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ORIGINAL ARTICLE

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Phase I studies of nogitecan hydrochloride for Japanese

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Abstract
Background. SmithKline Beecham synthesized camptothecin analogs and identified nogitecan hydrochloride (topotecan) with a broad spectrum of antitumor activity and less toxicity than camptothecin. Because preclinical and overseas clinical data indicated the antitumor effect of nogitecan hydrochloride with a 5-day repeat-dose schedule, we carried out phase I studies in Japan to determine the maximum tolerated dose (MTD), pharmacokinetics, and antitumor effect of nogitecan hydrochloride.
Methods. Phase I studies of nogitecan hydrochloride given by single and 5-day repeat dosing were carried out in patients with various solid tumors at 15 medical institutions in Japan. Pharmacokinetic evaluations were performed for both single and 5-day repeated dosing.
Results. The dose-limiting factor (DLF) was reversible leucopenia, and the maximum tolerated dose (MTD) was higher than 22.5 mg/m^2 in the single-dose study. In the 5-day repeat-dose study, the DLF was also reversible leucopenia, and the MTD was estimated to be 1.5 mg/m^2 per day. The plasma concentration of nogitecan hydrochloride increased with increasing dose, and the half-life after single dosing ranged from 3 to 5 h. There was no evidence of accumulation or delayed excretion during 5-day repeat dosing.
Conclusion. Based on these results and the finding that there were responders among patients treated at 1.5 mg/m^2 per day by 5-day repeat dosing in overseas studies, 5-day repeat dosing of 1.2 mg/m^2 per day, one dose level lower than the MTD, was selected for phase II studies in Japan.

Key words Topoisomerase I inhibitor · Topotecan · Phase I study

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Introduction

The National Cancer Institute (NCI) in the United States found the antitumor activity of an extract from *Camptotheca acuminata*, of Chinese origin, in the 1950s, and, in 1966, Wall and co-workers[1] isolated camptothecin, which was found to be a selective topoisomerase I inhibitor.[2,3] In the 1970s, the NCI conducted a clinical study of camptothecin, but terminated its development due to serious toxicity.[4–6]

SmithKline Beecham synthesized camptothecin analogs and identified nogitecan hydrochloride (topotecan) with a

broad spectrum of antitumor activity and less toxicity than camptothecin.[7,8] Overseas, SmithKline Beecham started a phase I study to determine the dosage and administration of nogitecan hydrochloride in 1989, and 5-day repeat dosing was selected as it was tolerated and was expected to be effective against tumors.[9]

Because the preclinical and overseas clinical data indicated the antitumor effect of nogitecan hydrochloride with 5-day repeat dosing, we carried out phase I studies in Japan. This article reports the maximum tolerated dose (MTD), pharmacokinetics, and antitumor effect of nogitecan hydrochloride.

Patients and methods

Patients

A single-dose study and a 5-day repeat-dosing study were conducted from January 1992 to April 1993 at the 15 medical institutions listed in Table 1.

Patients who met the following criteria were selected: (1) patients with histologically or cytologically confirmed malignant solid tumors; (2) patients who did not respond to the standard treatment or for whom there was no appropriate treatment; (3) patients who had adequate organ function to evaluate the adverse reactions of nogitecan hydrochloride ($4000/mm^3 \leq$ WBC count $\leq 12000/mm^3$; platelet count, $\geq 100000/mm^3$; hemoglobin, ≥ 9.5 g/dl; GOT, GPT, and alkaline phosphatase [ALP], ≤ 2 times the upper limit of their respective normal ranges at each medical institution; total bilirubin, ≤ 1.5 mg/dl; serum creatinine, $\leq$ the upper limit of the normal range at each medical institution); (4) patients with a performance status (PS) of 0–2; (5) patients who had a predicted life expectancy of 3 or more months; (6) patients who had been off the previous therapy, with at least 2 weeks having passed for biological response modifiers (BRMs), hormone preparations, and metabolic inhibitors, and 4 weeks for other therapies; (7) patients aged from 15 to 75 years; (8) inpatients; (9) patients who had given their consent to participate in the investigation; (10) patients with no history of drug hypersensitivity; (11) patients with no symptoms associated with metastasis in the brain, no ascites, no subileus, and no severe complication; and (12) patients who were not pregnant or nursing or who would not be come pregnants. Others whom the investigator considered ineligible were excluded. Patients were registered at the central registration center by telephone and the center confirmed the eligibility of each patient. The study was monitored by a Steering Committee, and updated information was provided to each investigator by letter from the chief investigator as needed.

Written informed consent was obtained from each patient. The studies were carried out according to the clinical protocol reviewed and approved by the institutional review boards of each medical institution in accordance with the Declaration of Helsinki (1975).

Dosage and administration

Single-dose study

A starting dose of 5 mg/m^2 was selected because one-tenth of the lethal dose (LD_{10}) in mice was 7.485 mg/m^2.

5-Day repeat-dose study

A starting dose of 0.5 mg/m^2 per day was selected because LD_{10} for 5-day repeat-dosing in mice was 1.38 mg/m^2 per day and one-third of the toxic dose low (TDL) in dogs was 0.46–1.3 mg/m^2 per day.

Table 1. Medical institutions and investigators

Medical institution	Department	Principal investigator* and investigator
Nippon Medical School	Respiratory Medicine (now, Internal Medicine IV)	Hisanobu Niitani*, Kunihiko Kobayashi, Mitsunori Hino
Osaka Prefectural Habikino Hospital	Internal Medicine	Masahiro Fukuoka*, Nobuhide Takifuji
National Kinki Central Hospital	Internal Medicine	Kiyoyuki Furuse*, Nagahisa Kodama
The Center for Adult Diseases, Hyogo	Obstetrics and Gynecology	Kunio Takeuchi*, Kazuo Hasegawa
Saitama Cancer Center	Respiratory Medicine	Shuichi Yoneda*
Tsuboi Hospital	Internal Medicine	Koichi Hasegawa*, Koichi Yamada
Kinki University School of Medicine	Obstetrics and Gynecology	Kiichiro Noda*, Kaichiro Yamamoto
Research Institute for TBC and Cancer, Tohoku University[a]	Clinical Cancer Chemotherapy[a]	Ryunosuke Kanamaru*, Mariko Kanbe
Teikyo University School of Medicine, Mizonokuchi Hospital	Internal Medicine	Hisashi Furue*, Masashi Suminaga
Cancer Institute Hospital	Medical Oncology	Noboru Horikoshi*, Keisuke Aiba
Research Institute for Microbial Diseases, Osaka University	Surgery, Clinical Division	Tetsuo Taguchi*, Jun Ohta, Masahide Fujita
Osaka City University Medical School	Surgery II	Hiroaki Kinoshita*, Ken Morimoto
Okayama University Medical School	Internal Medicine II	Ikuro Kimura*, Taisuke Ohnoshi
Tokyo Metropolitan Komagome Hospital	Surgery	Ken Tominaga*
Hyogo College of Medicine	Internal Medicine IV	Takashi Shimoyama*, Tadatsugu Ohno

The medical institutions are listed in order of the number of patients enrolled in this study
[a]Changed to "Tohoku University School of Medicine, Clnical Oncology"

