-year overall estimated survival rates were 71.4, 42.9, and 32.7%, respectively. The median overall survival time was 23.1 months.

Relationship between esophagitis and plasma AAG levels

The principle toxicity on this regimen was esophagitis. Another DLT, grade 3 fatigue occurred in only two patients, and hematologic toxicity was mild. We, therefore, examined the relationship between plasma AAG levels and grade of esophagitis. Plasma AAG was measured in 12 patients prior to the start of the treatment, and the baseline AAG level of the patients who experienced grade 2 or 3 esophagitis was significantly higher ($P=0.04$) than that of the patients who experienced grade 0 or 1 esophagitis (grade 0/1, mean AAG level = 168 pg/ml vs. grade 2/3, mean AAG level = 83 pg/ml: Fig. 3).

Discussion

We conducted a phase I study of cisplatin and docetaxel administered in weekly infusions concomitant with conventional TRT in patients with unresectable stage IIIA/IIIB NSCLC. This is the first study that examined schedule and dose of weekly docetaxel in combination fixed dose of cisplatin 25 mg/m^2 concomitant with TRT. The recommended dose and schedule were determined to be cisplatin 25 mg/m^2 and docetaxel 20 mg/m^2 on days 1, 8, 15 of every 4 weeks, respectively. Esophagitis and neutropenia were by far the severest toxicities in this

Table 4 Non-hematologic toxicity

Dose level of docetaxel	No. of patients	Esophagitis		Fatigue		Nausea		Pneumonitis	
		Grade		Grade		Grade		Grade	
		2	3	2	3	2	3	2	3
Split schedule									
20 mg/m^2	6	3	1	0	0	2	0	1	0
25 mg/m^2	7	1	2	0	1	1	0	1	0
Continuous schedule									
20 mg/m^2	7	3	2	1	1	2	0	0	0

Table 5 Response at each dose level

Dose level of docetaxel	No. of patients	Response				Response rate
		CR	PR	SD	PD	
Split schedule						
20 mg/m^2	7	2	5	0	0	7/7100%
25 mg/m^2	7	2	5	0	0	7/7100%
Continuous schedule						
20 mg/m^2	7	1	4	1	0	5/771%
Total	21	5	14	1	1	19/2190%

study, while pulmonary toxicity was almost nonexistent. The pulmonary toxicity associated with concurrent chemoradiotherapy using third generation anticancer agents is frequently serious and fatal. When cisplatin and paclitaxel were combined with concurrent TRT, grade 3 or more late lung toxicity in 20%, including grade 5 in 8% was reported [21]. The incidence of grade 3 or more pulmonary toxicity in the studies of cisplatin and docetaxel concomitant with TRT has been low. Grade 3 pneumonitis occurred in 4.8% of patients in the study by Kiura et al. [22], and no grade 3 or more pulmonary toxicity was reported by Wu et al. [23].

Wu et al. [23] conducted a phase I study of weekly docetaxel and cisplatin concomitant with thoracic radiotherapy in stage III NSCLC and reported that the recommended dose was docetaxel 20 mg/m^2 plus cisplatin 20 mg/m^2 weekly. This dose is almost the same as in our study, but the dose intensity of docetaxel at the recommended dose was slightly lower in our study (docetaxel: 14 mg/m^2/week) than in the Wu study (docetaxel: 20 mg/m^2/week). The reason for this difference may be the dose of cisplatin.

Unfortunately, three-dimensional treatment planning and conformal radiotherapy were not available in the present study. Therefore, it was not possible to analyze a relationship between degree and frequency of toxicities and various dose-volume parameters including V20 or the maximum esophageal point dose. The acute toxicities are closely related to the dose-volume parameters of the normal tissues [24–26]. The degree and frequency of toxicities could be reduced by three-dimensional conformal radiation therapy, which can restrict the dose and volume of the normal tissues compared with conventional two-dimensional technique.

The response rate of 90%, median survival time of 23.1 months, and 2-year survival time of 42.9% obtained in our study are very encouraging. One reason for these favorable results may be that the weekly docetaxel and cisplatin not has only radiosensitizing activity but systemic chemotherapeutic activity. Ohe et al. [27] are currently evaluating docetaxel and cisplatin administered in three consecutive weekly infusions as systemic chemotherapy for advanced NSCLC. Thirty-three elderly patients with advanced NSCLC were enrolled in their phase II study of docetaxel 20 mg/m^2 and cisplatin 25 mg/m^2 on days 1, 8, and 15, doses which are similar to the recommended doses and schedule in our study. The overall response rate was 52%, the complete response rate was 6% and the median survival time was 12.4 months. Both response rate and median survival time in their study are promising and the results suggest that a docetaxel dose of 20 mg/m^2/week plus cisplatin dose of 25 mg/m^2/week has an antitumor effect as systemic chemotherapy.

The correlation with AAG was not a primary objective and this was not essential in this study. Thus, we could collect only 12 samples. The baseline AAG

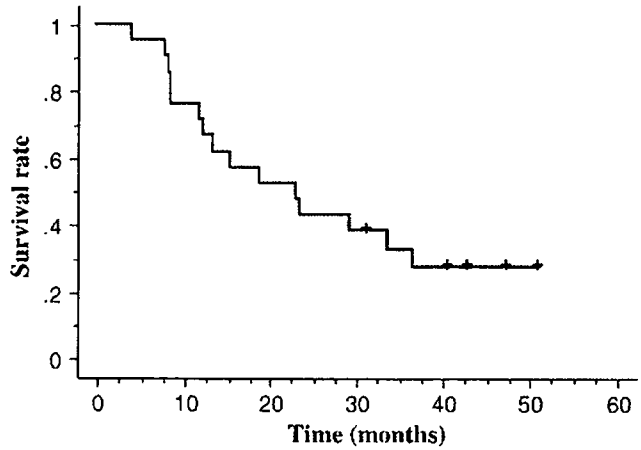

Fig. 2 Overall survival of patients treated with weekly docetaxel and cisplatin concomitant with TRT

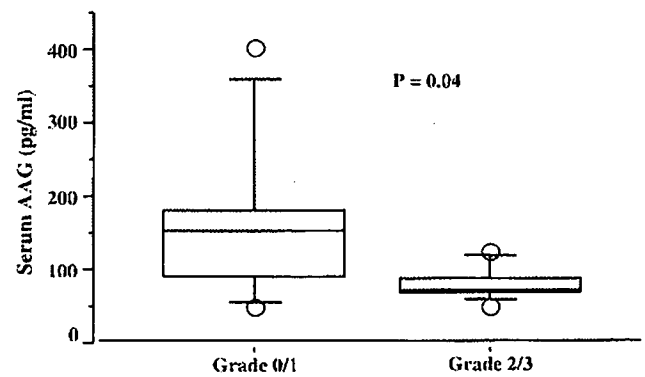

Fig. 3 Relationship between toxicity grade of esophagitis and serum AAG level