Phase I study of cisplatin, vinorelbine, and concurrent thoracic radiotherapy for unresectable stage III non-small cell lung cancer

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To determine the recommended phase II dose of vinorelbine in combination with cisplatin and thoracic radiotherapy (TRT) in patients with unresectable stage III non-small cell lung cancer (NSCLC), 18 patients received cisplatin (80 mg/m^2) on day 1 and vinorelbine (20 mg/m^2 in level 1, and 25 mg/m^2 in level 2) on days 1 and 8 every 4 weeks for 4 cycles. TRT consisted of a single dose of 2 Gy once daily for 3 weeks followed by a rest of 4 days, and then the same TRT for 3 weeks to a total dose of 60 Gy. Fifteen (83%) patients received 60 Gy of TRT and 14 (78%) patients received 4 cycles of chemotherapy. Ten (77%) of 13 patients at level 1 and all 5 patients at level 2 developed grade 3–4 neutropenia. Four (31%) patients at level 1 and 3 (60%) patients at level 2 developed grade 3–4 infection. None developed ≥grade 3 esophagitis or lung toxicity. Dose-limiting toxicity was noted in 33% of the patients in level 1 and in 60% of the patients in level 2. The overall response rate (95% confidence interval) was 83% (59–96%) with 15 partial responses. The median survival time was 30.4 months, and the 1-year, 2-year, and 3-year survival rates were 72%, 61%, and 50%, respectively. In conclusion, the recommended dose is the level 1 dose, and this regimen is feasible and promising in patients with stage III NSCLC. (Cancer Sci 2004; 95: 691–695)

Stage III locally advanced non-small cell lung cancer (NSCLC) accounts for about 25% of all lung cancer cases.[1)] Successful treatment of this disease rests on the control of both clinically apparent intrathoracic disease and occult systemic micrometastases, and therefore a combination of systemic chemotherapy and thoracic radiotherapy is indicated in many patients with good performance status and no pleural effusion.[2)] Concurrent chemoradiotherapy is superior to the sequential approach, as shown by recent phase III trials in unresectable stage III NSCLC, in which the median survival time was 15.0 to 17.0 months in the concurrent arm and 13.3 to 14.6 months in the sequential arm, although acute esophagitis was more severe in the concurrent arm.[3–5)] Chemotherapy regimens combined with simultaneous thoracic radiotherapy have consisted of cisplatin plus etoposide and cisplatin plus vinca alkaloids,[3, 4)] and a combination of cisplatin plus vindesine, with or without mitomycin, has been widely used in Japan.[5–8)]

Vinorelbine, a new semisynthetic vinca alkaloid with a substitution in the catharanthine ring, interacts with tubulin and microtubule-associated proteins in a manner different from the older vinca alkaloids, and it more selectively depolymerizes microtubules in mitotic spindles.[9)] Several randomized trials have shown vinorelbine to be more active against advanced or metastatic NSCLC than vindesine as a single agent or in combination with cisplatin.[10–13)] Thus, incorporation of vinorelbine into concurrent chemoradiotherapy instead of vindesine is an important strategy for the treatment of locally advanced NSCLC. The objective of this study was to determine the maximum tolerated dose (MTD) and recommended dose of vinorelbine for phase II studies in combination with cisplatin, with or without mitomycin, and thoracic radiotherapy for patients with unresectable stage III NSCLC. We planned to start with the cisplatin and vinorelbine combination and then add mitomycin.

Patients and Methods

Patient selection. The eligibility criteria were: histologically or cytologically proven NSCLC; unresectable stage IIIA or IIIB disease; no previous treatment; measurable disease; tumor within an estimated irradiation field no larger than half the hemithorax; age between 20 years and 74 years; Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1[14)]; adequate bone marrow function (12.0×10^9/liter ≥white blood cell [WBC] count $\geq4.0\times10^9$/liter, neutrophil count $\geq2.0\times10^9$/liter, hemoglobin ≥10.0 g/dl, and platelet count $\geq100\times10^9$/liter), liver function (total bilirubin ≤1.5 mg/dl and transaminase ≤twice the upper limit of the normal value), and renal function (serum creatinine ≤1.5 mg/dl and creatinine clearance ≥60 ml/min); and a PaO_2 of 70 Torr or more. Patients were excluded if they had malignant pleural or pericardial effusion, active double cancer, a concomitant serious illness, such as uncontrolled angina pectoris, myocardial infarction in the previous 3 months, heart failure, uncontrolled diabetes mellitus, uncontrolled hypertension, interstitial pneumonia or lung fibrosis identified by a chest X-ray, chronic obstructive lung disease, infection or other diseases contraindicating chemotherapy or radiotherapy, pregnancy, or breast-feeding. All patients gave their written informed consent.