Fig. 1. Patient disposition

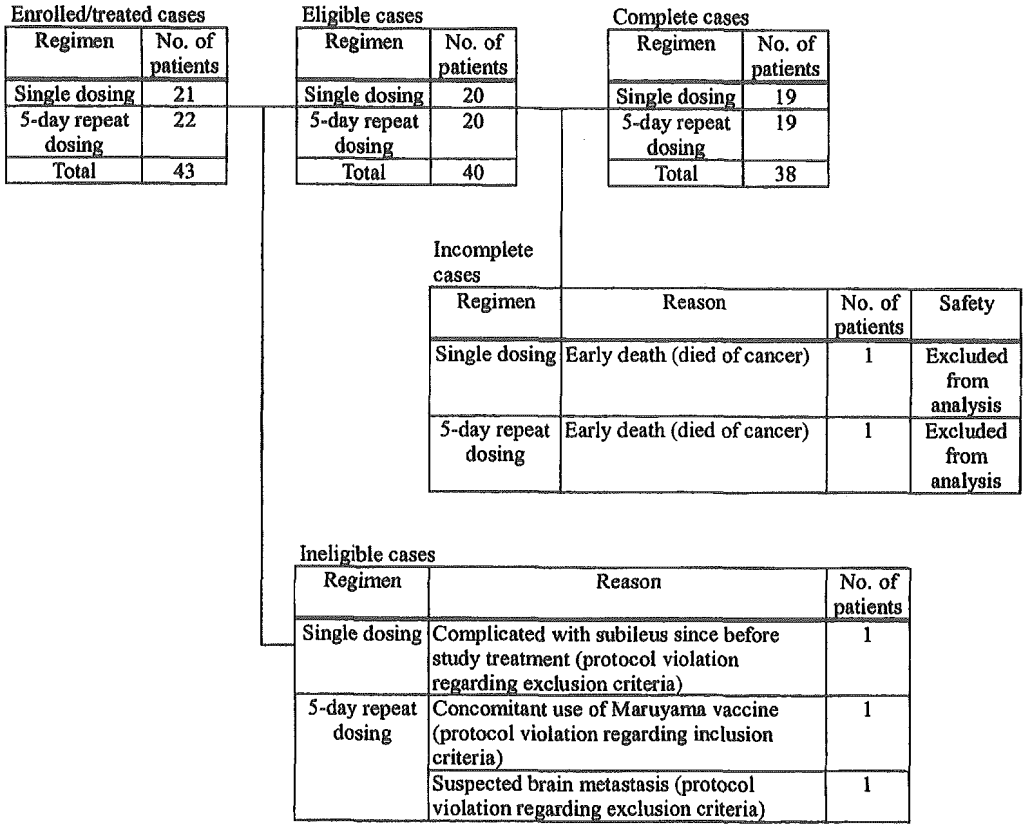

Table 2. Patient characteristics

Baseline characteristics		Single dosing	5-Day repeat dosing
No. of patients included in analysis		19	19
Age (years)	40–49	1	3
	50–59	3	6
	60–69	13	7
	70–75	2	3
	Range	45–73	40–75
	Mean (SD)	63.1 (6.6)	61.3 (9.0)
Cancer class	Lung cancer SCLC	0	1
	NSCLC	11	9
	Colorectal cancer	1	3
	Rectal cancer	0	1
	Colon cancer	0	1
	Ovarian cancer	0	2
	Cervical cancer	2	0
	Uterine cancer	2	0
	Breast cancer	2	0
	Pharyngeal cancer	1	0
	Pleural mesothelioma	0	1
	Submandibular cancer	0	1
Previous therapy	No	2	1
	Yes	17	18

SCLC, Small-cell lung cancer; NSCLC, non-small-cell lung cancer

In both studies, the dose was to be increased according to the modified Fibonacci's method. Also, in the 5-day repeat-dose study, the dose escalation plan was based on the results of the preceding single-dose study. A higher dose level was selected after safety evaluation at the previous dose level. In the 5-day repeat-dose study, the safety was evaluated by selecting the total dose not exceeding the highest dose given by single administration.

Nogitecan hydrochloride was dissolved in 100ml of physiological saline and administered intravenously by

Table 3. Subjective/objective adverse drug reactions and laboratory abnormalities (single-dose study)

Dose (mg/m^2)	5 (1 n)				10 (2 n)				15 (3 n)				20 (4 n)				22.5 (4.5 n)			
No. of patients included in analysis	4				4				5				3				3			
Grade	G1	G2	G3	G4	G1	G2	G3	G4	G1	G2	G3	G4	G1	G2	G3	G4	G1	G2	G3	G4
Nausea/vomiting	1			–		1		–	1	1		–		1		–				–
Anorexia	1	1		–	1			–	1	2		–		1		–	1			–
Stomatitis										1										
Dyspnea																		1		
Headache													1				1			
Dull headache																	1			
Skin symptoms																	1			
Hematuria				–				–		1		–				–				–
Fever				–		1		–	1	3		–	2			–	2	1		–
Fatigue			1			1					1		1				1	2		
Alopecia				–				–			1	–	1			–		1		–
Weight decrease		1																		
Aggravated condition			1						1	1			1							
Hemoglobin	2		1			1				1	1								1	
WBC count		1			1	1			1			1	1		1		1			1
Neutrophil count		1				1	1		1			2		1		1	1		1	
Platelet count	1				1						1		1		1			1		
GOT	1								1				1				1			
GPT	1								1					1			1			
ALP	2	1			1				2				1				1			
Total bilirubin													1							
BUN	2												1							
Creatinine	1																			
Urinary protein	1				1															

1n = $5\,mg/m^2$ at single dosing

drip infusion over a period of 30 min. The test product was provided by SmithKline Beecham Seiyaku (Tokyo, Japan).

During the observation period, the concomitant use of any drugs or therapies that may affect the evaluation of nogitecan hydrochloride, such as anticancer drugs (including hormones), BRMs, radiotherapy,surgery, and investigational drugs, was prohibited.

However, this was amended after granulocyte colony stimulating factor (G-CSF) became available, so that a G-CSF preparation could be administered only when a patient developed grade 4 leukopenia.

Evaluation

The following parameters were examined: clinical findings (body temperature, heart rate, respiration rate, body weight, PS, subjective symptoms/objective signs), electrocardiography, chest X-ray, and laboratory tests (WBC count, WBC classification, neutrophil count, red blood cell count, hemoglobin, platelet count, total protein, albumin, GOT, GPT, ALP, lactate dehydrogenase [LDH], total bilirubin, blood urea nitrogen [BUN], creatinine, blood electrolytes, urinalysis, tumor markers). Adverse drug reactions observed during the study were assessed according to the "Grading of side effects" in the *Criteria for the evaluation of the clinical effects of solid cancer chemotherapy* established by the Japan Society of Clinical Oncology.[10]

The MTD was evaluated as the dose that led to grade 2, 3, or 4 non-hematologic toxicity and/or grade 3 or 4 hematologic toxicity in two-thirds or more of the patients.

Tumor findings were obtained before study treatment and whenever necessary after study treatment. Antitumor effects were evaluated according to the *Criteria for the evaluation of the clinical effects of solid cancer chemotherapy* established by the Japan Society of Clinical Oncology.[10]

Pharmacokinetics

Baseline and 0- to 48-h plasma concentrations and baseline and 0- to 48-h urinary concentrations were determined by a HPLC-fluorescence method in the single-dose study, and these concentrations were determined on days 1 and 5 in the 5-day repeat-dose study.

Pharmacokinetic parameters were calculated by the moment analysis method. The maximum plasma concentration (C_{max}) was determined directly from the measured values. The areas under the plasma concentration versus time curves ($AUC_{0\text{-}t}$) were calculated by using the values between 0 and the last data point. The half-life ($t_{1/2}$), total body clearance (CL), apparent steady-state volume of distribution (V_{ss}), and renal clearance (CLr) were calculated by the following equations:

$$t_{1/2} = -\ln 2/k$$
$$CL = D/AUC_{0\text{-}t}$$
$$V_{ss} = CL \times \text{mean residence time (MRT)}$$
$$CLr = Ae\ (mg)/AUC_{0\text{-}t}$$

Table 4. Changes in WBC, neutrophil, and platelet counts, and hemoglobin (single-dose study)

Dose (mg/m^2 per day)	WBC count			Neutrophil count			Platelet count			Hemoglobin		
	Nadir ($/mm^3$)	No. of days to nadir	No. of days to recovery[a]	Nadir ($/mm^3$)	No. of days to nadir	No. of days to recovery[a]	Nadir ($\times 10^4/mm^3$)	No. of days to nadir	No. of days to recovery[a]	Nadir (g/dl)	No. of days to nadir	No. of days to recovery[a]
5.0	5200 (2900–9200)	6.5	9	2893.5 (1276–5700)	7	9	14.65 (9.6–22.1)	7	12	10.1 (7.4–11.4)	10.5	–
10.0	3600 (2800–4300)	7.5	8	1902 (832–3203.5)	7.5	11	16.8 (9.7–24.0)	7.5	14	11.5 (8.2–14.5)	10	20
15.0	4830 (300–5200)	8	16.5	1743.63 (0–3111)	14	14	16.5 (3.0–22.6)	7	15	11.0 (7.3–13.0)	9	23.5
20.0	3000 (1100–4100)	9	18	1260 (96–2952)	14	17	8.5 (4.7–13.9)	8	14.5	11.7 (11.0–12.0)	11	–
22.5	3800 (800–4300)	7	14.5	1976 (512–2430)	14	18	11.7 (5.7–19.3)	7	15	12.1 (7.6–12.8)	14	–

Values are medians, with ranges (minimum to maximum) in parentheses
[a]No. of days from nadir to recovery, ≥4000/mm^3 for WBC count, ≥2000/mm^3 for neutrophil count, ≥100000/mm^3 for platelet count, and ≥9.5 g/dl for hemoglobin

where k is slopes of log regression curves of plasma concentrations versus time (calculated by extrapolation using appropriate terminal points) and Ae (mg) is amount of excretion.

Results

Patients and their characteristics

Patient disposition and characteristics are shown in Fig. 1 and Table 2, respectively.

Single-dose study

Nineteen patients were included in the safety analysis, after the exclusion of 1 ineligible patient who had subileus as a complication, and 1 patient who died of cancer, who was regarded as an incomplete case. The majority of patients, i.e., 11, had non-small-cell lung cancer. Of 17 previously treated patients, 15 patients had a history of chemotherapy.

5-Day repeat-dose study

One patient with brain metastasis before the study treatment and another who was treated continuously with Maruyama vaccine were considered ineligible, and one patient, who died of cancer soon after the study treatment, was considered an incomplete case. After the exclusion of these patients, 19 patients (complete cases) were included in the safety analysis. Nine patients had non-small-cell lung cancer, and 10 patients had some complications. Of 18 previously treated patients, 17 patients had a history of chemotherapy.

MTD and dose-limiting factor (DLF)

Single-dose study

Table 3 shows the subjective/objective adverse drug reactions and laboratory abnormalities reported in the single-dose study, and Table 4 shows the changes in WBC, neutrophil, and platelet counts, and hemoglobin. Subjective/objective adverse drug reactions were nausea/vomiting, anorexia, dyspnea, fever, and fatigue, most of which were grade 1 or 2. Grade 3 or 4 adverse drug reactions were seen for fatigue (two cases), alopecia (one case), and aggravated condition (one case).

Grade 3 or 4 laboratory abnormalities were leucopenia, neutropenia, anemia, and thrombocytopenia, and all of them were reversible. The nadirs of WBC and neutrophil counts decreased dose-dependently, and those at the highest dose of 22.5 mg/m^2 were 3800/mm^3 and 1976/mm^3, respectively. The numbers of days to nadir were similar at all dose levels, being 6.5–9 days for the WBC count and 7–14 days for the neutrophil count. The nadir of the platelet

Table 5. Subjective/objective adverse drug reactions and laboratory abnormalities (5-day repeat-dose study)

Dose (mg/m² per day)	0.5 (1 n)				0.75 (1.5 n)				1.0 (2 n)				1.2 (2.4 n)				1.5 (3 n)			
No. of patients included in analysis	4				3				3				4				5			
Grade	G1	G2	G3	G4	G1	G2	G3	G4	G1	G2	G3	G4	G1	G2	G3	G4	G1	G2	G3	G4
Nausea/vomiting				–				–			1	–		2	1	–	1	1	1	–
Anorexia	1			–	2			–	2			–	1	3		–	3		1	–
Diarrhea													1							
Fever				–		1		–		1		–				–		1		–
Fatigue						1			1				1	1			1	1	1	
Impaired hearing													1							
Alopecia				–	1			–	1			–		1		–		2		–
Stomatitis																	1			
Weight decrease																		1		
Aggravated condition																		1		
Hemoglobin			1		1	2			2	1			1		3		2	2		
WBC count		2			1	1	1			1	2				3	1		1	3	1
Neutrophil count		1					2				2	1		1	1	2			2	3
Platelet count			1		1					1				1	3		2		1	1
GQT	1	1			1				1								1			
GPT	3				1												2			
ALP						1				1			1		1			1		
BUN	1																1			
Creatinine	1																			
Urinary protein		1																		

1n = 0.5 mg/m² at 5-day repeat dosing

count decreased approximately dose-dependently, and the median value was 117000/mm³ at the highest dose. There was no dose-dependent decrease in the nadir of the hemoglobin value.

Myelosuppression, including decreased hemoglobin, and leucopenia, neutropenia, and thrombocytopenia, was observed at the starting dose of 5 mg/m² and above. In particular, leucopenia and neutropenia were intensified with increasing dose, but grade 3 or 4 anemia, leucopenia, and neutropenia were observed in only one of three patients treated at the highest dose of 22.5 mg/m². It seemed that the doses investigated in this study had not reached the MTD, when we considered other laboratory data, subjective symptoms, and objective findings. However, the dose was not increased further, because the MTD was shown to be 22.5 mg/m² in the overseas clinical study, and overseas clinical studies suggested that the 5-day repeat-dose, rather than the single dose, was effective. Therefore, the MTD was estimated to be ≥22.5 mg/m².

5-Day repeat-dose study

Table 5 shows subjective/objective adverse drug reactions and laboratory abnormalities in the 5-consecutive-day administration study, and Table 6 shows changes in WBC, neutrophil, and platelet counts, and hemoglobin. The incidence and severity of subjective/objective adverse drug reactions increased with increasing dose. Grade 3 or 4 adverse drug reactions were nausea/vomiting, anorexia, and fatigue. Other subjective/objective adverse drug reactions were diarrhea, fever, impaired hearing, alopecia, stomatitis, weight decrease, and aggravated condition, which were grade 1 or 2. Grade 3 or 4 laboratory abnormalities were leucopenia, neutropenia, anemia, thrombocytopenia, and elevation of ALP. The incidence and severity increased with increasing dose, but all events were reversible.

At the highest dose, of 1.5 mg/m², the median values for WBC count and neutrophil count at nadir were 1400/mm³ and 481.14/mm³, respectively. The number of days to nadir ranged from 12 to 15.5 for the WBC count and from 13 to 15 for the neutrophil count in all patients, findings which were similar to those in the single-dose study. The number of days to recovery was 21–28 for the WBC count (4000/mm³), and 21–32.5 for the neutrophil count (2000/mm³). The nadirs of the platelet count and hemoglobin decreased dose-dependently, being 78000/mm³ and 9.9 g/dl at the highest dose. The nadirs of the WBC, neutrophil, and platelet counts, and hemoglobin, at the highest dose were lower in the 5-day repeat-dose study than in the single-dose study.

In three patients treated at 1.0 mg/m² per day, grade 3 or 4 hematological toxicity findings were leucopenia (two cases) and neutropenia (three cases). Grade 4 neutropenia was observed in one patient. All patients recovered without treatment. Although the MTD was defined as the dose at which grade 2 or above adverse drug reactions (grade 3 or above for hematological parameters) occurred in two-thirds or more patients, the dose was increased to 1.5 mg/m² per day because all the above symptoms were reversible without treatment, and because G-CSF support for myelosuppresion was developed and widely used during the study.

In five patients treated at 1.5 mg/m² per day, grade 3 or 4 hematological toxicity findings were leucopenia (four cases), neutropenia (five cases), and thrombocytopenia (two cases). Grade 4 leucopenia was observed in one patient, grade 4 neutropenia in three patients, and grade 4 thrombocytopenia in one patient. All symptoms resolved

Table 6. Changes in WBC, neutrophil, and platelet counts, and hemoglobin (5-day repeat-dose study)

Dose (mg/m^2 per day)	WBC count			Neutrophil count			Platelet count			Hemoglobin		
	Nadir ($/mm^3$)	No. of days to nadir	No. of days to recovery[a]	Nadir ($/mm^3$)	No. of days to nadir	No. of days to recovery[a]	Nadir ($\times 10^4/mm^3$)	No. of days to nadir	No. of days to recovery[a]	Nadir (g/dl)	No. of days to nadir	No. of days to recovery[a]
0.5	3500 (2100–5110)	15.5	27.5	2188 (1144–3087.4)	15	–	12.9 (3.7–24.0)	13.5	20	11.5 (7.2–11.9)	15.5	–
0.75	2500 (1800–3800)	14	27	621 (522–3078)	14	32.5	10.5 (9.0–12.5)	13	16	8.7 (8.5–10.8)	13	32
1.0	1800 (1700–2000)	15	28	684 (238–780)	15	28	11.9 (5.1–17.5)	14	20	9.5 (8.5–9.6)	15	63
1.2	1500 (900–1800)	13	21.5	571.5 (299–1054)	13	21	4.1 (3.5–6.9)	13	20.5	7.45 (7.0–10.7)	20	20
1.5	1400 (200–2430)	12	21	481.14 (20–585)	14	21	7.8 (1.7–13.0)	12	16.5	9.9 (8.0–11.1)	17	–

Values are medians, with ranges (minimum to maximum) in parentheses
[a]No. of days from nadir to recovery, $\geq 4000/mm^3$ for WBC count, $\geq 2000/mm^3$ for neutrophil count, $\geq 100000/mm^3$ for platelet count, and ≥ 9.5 g/dl for hemoglobin

without treatment, or with G-CSF, platelet, or blood transfusion. In consideration of the hematological toxicity findings observed at 1.5 mg/m^2 per day and the data for 1.25 mg/m^2 per day from an overseas clinical study, it was decided to evaluate the safety by reducing the dose by 20%, to 1.2 mg/m^2 per day. At 1.2 mg/m^2 per day, grade 3 or 4 leucopenia and neutropenia occurred in four and three of four patients, respectively, and grade 3 or 4 thrombocytopenia occurred in three of four patients.

One patient died of sepsis resulting from cachexia, associated with cancerous peritonitis, 9 days after single-dose administration at 10 mg/m^2.

Pharmacokinetics

Single-dose study

Table 7 shows the pharmacokinetic parameters obtained from the single-dose study. The plasma concentration of nogitecan hydrochloride reached the maximum (C_{max}) at the end of infusion, and decreased in a biphasic pattern with half-lives ($t_{1/2}$) of 3–5 h at all dose levels. In the urine, 40%–60% of the administered dose was excreted by 24 h after dosing at all dose levels.

5-Day repeat-dose study

Table 8 shows the pharmacokinetic parameters obtained from the 5-day repeat-dose study. The plasma concentrations of nogitecan and total nogitecan reached C_{max} at the end of infusion both on day 1 and on day 5, and decreased in a biphasic pattern. About 45%–60% of the administered dose was recovered from the urine in 24 h after the start of repeat dosing on day 1 and day 5, suggesting no accumulation or delayed excretion after the repeat dosing.

Antitumor effects

Reduction in tumor size was not observed in any patients treated once or for 5 consecutive days.