Pretreatment evaluation. The pretreatment assessment included a complete blood cell count and differential count, routine chemistry determinations, creatinine clearance, blood gas analysis, electrocardiogram, lung function testing, chest X-rays, chest computed tomographic (CT) scan, brain CT scan or magnetic resonance imaging, abdominal CT scan or ultrasonography, and radionuclide bone scan.

Treatment schedule. The dose levels and doses of each anticancer agent are shown in Table 1. Cisplatin and vinorelbine were administered at dose levels 1 and 2. It was planned to give cisplatin, vinorelbine, and mitomycin at dose levels 3–5, but because the MTD was determined to be dose level 2, dose levels 3–5 were not used. Cisplatin was administered on day 1 by intravenous infusion over 60 min together with 2500 to 3000 ml of fluid for hydration. Vinorelbine diluted in 40 ml of normal saline was administered by bolus intravenous injection on days 1 and 8. All patients received prophylactic antiemetic ther-

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apy consisting of a 5HT3-antagonist and a steroid. This chemotherapy regimen was repeated every 4 weeks for 4 cycles.

Thoracic radiotherapy with photon beams from a liniac or microtron accelerator with energy between 6 and 10 MV at a single dose of 2 Gy once daily given 15 times over 3 weeks was begun on day 2 of the first cycle of cisplatin and vinorelbine chemotherapy, and followed by a short rest period of 4 days. The same radiotherapy was begun on day 1 of the second cycle of chemotherapy to a total dose of 60 Gy. The clinical target volume (CTV) was based on conventional chest X-ray and CT scans, and included the primary lesion (CTV1), involved lymph nodes whose short diameter was 1 cm or larger (CTV2), and the ipsilateral pulmonary hilum and bilateral mediastinum area (CTV3). Anterior and posterior parallel opposed fields encompassed the initial planned target volume (PTV), consisting of CTV1–3 with the superior and inferior field margins extended to 1 to 2 cm and the lateral field margins extended to 0.5 cm for respiratory variation and fixation error. The boost PTV included only CTV1–2 based on the second CT scans with the same margins. The spinal cord dose was limited to 40 Gy by using oblique parallel opposed fields.

Toxicity assessment and treatment modification. Complete blood cell counts and differential counts, routine chemistry determinations, and a chest X-ray were performed once a week during the course of treatment. Acute toxicity was graded according to the NCI Common Toxicity Criteria version 2.0 issued in 1998, and late toxicity associated with thoracic radiotherapy was graded according to the RTOG Late Radiation Morbidity Scoring Schema.[15] Vinorelbine administration on day 8 was omitted if any of the following toxicities was noted: WBC count $<3.0\times10^9$/liter, neutrophil count $<1.5\times10^9$/liter, platelet count $<100\times10^9$/liter, elevated hepatic transaminase level or total serum bilirubin ≥grade 2, fever ≥38°C, or performance status ≥2. Subsequent cycles of chemotherapy were delayed if any of the following toxicities was noted on day 1: WBC count $<3.0\times10^9$/liter, neutrophil count $<1.5\times10^9$/liter, platelet count $<100\times10^9$/liter, serum creatinine level ≥1.6 mg/dl, elevated hepatic transaminase level or total serum bilirubin ≥grade 2, fever ≥38°C, or performance status ≥2. The doses of cisplatin and vinorelbine were reduced by 25% in all subsequent cycles if any of the following toxicities was noted: WBC count $<1.0\times10^9$/liter, platelet count $<20\times10^9$/liter, or grade 3 or severer non-hematological toxicity, except for nausea and vomiting. The dose of cisplatin was reduced by 25% in all subsequent cycles if the serum creatinine level was elevated to 2.0 mg/dl or higher. Thoracic radiotherapy was suspended if any of the following toxicities was noted: WBC count $<1.0\times10^9$/liter, platelet count $<20\times10^9$/liter, esophagitis ≥grade 3, fever ≥38°C, performance status ≥3, or PaO_2 <70 Torr. Thoracic radiotherapy was terminated if this toxicity persisted for more than 2 weeks. Granulocyte colony-stimulating factor support was used if the neutrophil count was $<0.5\times10^9$/liter for more than 4 days, the WBC count was $<1.0\times10^9$/liter, or febrile neutropenia ≥grade 3 was noted.

Dose-limiting toxicity, MTD, and recommended dose for phase II studies. The dose-limiting toxicity (DLT) was defined as a neutrophil count $<0.5\times10^9$/liter lasting 4 days or longer, febrile neutropenia ≥grade 3, platelet count $<20\times10^9$/liter, grade 3 or more severe non-hematological toxicity other than nausea and vomiting, and patient's refusal to receive subsequent treatment. Doses were escalated according to the frequency of DLT evaluated during the first and second cycles of chemotherapy and thoracic radiation. Six patients were initially enrolled at each dose level. If one or none of them experienced DLT, the next cohort of patients was treated at the next higher dose level. If 2 of the 6 patients experienced DLT, then 6 additional patients were enrolled at the same dose level to make a total of 12 patients. If 4 or fewer patients experienced DLT, the next cohort of patients was treated at the next higher dose level. If 5 or more of the 12 patients experienced DLT, that level was considered to be the MTD. If 3 of the initial 6 patients experienced DLT, that level was considered to be the MTD. The recommended dose for phase II trials was defined as the dose preceding the MTD.

Table 1. Dose level and the dose of each anticancer agent

Dose level	Cisplatin (mg/m²)	Vinorelbine (mg/m²)	Mitomycin (mg/m²)
−1	80	15	—
1	80	20	—
2	80	25	—
3	80	15	8
4	80	20	8
5	80	25	8

Response evaluation. Objective tumor response was evaluated according to the WHO criteria issued in 1979.[16] A complete response (CR) was defined as the disappearance of all known disease for at least 4 weeks with no new lesions appearing. A partial response (PR) was defined as an at least 50% decrease in total tumor size for at least 4 weeks without the appearance of new lesions. No change (NC) was defined as the absence of a partial or complete response with no progressive or new lesions observed for at least 4 weeks. Progressive disease was defined as a 25% or greater increase in the size of any measurable lesion or the appearance of new lesions.

Study design, data management, and statistical considerations. This study was designed as a phase I study at two institutions, the National Cancer Center Hospital and Kanagawa Cancer Center. The protocol and consent form were approved by the Institutional Review Board of each institution. Registration was conducted at the Registration Center. Data management, periodic monitoring, and the final analysis were performed by the Study Coordinator. A patient accrual period of 24 months and a follow-up period of 18 months were planned. Overall survival time and progression-free survival time were estimated by the Kaplan-Meier method.[17] Survival time was measured from the date of registration to the date of death due to any cause. Progression-free survival time was measured from the date of registration to the date of disease progression or death. Patients who were lost to follow-up without event were censored at the date of their last known follow-up.

Results

Registration and characteristics of the patients. From October 1999 to August 2000, 13 patients were registered at dose level 1 and 5 patients at dose level 2. The detailed demographic characteristics of the patients are listed in Table 2. All patients had unresectable IIIA-N2 or IIIB disease. One of the 6 patients enrolled at dose level 1 developed bacterial meningitis during the second cycle of chemotherapy, and that case is described in detail elsewhere.[18] We did not include it in the assessment of DLT, because the bacterial meningitis was not specifically related to treatment. We registered another patient at the same dose level, and 2 cases of DLT were noted among the initial 6 patients evaluable for DLT. We added another 6 patients, and DLT was noted in 4 of the 12 patients registered at the dose level 1. Of the 5 patients registered at level 2, 3 patients developed DLT. This dose level was determined to be the MTD, and patient accrual to this study was terminated.