Discussion

As reported with camptothecin, nogitecan hydrochloride is considered to inhibit DNA synthesis by binding reversibly to DNA-topoisomerase I complex. In vitro, various tumor cells were found to be sensitive to nogitecan hydrochloride, and in vivo, the antitumor effects of nogitecan hydrochloride were shown against established human tumor cell lines, such as small-cell lung cancer, non-small-cell lung cancer, and ovarian carcinoma.[11,12]

Nogitecan hydrochloride belongs to the same class as irinotecan hydrochloride (CPT-11), which has already been approved in Japan, but the following differences between

Table 7. Pharmacokinetic parameters and urinary excretions after single administration of nogitecan HCl

Dose (mg/m^2)	No. of patients included in analysis	Pharmacokinetic parameters				
		C_{max} (ng/ml)	AUC_{0-t} (ng·h/ml)	$t_{1/2}$ (h)	CL (ml/min)	V_{ss} (l)
			Nogitecan			
5	2	114.65	162.44	2.96	42.15	79.1
10	4	263.80 ± 82.41	346.80 ± 90.04	3.06 ± 1.31	44.34 ± 15.86	83.4 ± 29.7
15	5	395.07 ± 291.55	644.43 ± 318.17	4.58 ± 1.47	40.88 ± 25.58	105.8 ± 40.9
20	3	443.49 ± 167.92	832.28 ± 165.93	4.54 ± 0.19	38.48 ± 13.01	130.7 ± 53.9
22.5	3	836.33 ± 740.09	1073.81 ± 578.49	4.74 ± 0.26	34.62 ± 18.81	112.8 ± 83.3
			Total nogitecan			
5	4	174.09 ± 16.93	610.24 ± 237.71	5.41 ± 2.84	12.20 ± 4.16	47.2 ± 8.9
10	4	409.55 ± 156.70	972.69 ± 292.47	4.77 ± 2.53	15.81 ± 4.90	53.1 ± 18.5
15	5	552.72 ± 315.16	1920.29 ± 1040.48	6.61 ± 2.07	13.31 ± 6.94	55.0 ± 17.1
20	3	810.47 ± 123.04	2850.43 ± 194.00	7.08 ± 0.72	10.82 ± 1.80	55.7 ± 9.1
22.5	3	1152.10 ± 758.08	2740.50 ± 780.11	6.32 ± 1.62	11.80 ± 4.23	51.6 ± 21.3

Dose (mg/m^2)	No. of patients included in analysis	Urinary excretion of total nogitecan (% of dose)	
		0–24 h	0–48 h
5	4	44.2 ± 15.6	46.8 ± 17.2
10	4	62.2 ± 15.9	63.4 ± 15.9
15	5	35.0 ± 20.9	38.0 ± 22.7
20	3	61.3 ± 8.1	62.8 ± 8.0
22.5	3	39.0 ± 21.3	45.8

Values are means ± SD
Nogitecan, nogitecan HCl (closed lactone ring form); Total nogitecan, nogitecan HCl (closed lactone ring form + open lactone ring form); C_{max}, Maximum plasma concentration; $t_{1/2}$, half-life; CL, total body clearance; V_{ss}, apparent steady-state volume of distribution

the two agents have been noted, in terms of pharmacokinetics and adverse drug reaction profiles. The DLFs of CPT-11 were myelosuppression and unforeseeable severe diarrhea,[13,14] while reversible leucopenia is the only DLF for nogitecan hydrochloride. The unchanged nogitecan hydrochloride exerts its antitumor effect, and is excreted predominantly via the kidneys. On the other hand, the active entity of CPT-11, and its active metabolite, SN-38, are excreted mainly in the bile, part of which is reabsorbed into the intestinal tract.[15–19] These facts indicate that the plasma concentrations of CPT-11 and SN-38 are more variable, and thus it is easier to predict the pharmacokinetics of nogitecan hydrochloride.

We conducted the present single-dose phase I study before the start of the 5-day repeat-dose study, to investigate the pharmacokinetics/pharmacodynamics (PK/PD) and to create a dose escalation plan for the 5-day repeat-dose study. Also, it was thought that the PK/PD and safety data would be valuable for further investigation of other administration schedules, although the preclinical data suggested that nogitecan hydrochloride was schedule-dependent, and overseas clinical studies suggested that 5-day repeat-dosing, rather than a single-dose, was effective.

Our 5-day repeat-dose study had been started before G-CSF was introduced to medical practice, and while our study was ongoing, G-CSF was approved and introduced to medical practice. This changed the thoughts on myelosuppresion induced by cytotoxic drugs. Therefore, assessments of dose escalation and the MTD were made, taking account of this change. At 1.2 and 1.5 mg/m^2 per day, grade 3 or 4 hematological toxicity was observed in all patients, and the numbers of patients with grade 3 or 4 leucopenia and neutropenia were similar. But grade 4 hematological toxicity was observed in two of four patients at 1.2 mg/m^2 per day and in four of five patients at 1.5 mg/m^2 per day. At 1.5 mg/m^2 per day, grade 4 neutropenia and thrombocytopenia were observed in three and one of five patients, respectively, and at 1.2 mg/m^2 per day, grade 4 neutropenia and thrombocytopenia were observed in two and none of four patients, respectively.

In consideration of the hematological toxicity findings being more severe at 1.5 mg/m^2 per day than at 1.2 mg/m^2 per day, and in consideration that the MTD was estimated to be 2.0 mg/m^2 per day in the overseas 5-day repeat-dose study, and the overseas recommended dose was 1.5 mg/m^2 per day, we estimated the MTD to be 1.5 mg/m^2 per day and leucopenia to be the DLF of nogitecan hydrochloride.

In our 5-day repeat-dose study, an antitumor effect was not observed in any patients. However, there were responders among patients treated at 1.5 mg/m^2 per day for 5 consecutive days in overseas studies.[20–22] One dose level lower than the MTD for nogitecan hydrochloride, 1.2 mg/m^2 per day, by 5-consecutive-day administration, was selected as a safe regimen with which to progress to phase II trials.

Table 8. Pharmacokinetic parameters and urinary excretion on day 1 and day 5 of 5-day repeat administration of nogitecan HCl

Dose (mg/m^2 per day)	No. of patients included in analysis	Pharmacokinetic parameters				
		C_{max} (ng/ml)	AUC_{0-t} (ng·h/ml)	$t_{1/2}$ (h)	CL (ml/min)	V_{ss} (l)
Day 1			Nogitecan			
1.0	2	58.27	56.79	2.34	23.46	28.2
1.2	5	36.98 ± 20.46	46.91 ± 16.98	2.69 ± 1.07	42.74 ± 21.54	62.4 ± 20.9
1.5	4	86.12 ± 67.62	84.23 ± 29.53	2.51 ± 0.99	29.34 ± 14.17	46.3 ± 30.9
			Total nogitecan			
1.0	3	78.20 ± 34.37	135.10 ± 41.17	2.86 ± 0.30	10.56 ± 4.38	20.2 ± 4.8
1.2	5	50.75 ± 24.34	110.07 ± 25.82	2.82 ± 0.51	16.46 ± 4.85	38.1 ± 11.3
1.5	5	88.15 ± 57.61	170.48 ± 59.76	2.85 ± 1.29	13.70 ± 4.66	32.7 ± 11.5
Day 5			Nogitecan			
1.0	2	47.13	70.43	3.28	21.84	42.3
1.2	5	34.35 ± 17.84	54.65 ± 24.01	4.25 ± 2.87	35.68 ± 12.45	80.5 ± 23.0
1.5	3	39.51 ± 21.20	84.82 ± 75.00	3.63 ± 2.26	40.32 ± 26.64	84.5 ± 54.9
			Total nogitecan			
1.0	3	53.97 ± 34.27	149.57 ± 57.56	3.59 ± 1.65	10.06 ± 5.09	28.4 ± 12.1
1.2	5	45.81 ± 16.25	125.32 ± 37.18	3.65 ± 2.28	14.57 ± 3.75	39.6 ± 6.5
1.5	4	48.61 ± 15.43	168.13 ± 99.26	3.18 ± 1.70	15.63 ± 7.47	42.1 ± 12.9

Dose (mg/m^2 per day)	No. of patients included in analysis	Urinary excretion of total nogitecan (% of daily dose) 0–24 h
Day 1 0.5	4	66.5 ± 19.7
0.75	3	68.1 ± 12.5
1.0	3	62.8 ± 24.4
1.2	5	49.8 ± 11.5[b]
1.5	5	54.1 ± 25.2[a]

Dose (mg/m^2 per day)	included in analysis	No. of patients	0–24 h	0–48 h
Day 5	0.5	4	61.0 ± 29.1	66.8 ± 31.3[b]
	0.75	3	62.9 ± 3.9	64.3[c]
	1.0	3	59.3 ± 11.4	62.5 ± 12.1
	1.2	5	45.9 ± 17.4	50.5 ± 14.1
	1.5	5	59.4 ± 22.2	62.7 ± 22.9

Values are means ± SD
Nogitecan, Nogitecan HCl (closed lactone ring form); total nogitecan, nogitecan HCl (closed lactone ring form) + nogitecan HCl (open lactone ring form)
[a] $n = 4$
[b] $n = 3$
[c] $n = 2$

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Phase III Study of Concurrent Versus Sequential Thoracic Radiotherapy in Combination With Mitomycin, Vindesine, and Cisplatin in Unresectable Stage III Non–Small-Cell Lung Cancer

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Purpose: A phase III study was performed to determine whether concurrent or sequential treatment with radiotherapy (RT) and chemotherapy (CT) improves survival in unresectable stage III non-small-cell lung cancer (NSCLC).

Patients and Methods: Patients were assigned to the two treatment arms. In the concurrent arm, chemotherapy consisted of cisplatin (80 mg/m^2 on days 1 and 29), vindesine (3 mg/m^2 on days 1, 8, 29, and 36), and mitomycin (8 mg/m^2 on days 1 and 29). RT began on day 2 at a dose of 28 Gy (2 Gy per fraction and 5 fractions per week for a total of 14 fractions) followed by a rest period of 10 days, and then repeated. In the sequential arm, the same CT was given, but RT was initiated after completing CT and consisted of 56 Gy (2 Gy per fraction and 5 fractions per week for a total of 28 fractions).

Results: Three hundred twenty patients were entered onto the study. Pretreatment characteristics were well balanced between the treatment arms. The response rate for the concurrent arm was significantly higher (84.0%) than that of the sequential arm (66%) (P = .0002). The median survival duration was significantly superior in patients receiving concurrent therapy (16.5 months), as compared with those receiving sequential therapy (13.3 months) (P = .03998). Two-, 3-, 4-, and 5-year survival rates in the concurrent group (34.6%, 22.3%, 16.9%, and 15.8%, respectively) were better than those in the sequential group (27.4%, 14.7%, 10.1%, and 8.9%, respectively). Myelosuppression was significantly greater among patients on the concurrent arm than on the sequential arm (P = .0001).

Conclusion: In selected patients with unresectable stage III NSCLC, the concurrent approach yields a significantly increased response rate and enhanced median survival duration when compared with the sequential approach.

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IN THE LAST DECADE, several randomized trials have evaluated the use of chemotherapy with radiotherapy in the treatment of patients with unresectable stage III non–small-cell lung cancer (NSCLC).[1] Some trials that used cisplatin-based chemotherapy showed small but definite improvements in survival compared with trials that used radiotherapy.[2-4] A patient-based meta-analysis of 3,033 patients in 22 randomized clinical trials was recently reported.[5] This analysis indicated a 9% reduction in the annual risk of death, with a consequent improvement in 2-year survival from approximately 16% to approximately 19%. For the trials that used cisplatin-based chemotherapy, the chemotherapy produced a 13% reduction in the risk of death. The most convincing evidence is derived from induction chemotherapy with vinblastine and cisplatin followed by radiotherapy, and this treatment strategy is now an appropriate option for selected patients with unresectable stage III NSCLC. These data together suggest that sequential cisplatin-based chemotherapy followed by radiotherapy is the current standard therapy for unresectable stage III NSCLC.

In our prior trial, patients with locally advanced NSCLC were randomized to chemotherapy with or without radiotherapy.[6] Median survival was similar in the two cohorts of patients, but long-term survival was clearly superior in the patients who received both cisplatin-based chemotherapy and radiotherapy. Local relapse was greater in the patients who were given chemotherapy alone. This trial provided evidence that chemotherapy has an inadequate effect on local tumor control. Radiotherapy to bulky disease in the

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thorax was thus an important part of combined-modality treatment. We concluded that both chemotherapy and radiotherapy are essential in the treatment of locally advanced NSCLC.

Despite the superiority of combined treatments over chemotherapy alone, the response rate for chemotherapy followed by radiotherapy was still only 50%. In contrast, our phase II study of concurrent radiotherapy and chemotherapy with mitomycin (MMC), vindesine (VDS) and cisplatin for unresectable stage III NSCLC showed a response rate of 87%, a median survival of 16 months, and a 2-year survival rate of 37%.[7] These results encouraged us to proceed with further study.

We thus initiated a randomized trial to evaluate the therapeutic significance of concurrent radiotherapy and chemotherapy in combination with MMC, VDS, and cisplatin (MVP regimen) compared with sequential therapy for patients with unresectable stage III NSCLC.

PATIENTS AND METHODS

Patients

We entered 320 patients with histologically or cytologically confirmed unresectable stage III NSCLC. Staging for entry criteria was performed according to the lung cancer staging system of the International Union Against Cancer.[8] Patients with T3N0 or T3N1 disease and pleural effusion were excluded. Eligibility criteria included age of younger than 75 years; measurable or assessable lesions; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2; a required radiation field of less than one half of one lung; no prior chemotherapy, thoracic radiotherapy, or thoracic surgery; and no active concomitant malignancies. Patients with prior malignancies who had been disease-free for more than 5 years were eligible. Patients also were required to have no abnormal hematologic (leukocyte count $\geq$ 4,000/μL, platelet count [PLT] $\geq$ 100,000/μL), hepatic (bilirubin $<$ 1.5 mg/dL, AST/ALT $<$ twice the upper limit of normal), renal (serum creatinine $<$ 1.5 mg/dL), pulmonary (partial pressure of arterial oxygen $\geq$ 70 mm Hg), and cardiac functions. All patients gave informed consent to participate in the study.

Patients were staged with routine chest roentgenography, conventional chest tomography; chest computed tomography scan (CT), CT scan of the brain and abdomen, bone scintigraphy, and bronchoscopy.

Treatment Schedule

Patients were stratified by institute, PS, and stage and were then randomly assigned to receive either MVP with concurrent radiotherapy or MVP followed by radiotherapy.

In the concurrent schedule, chemotherapy consisted of VDS (3 mg/m^2 on days 1 and 8), cisplatin (80 mg/m^2 on days 1), and MMC (8 mg/m^2 on days 1). This chemotherapy was repeated every 4 weeks and was administered in two courses. The dose was modified on the basis of blood cell counts and renal function on the day of therapy. VDS was administered at the full calculated dose unless the leukocyte count was less than 2,000/μL or the PLT count was less than 50,000/μL on day 8 or 36 of therapy. If either the leukocyte count or PLT count were below these levels, VDS administration was withheld until counts recovered, at which time it was reinstituted at the full dosage. If the leukocyte count was less than 3,000/μL or the PLT count was less than 75,000/μL on day 29, then chemotherapy was withheld until counts recovered. If grade 4 hematologic toxicity, according to World Health Organization (WHO) criteria,[9] occurred during the first course, then doses of VDS and MMC were reduced to 75%. Cisplatin was permanently discontinued at any time when the serum creatinine level was greater than 2 mg/dL.

On day 2 of chemotherapy, radiation was begun using a linear accelerator ($\geq$ 4 MeV) or cobalt-60 at a dose of 2 Gy/fraction given 14 times for 3 weeks and then followed by a rest period of 10 days. The dose was administered in five fractions per week; one fraction was delivered each day from two opposing anteroposterior fields. After a 10-day rest period, radiation was again administered at a dose of 2 Gy given 14 times for 3 weeks. The total dose of 56 Gy was administered to a volume that included the primary tumor along with the involved hilar and mediastinal lymph nodes with a 1.5-cm margin and around the contralateral noninvolved hilar and mediastinal lymph nodes with 1-cm margin. The supraclavicular fossa was included in the radiation port only if it was clinically involved, and a total dose of 56 Gy was administered. If it was possible to reduce the radiation field after administering 40 Gy, then an additional 16 Gy was given to a reduced field. The spinal cord was excluded from the irradiated volume at 40 Gy by use of parallel, opposed oblique fields.

Patients in the sequential therapy group received the same chemotherapy as patients in the concurrent therapy group. After completing two courses of chemotherapy, patients received radiotherapy that consisted of 56 Gy in 28 fractions of 2 Gy each (5 days each week, given over a period of 5 weeks). Radiation fields and criteria of exclusion of spinal cord were the same as in patients receiving the concurrent schedule.

If patients responded to chemotherapy (sequential) or chemoradiotherapy (concurrent), then one or more cycles of chemotherapy were given to patients after radiotherapy on both arms, if possible.

If grade 4 radiation-induced esophagitis occurred (according to ECOG criteria), then radiotherapy was withheld until esophagitis recovered to grade 3. If leukocyte count was grade 4, then radiotherapy was withheld until it recovered to grade 3. Partial pressure of arterial oxygen was measured every week, and if it worsened to 10 mm Hg or greater, then radiotherapy was withheld until recovery; likewise, if body temperature was greater than 38°C, then radiotherapy was withheld until body temperature returned to normal.

Evaluation

To assess response and toxicity, all patients underwent a complete blood cell count; blood chemistries (including AST, ALT, alkaline phosphatase, lactate dehydrogenase, bilirubin, creatinine, and blood urea nitrogen), urinalysis, and chest x-rays were performed once per week during the treatment period. The follow-up study of the roentgenographic examination was usually performed with posteroanterior chest x-ray on all patients every week until determination of response; if lesions were not measurable on the posteroanterior chest x-ray, then conventional tomography or CT scan was used.

Response and toxicity were evaluated according to WHO criteria,[9] but grading of esophageal toxicity caused by radiation was defined according to the ECOG criteria.[10] Extramural reviewers evaluated the eligibility, assessability, and response in each patient. A complete response (CR) was defined as the disappearance of all measurable lesions for at least 4 weeks. A partial response (PR) was defined as a more than 50% decrease in the sum of the products of the greatest perpendicular diameters of all measurable lesions for at least 4 weeks without the development of new lesions. No change (NC) was defined as a less than 50% reduction or less than 25% increase in the products of the greatest perpendicular of all the lesions without any evidence of new lesions for at least 4 weeks. Progression of disease (PD) was defined as

an increase of more than 25% or the appearance of new lesions. Response in both arms was generally evaluated 1 month after completing radiotherapy, except for PD.

Study Design and Statistical Analysis

The trial was designed as a prospective, randomized, nonblinded study. The central office stratified patients according to institutes, PS, and stage and then randomly assigned the patients in each stratum to receive either concurrent therapy or sequential therapy using a computer-generated list.

A sample size of 320 patients was planned to provide a power of 80% to detect an improvement in the 2-year survival rate (from 20% to 30%) at a significance level for two-sided test with alpha of 0.05 and beta of 0.20. Survival was calculated from the date of randomization to death or last follow-up evaluation. Actuarial survival curves were calculated by the Kaplan-Meier method[11] and were compared for statistical significance using the log-rank test.[12]

To assess differences between proportions, *P* values were calculated with the χ^2 test[13] and the Fisher's exact probability test[14]; the Mann-Whitney *U* test was used to assess significant differences between the two proportions.[15] The influence of variables for survival was studied by univariate and multivariate analyses. Multivariate analysis of prognostic variables for survival was carried out using a logistic regression model.[16] Survival was calculated from the date of randomization until the date of death or last follow-up appointment.

RESULTS

Patient Characteristics

Between August 1992 and December 1994, 320 patients were enrolled at the 27 institutions participating in this study. Five patients were later found to be ineligible: two patients had distant metastasis, one had severe anemia and required blood transfusion, and one enrolled twice. Of the 315 eligible patients, one patient withdrew informed consent after enrollment. Thus 314 patients were assessable for survival, response, and toxicity.

The clinical characteristics of the patients are listed in Table 1. Four patients were evaluated as T3N0M0 or T3N1M0 disease by extramural review. All prognostic factors were distributed equally between the two treatment arms.

Table 1. Patient Characteristics

Characteristic	Concurrent Therapy (no. of patients)	Sequential Therapy (no. of patients)	*P*
No. of eligible patients	156	158	
Age, years			
Median	64	63	.8255
Range	40-75	39-75	
Sex			
Male	135	134	.662
Female	21	24	
Stage of disease			
IIIA	48	49	.963
IIIB	108	109	
PS			
0	40	31	.346
1	107	120	
2	9	7	
10% weight loss			
No	139	136	.416
Yes	17	22	
Histology			
Squamous cell	76	72	.520
Adenocarcinoma	66	68	
Large cell	14	16	
Other	0	2	
TNM			
T3N1-0M0	3	1	.788
T1-3N2M0	41	43	
T1-3N3M0	40	41	
T4N0-3M0	72	73	
Supraclavicular lymph node			
Ipsilateral	20	16	.745
Contralateral	4	5	
Bilateral	5	3	
Tumor location			
Upper lobe	117	108	.191
Other sites	39	50	
Radiation equipment used			
Cobalt-60	6	7	.795
Linear accelerator	150	151	

Abbreviation: TNM, American Joint Committee on Cancer tumor-node-metastasis staging system.

Response

On the treatment arm in which patients received concurrent therapy, 131 patients had responses (84.0%; 95% confidence interval, 78.22% to 89.73%), including four patients (2.6%) with CR, 127 (81.4%) with PR, 17 (10.9%) with NC, and five (3.2%) with PD; three patients (1.9%) could not be evaluated for response. On the treatment arm in which patients received sequential therapy, 105 patients had responses (66.4%; 95% confidence interval, 59.09% to 73.82%), including two (1.3%) with CR, 103 (65.1%) with PR, 41 (26.0%) with NC, and nine (5.7%) with PD; three patients (1.9%) could not be evaluated for response. There was thus a significant difference in response (CR + PR) between the two arms ($P = .0002$).

Treatment Toxicity

Treatment-related toxicity of both treatment arms is listed in Table 2. Myelosuppression occurred more frequently in patients on the concurrent arm than the sequential arm ($P = .0001$). The incidence of esophageal toxicity was identical for patients on both treatment arms.

Survival

Survival analysis was performed after a median follow-up period of 5 years in November 1998. Twenty-seven patients are still alive and disease-free in the concurrent treatment group, whereas 19 are alive and disease-free in the sequen-

Table 2. Toxicity (WHO grade) by Treatment Arm

	Treatment Arm								
	Concurrent (n = 156)				Sequential (n = 158)				
	1	2	3	4	1	2	3	4	*P*
Hemoglobin	13	61	2	14	35	63	44	8	< .0001
Leukocyte	0	2	35	119	7	28	82	39	< .0001
Platelet	22	37	55	27	35	32	31	6	< .0001
AST	23	5	4	2	37	3	4	1	.2416
ALT	36	11	5	2	42	10	4	1	.9267
Serum creatinine	12	2	1	0	14	1	0	0	.9416
Esophagitis	76	18	4	0	76	23	3	0	.9589
Stomatitis	23	5	1	0	22	1	0	0	.1787
Nausea/vomiting	47	55	34	2	44	60	30	4	.9612
Diarrhea	39	6	2	0	37	6	1	0	.6434
Pulmonary	6	2	1	1	8	1	1	1	.8598
Infection	32	27	5	0	33	21	3	0	.2735
Peripheral neuropathy	21	5	0	0	22	2	1	3	.7797

tial treatment group. The median survival duration among patients in the concurrent group was 16.5 months, compared with 13.3 months among patients in the sequential group (Fig 1), demonstrating a significant difference between the two groups (log-rank test, $P = .03998$). Survival rates in the concurrent group of 64.1% at 1 year, 34.6% at 2 years, 22.3% at 3 years, 16.9% at 4 years, and 15.8% at 5 years were better when compared with 54.8%, 27.4%, 14.7% 10.1%, and 8.9%, respectively, in the sequential group. If patients with supraclavicular nodes were excluded from the analysis, then the median survival duration of patients in the concurrent group with disease confined to the thorax was 16.8 months, as compared with 13.8 months for those in the sequential group ($P = .0185$). In this selected group, survival rates in the concurrent group were better at 65.1% at 1 year, 36.5% at 2 years, 25.2% at 3 years, 19.4% at 4 years, and 17.9% at 5 years, compared with 56.4%, 27.8%, 14.3%, 9.8%, and 7.1%, respectively, in the sequential group.

Five patients who had an apparent response after completion of radiotherapy and chemotherapy received surgery. Of these five patients, two in the sequential group had a complete resection and are alive 3 years and 4 years after therapy. However, the remaining two patients in the concurrent group and one patient in the sequential group had incomplete resection and died of recurrence 15, 16, and 33 months after therapy.

Multivariate analysis for each pretreatment variable was performed. PS ($0 + 1$ *v* 2, $P = .00097$) and arm (concurrent *v* sequential, $P = .03998$) were most significantly related to survival. Age (< 65 *v* ≥ 65, $P = .94650$), sex (male *v*

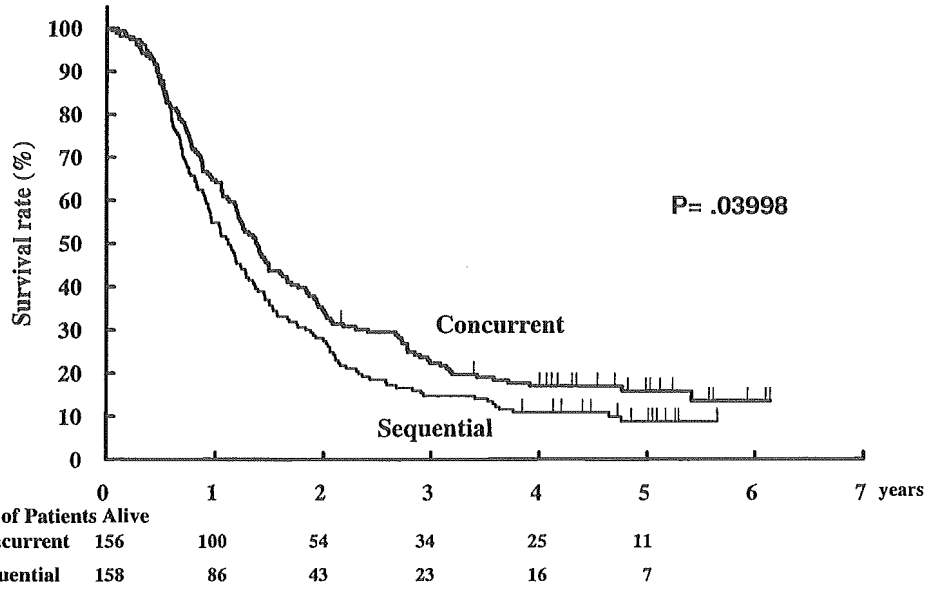

Fig 1. Overall survival in patients with NSCLC according to treatment group.

Table 3. First Site of Relapse

Site	Concurrent Therapy No. of Patients	%	Sequential Therapy No. of Patients	%	P
No. of patients	147		145		
No. of relapse cases	117	79.6	120	82.8	.550
Local	48	32.7	57	39.3	.273
Alone	42		49		
+ Distant	6		8		
Brain	28	19.0	13	9.0	.018
Alone	25		12		
+ Other sites	3		1		
Supraclavicular LN	3	2.0	10	6.9	.051
Alone	1		8		
+ Other sites	2		2		
Pleura	11	7.5	7	4.8	.467
Alone	9		4		
+ Other sites	2		3		
Pulmonary	12	8.2	10	6.9	.825
Alone	8		9		
+ Other sites	4		1		
Bone	8	5.4	13	9.0	.266
Alone	6		10		
+ Other sites	2		3		
Adrenal	3	2.0	4	2.8	.722
Alone	2		2		
+ Other sites	1		2		
Liver	4	2.7	5	3.4	.749
Alone	3		2		
+ Other sites	1		3		
Abdomen	4	2.7	2	1.4	.684
Alone	3		2		
+ Other sites	1		0		
Others	9	6.1	13	9.0	.384
Alone	7		9		
+ Other sites	2		4		

Abbreviation: LN, lymph nodes.

female, $P = .71105$), disease extent (with *v* without supraclavicular lymph node metastasis, $P = .36316$), and histology (squamous cell *v* nonsquamous, $P = .78291$) were not significantly related to survival. The regression model showed that PS ($P = .0008$) and arm ($P = .0340$) were the only independent prognostic indicators for survival in this population.

Relapse Sites

The first relapse sites at the median follow-up time of 5 years in 294 patients who had CR, PR, and NC after therapy on both arms are listed in Table 3. Of 148 patients on the concurrent arm, a first relapse occurred in 117 patients, and 31 were disease-free. Of 146 patients on the sequential arm, a first relapse occurred in 20 patients, and 25 were disease-free. Information regarding relapse for one patient who had NC after therapy and died of lung cancer was not obtained. There was no difference between the two groups regarding rate of local relapse. The incidence of brain metastasis on the concurrent arm was significantly higher than that of the sequential arm ($P = .018$), but metastasis in supraclavicular lymph node occurred more frequently in the sequential arm ($P = .0501$).

For these patients with measurable lesions, there was no difference in failure-free survival between the two groups (8.3 *v* 8.0 months, $P = .1518$; Fig 2).

Treatment Delivery

Table 4 outlines the delivery of treatment. One hundred forty-six (93.6%) of 156 patients assigned to the concurrent therapy arm and 151 (95.6%) of 158 patients assigned to the sequential arm received chemotherapy delivered as defined by the protocol (≥ two courses). Seventy-nine (59%) of 156

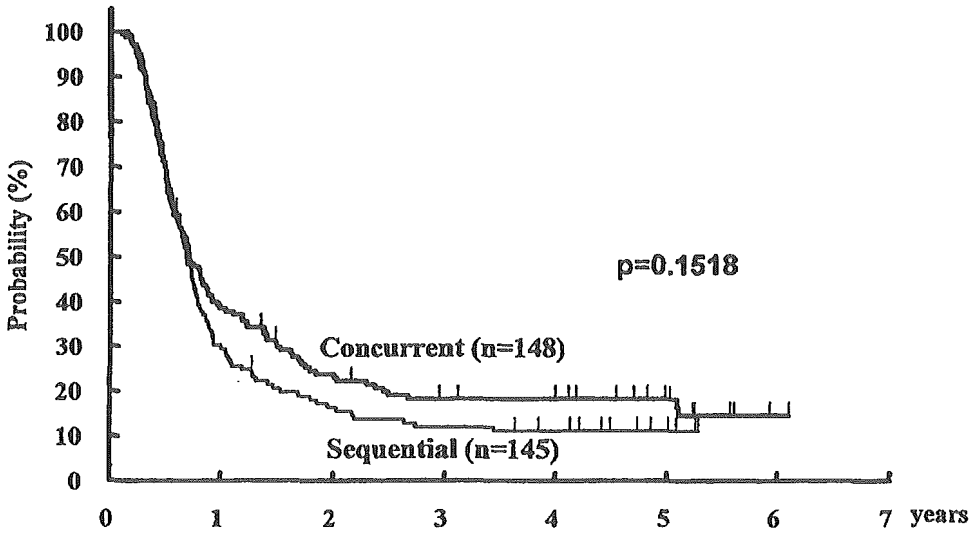

Fig 2. Failure-free survival among assessable patients according to treatment group.

Table 4. Treatment Delivery

	Concurrent Therapy (no. of patients)		Sequential Therapy (no. of patients	
Total no. of patients	156		158	
No. of chemotherapy courses				
0	0		1	
1	10		6	
2	67		112	
3	58		31	
4	21		8	
Mean	2.55	2.18		
Radiation dose, Gy				
< 56	20		27	
56	129		120	
> 56	7		11	
Mean	54.3	55.3		
Range	26-60	20-70		

patients on the concurrent arm and 39 (24.7%) of 158 patients on the sequential arm received three to four courses of chemotherapy. Thus patients treated with the concurrent therapy were given more chemotherapy courses compared with patients treated with the sequential therapy (P = .0001). Patients in the concurrent therapy group and in the sequential therapy group received a mean of 2.55 and 2.18 courses of chemotherapy, respectively.

On the other hand, 136 (87.2%) of 156 patients on the concurrent arm and 129 (81.6%) of 158 patients on the sequential arm received ≥ 56 Gy of radiotherapy. The mean dose in irradiation was identical on both arms (concurrent *v* sequential, 54.3 *v* 55.3).

Accordingly, 128 (82.1%) of 156 patients on the concurrent arm and 131 (82.9%) of 158 on the sequential arm received chemotherapy (≥ two courses) and radiotherapy (≥ 56 Gy) delivered as defined by the protocol. Compliance with protocol of chemotherapy and radiotherapy was acceptable in that approximately 80% of patients received treatment per protocol or with minor differences in protocol delivery.

DISCUSSION

The combination of radiotherapy and chemotherapy using cisplatin-based regimens has been extensively investigated for application in locally advanced NSCLC. Recent trials conducted by Le Chevalier et al,[2,17] Dillman et al,[3] and Sause et al[18] demonstrated a benefit in the sequential approach.

The median survival time (13.4 months) and 2- and 3-year survival rates (27.2% and 13.7%, respectively) in the sequential group from our study seem similar to the results observed in the trials of Dillman et al (median survival time, 13.7 months; 2- and 3-year survival rates, 26% and 24%, respectively),[3] Sause et al (median survival time, 13.8 months),[18] and Le Chevalier et al (median survival time, 12 months; 2- and 3-year survival rates, 21% and 1%).[2] The results of our trial further demonstrate a significant survival advantage for the concurrent approach compared with the sequential approach. The median survival duration in the concurrent approach demonstrated an improvement of 3 months over that of the sequential approach (16.5 *v* 13.3 months), but the improvement in long-term (2 to 5 years) survival rates in the concurrent approach was slightly better (< 10%) when compared with the sequential approach.

The Radiation Therapy Oncology Group14 (73-01) previously reported a randomized study of various irradiation doses and fractionation schedules in radiotherapy for NSCLC.[19] The 60-Gy continuous schedule was superior to the same dose given in a split-course fashion. However, we often experienced irregular interruption of radiotherapy in a pilot study of concurrent continuous radiotherapy and the MVP regimen. The main cause of this interruption in radiotherapy was neutropenic fever. Thus in our phase II and current study, we chose regularly scheduled interruption (ie, split-course radiotherapy). In the current study, the incidence of esophagitis was identical for the concurrent and the sequential groups. However, Radiation Therapy Oncology Group 92-04, using a continuous schedule in the concurrent arm in a randomized phase II study comparing concurrent with sequential chemotherapy/radiation for advanced NSCLC, demonstrated that patients on the concurrent arm experienced significantly more acute and chronic esophagitis, although a twice-a-day fractionation schedule was used.[20] The low incidence of esophagitis in our study may be due to use of the split-course schedule in radiotherapy (grade 3 esophagitis in concurrent *v* sequential therapy, four of 156 patients *v* three of 158 patients). We believe that this schedule might help lessen the toxicity associated with concurrent radiotherapy and intensive chemotherapy and make treatment more acceptable to patients.

The timing of chemotherapy relative to radiotherapy may be important. Recently, we compared concurrent versus sequential radiotherapy and chemotherapy for limited-stage small-cell lung cancer (SCLC) in a randomized trial of 228 patients,[21] and our results suggested improved outcome for patients who receive concurrent therapy. The data supported a policy of administering thoracic radiation soon after initiation of chemotherapy for limited-stage SCLC.[22] Thus these trials for SCLC and NSCLC may support the general concept that early destruction of as many cancer cells as possible by combined-modality treatment is a therapeutic principle that may also apply to treatment of cancers other than lung cancers[22]; these trials may also support the concept

that direct enhancement of local control by simultaneous chemotherapy and radiotherapy may improve both local and long-term outcome.

In the delivery of chemotherapy in our current study, patients who were treated with concurrent therapy received significantly more chemotherapy courses (mean, 2.55 courses) when compared with patients treated with sequential therapy (mean, 2.18 courses). In a randomized trial by Le Chevalier et al,[2] patients who received chemotherapy followed by radiotherapy and who responded to chemotherapy were given three additional chemotherapy courses after radiotherapy. On the other hand, in the studies of Dillman et al[3] and Sause et al[18] with the same sequential approach, only two chemotherapy courses were administered before radiotherapy. Although no randomized study comparing the administration of additional chemotherapy versus no administration of additional chemotherapy after radiotherapy has been conducted, the survival results were identical among the three trials (median survival time, 12 to 13.8 months). No randomized trial has addressed the optimal duration of chemotherapy in combined radiotherapy and chemotherapy for locally advanced NSCLC.

The incidence of myelosuppression was higher among patients on the concurrent therapy arm than among patients on the sequential therapy arm. Further studies with this approach are warranted to improve toxicity. However, we experienced three treatment-related deaths in the sequential group and one in the concurrent group. This finding suggests that the concurrent approach is acceptable for selected patients with unresectable stage III NSCLC.

A 3-month improvement in median survival and better 2- and 3-year survival rates observed in the concurrent radiotherapy and MVP group are encouraging. At the same time, because approximately 70% of the patients in this series relapsed within 3 years, further improvements in the treatment are still needed. More effective chemotherapy must be developed and exploration of improved radiation therapy must be conducted to increase the benefit of this approach.

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APPENDIX

Additional participating institutions and specialists from the West Japan Lung Cancer Group include the following: National Kinki Central Hospital for Chest Diseases (M. Akira), Osaka Prefectural Habikino Hospital (T. Tada), Osaka City University (T. Nakazima), Kobe City General Hospital (H. Fukuda), Osaka Medical Center Cancer and Cardiovascular Diseases (M. Chatani), Aichi Cancer Center (S. Fuwa), Gifu Municipal Hospital (T. Sawa), Gifu University (K. Goto), National Kyoto Hospital (H. Asamoto), Kinki University (S. Nakajima), Osaka Teishin Hospital (K. Komuta), Osaka General Hospital (S. Negoro), Hyogo Medical College (T. Igarashi), Wakayama Rosai Hospital (T. Hoso), Hiroshima University (M. Yamakido), Kagawa Medical School (J. Takahara), Kagawa Prefectural Central Hospital (M. Kamei), Aso Izka Hospital (H. Yamamoto), Kumamoto Chuo Hospital (E. Kinuwaki), National Minamikyushu Hospital (F. Iwami), Nagasaki Municipal Citizens Hospital (M. Nakano), Saseho City General Hospital (J. Araki), Kumamoto Regional Medical Center (H. Senda), and Kyushu University (K. Nobutomo).

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Phase I trial of weekly docetaxel in elderly patients with non-small cell lung cancer

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Abstract

Recent experience with weekly administration of docetaxel has demonstrated less myelotoxicity and suggested that this regimen holds promise for elderly patients at the high risk of myelosuppression. However, in this phase I trial of weekly docetaxel conducted only in elderly patients (70 years old or more) with non-small cell lung cancer (NSCLC), the toxicity profile was markedly different from that in previous reports. The dose-limiting toxicities were neutropenia, diarrhea and infection, all of which were observed at a dose of 30 mg/m^2/week and the maximum-tolerated dose by protocol definition was 30 mg/m^2/week. Although other hematological and non-hematological toxicities observed in this treatment were generally moderate and were well tolerated by elderly patients with NSCLC, the risk of myelosuppression still requires careful attention.

Keywords: Chemotherapy; Docetaxel; Elderly; Non-small cell lung cancer; Phase I; Weekly

1. Introduction

Cisplatin-based chemotherapy is now considered standard treatment for advanced or metastatic non-small cell lung cancer (NSCLC) [1–5]. However, the number of elderly NSCLC patients, who frequently cannot undergo that treatment because of presence of comorbidities, has recently been increasing. The Italian study group reported that chemotherapy with vinorelbine was associated with longer survival than was best supportive care in elderly NSCLC patients [6,7], and Frasci et al. reported that a combined regimen of vinorelbine and gemcitabine yielded better survival than vinorelbine alone in elderly NSCLC patients on a small sample size trial (120 patients overall), which was interrupted by an interim-survival analysis [8]. Though, a larger randomized trial performed on 700 patients failed to demonstrate a similar survival benefit [9,10], suggesting that the role of this non-platinum doublet regimen for elderly patients is still controversial.

Docetaxel has demonstrated a high single-agent activity in both chemo-naive and refractory NSCLC [11–13]. The docetaxel dose in the majority of early clinical trials was 100 mg/m^2 administered once every 3 weeks, however, more than 90% of patients receiving this dose developed grade 3 or 4 neutropenia, and some required hospitalization to treat neutropenic fever. Even at a 60-mg/m^2 dose, grade 3 or 4 neutropenia was observed in more than 80% of patients in the Japanese trial [14].

Recent clinical trials have shown marked reductions in myelosuppression when docetaxel was administered on a weekly schedule [15,16]. In a phase I trial in patients with advanced refractory tumors, the maximum tolerated dose (MTD) of weekly docetaxel was 43 mg/m^2/week. Fatigue and asthenia were the dose-limiting toxicities (DLTs), and grade 3 leukopenia was observed in only 14% of patients [15]. A subsequent phase II trial in elderly NSCLC patients used a docetaxel dose of 36 mg/m^2 administered weekly for 6 weeks. An 18% response rate and moderate toxicities were reported [16]. However, 49% of the patients included were less

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than 70 years old (the youngest patient was 55 years old), and patients with good performance status (PS) and those with poor PS (PS 2) were mixed up regardless of their age in that trial. Thus, the safety of weekly docetaxel for the elderly patients only have not yet been reported.

This report describes results of a phase I trial of weekly docetaxel in elderly ($\geqslant 70$ years old) NSCLC patients with a good PS.

2. Methods

2.1. Eligibility

Patients with histologically confirmed NSCLC unsuitable for primary surgical treatment were enrolled in the study. Other eligibility criteria included having received $\leqslant 1$ previous chemotherapy regimen, presence of at least one measurable lesion, $\geqslant 70$ years of age, estimated life expectancy > 12 weeks, Eastern Cooperative Oncology Group (ECOG) PS 0 or 1, adequate hematopoietic reserve (absolute neutrophil count (ANC) $> 2000/\mu l$, platelet count $> 100\,000/\mu l$), adequate hepatic and renal function, including serum creatinine < 1.5 times the upper limit of normal, creatinine clearance > 60 ml/min, serum bilirubin $<$ 1.5 times the upper limit of normal, and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 2.0 times the upper limit of normal. Patients with symptomatic brain metastasis were ineligible. Patients with severe comorbidity were also ineligible. Signed informed consent forms were required for patient inclusion. The protocol was approved by the review board of each institution.

2.2. Dose escalation

Docetaxel was administered on days 1, 8, and 15 of each 28-day treatment cycle. The starting dose level was 25 mg/m^2; dose levels were escalated in 5 mg/m^2 increments. Six patients were treated at each dose level, and no intra-patient dose escalation was allowed.

On day 1 of each 28-day cycle, patients had to have an ANC $> 1500/\mu l$ and a platelet count $> 75\,000/\mu l$ to receive treatment. A treatment delay of up to 2 weeks was permitted to allow recovery of blood counts to $<$ grade 1 toxicity level (National Cancer Institute Common Toxicity Criteria, NCI-CTC). Docetaxel was administered on days 8 and 15 if the ANC was $>$ $1000/\mu l$ and platelet count $> 75\,000/\mu l$; docetaxel was not administered in the presence of grade 3/4 neutropenia, $>$ grade 2 thrombocytopenia, $>$ grade 2 nonhematologic toxicity other than nausea, vomiting, alopecia, or fatigue, or $>$ grade 3 nausea, vomiting, alopecia, or fatigue.

2.3. Drug administration

Docetaxel was diluted in 250 ml of 5% glucose solution and administered by 1-h intravenous infusion. Premedication with corticosteroid was recommended. No prophylactic granulocyte colony-stimulating factor (G-CSF) or prophylactic antibiotic support was planned.

2.4. Treatment evaluation

Complete and differential blood cell counts were performed on days 1, 8, 15, and 21 of each 28-day cycle. Biochemical analysis, including serum creatinine, electrolytes, alkaline phosphatase, bilirubin, AST, ALT, calcium, total protein, and albumin, was performed on the same day.

Toxic effects were assessed according to NCI-CTC. DLT was defined as toxicity during the first treatment cycle consisting of grade 4 neutropenia, $>$ grade 3 other hematologic toxicity, $>$ grade 2 non-hematologic toxicity other than nausea, vomiting, alopecia, and fatigue, or failure to start the next treatment cycle on day 42.

The MTD was defined as the dose level at which at least three patients experienced a DLT. All patients were to continue treatment unless their disease progressed and/or unacceptable toxicity occurred, the patient refused further treatment, or the physician decided to discontinue treatment.

Patients were evaluated for response according to the new guidelines of the World Health Organization (WHO), i.e. Response Evaluation Criteria in Solid Tumors (RECIST). During treatment, tumor response was assessed based on either clinical evaluation, computed tomography scans, and/or ultrasound every two cycles. Responding patients had tumor assessments repeated 4 weeks after the initial determination of response.

3. Results

Between May 2000 and February 2001, 11 patients were enrolled in the study. Patient characteristics are listed in Table 1. A total of 19 treatment cycles were administered, with a median of two cycles per patient (range, 1–2 courses). Six patients were treated at dose level 1 (25 mg/m^2/week) and 5 patients were treated at dose level 2 (30 mg/m^2/week). Three patients received only one treatment cycle because of disease progression (two patients) or the physician's decision (one patient). All patients were assessable for tumor response, and all cycles were assessable for toxicity. At dose level 2, DLTs were observed in three of five patients, and in accordance with the protocol, patient accrual was stopped.