Treatment delivery. Treatment delivery was generally well maintained, and it did not differ between the two dose levels (Table 3). Full dose (60 Gy) thoracic radiotherapy was completed in 77% and 100% of the patients at dose levels 1 and 2,

Table 2. Patients' characteristics

		Median (range)	*N* (%)
Number of patients			18
Gender	male		16 (89)
	female		2 (11)
Age	median (range)	59 (48–69)	
PS	0		4 (22)
	1		14 (78)
Body weight loss	<5%		12 (67)
	5–9%		4 (22)
	≥10%		2 (11)
T-factor	1		1 (6)
	2		6 (33)
	3		7 (39)
	4		4 (22)
N-factor	2		11 (61)
	3		7 (39)
Clinical stage	IIIA		9 (50)
	IIIB		9 (50)
Histology	adenocarcinoma		14 (78)
	squamous cell carcinoma		3 (17)
	adenosquamous carcinoma		1 (6)

Table 3. Treatment delivery

	Dose level 1 (*N*=13)	Dose level 2 (*N*=5)
	N (%)	*N* (%)
Initial irradiation field (cm^2)		
median (range)	171 (128–529)	182 (128–248)
Total dose of radiotherapy (Gy)		
60	10 (77)	5 (100)
50–59	1 (8)	0
<50	2 (15)	0
Delay of radiotherapy (days)[1)]		
<5	6 (60)	3 (60)
5≤	4 (40)	2 (40)
Number of chemotherapy cycles		
4	10 (77)	4 (80)
3	0	1 (20)
2	2 (15)	0
1	1 (8)	0
Omission of vinorelbine administration on day 8		
0	9 (69)	2 (40)
1	4 (31)	2 (40)
3	0	1 (20)

1) Evaluated in patients who received 60 Gy radiotherapy (*N*=15).

respectively. Delays in radiotherapy evaluated in patients who completed the full course of radiotherapy amounted to less than 5 days in 60% of the patients at both levels. Full cycles (4 cycles) of chemotherapy were administered to 77% and 80% of the patients at dose levels 1 and 2, respectively, but vinorelbine administration on day 8 was more frequently omitted at dose level 2 (Table 3).

Toxicity, MTD, and the recommended dose for phase II trials. Acute severe toxicity was mainly hematological (Table 4). Grade 3–4 leukopenia and neutropenia were noted in 77% and 100% of the patients at dose levels 1 and 2, respectively. Grade 3 anemia was observed in 23% and 20% of the patients at dose levels 1 and 2, respectively, but no blood transfusions were required. Thrombocytopenia was mild. Grade 4 transaminase elevation was observed in 1 patient during the first cycle of chemotherapy, but no subjective manifestations associated with liver dysfunction were noted. Chemotherapy was discontinued and the transaminases quickly decreased to within their normal ranges. Transient asymptomatic grade 3 hyponatremia was noted in 1 patient. Grade 3–4 infection was noted in 7 patients. Bacterial meningitis unassociated with neutropenia developed on day 6 of the second cycle of chemotherapy in 1 patient.[18)] The other grade 3–4 infections were all associated with neutropenia. Esophagitis was mild in this study, and no grade 3–4 esophagitis was noted. No deaths occurred during or within 30 days of therapy.

DLT was noted in 4 of the 12 (33%) evaluable patients at dose level 1, and in 3 of the 5 (60%) at dose level 2. Six of these 7 DLTs were grade 3–4 infection associated with neutropenia, and the other 1 was grade 4 transaminase elevation. Thus, we determined that dose level 2 was the MTD, and dose level 1 was recommended as the dose for phase II trials.

Table 4. Acute toxicity

Toxicity	Dose level 1 (*N*=13), Grade					Dose level 2 (*N*=5), Grade				
	1	2	3	4	3–4 (%)	1	2	3	4	3–4 (%)
Hematological										
Leukopenia	0	2	9	1	(77)	0	0	4	1	(100)
Neutropenia	1	1	7	3	(77)	0	0	1	4	(100)
Anemia	4	6	3	0	(23)	2	2	1	0	(20)
Thrombocytopenia	1	2	0	0	(0)	1	0	0	0	(0)
Non-hematological										
AST	2	0	0	1	(8)	1	0	0	0	(0)
ALT	7	0	0	1	(8)	0	1	0	0	(0)
Total bilirubin	2	1	0	0	(0)	2	0	0	0	(0)
Creatinine	2	2	0	0	(0)	1	0	0	0	(0)
Hyponatremia	6	0	1	0	(8)	1	0	0	0	(0)
Infection	1	3	2	2	(31)	0	0	3	0	(60)
Nausea	4	1	0	0	(0)	3	0	0	0	(0)
Diarrhea	0	1	0	0	(0)	0	0	0	0	(0)
Stomatitis	2	0	0	0	(0)	0	2	0	0	(0)
Esophagitis	6	1	0	0	(0)	4	0	0	0	(0)
Sensory neuropathy	2	0	0	0	(0)	0	0	0	0	(0)

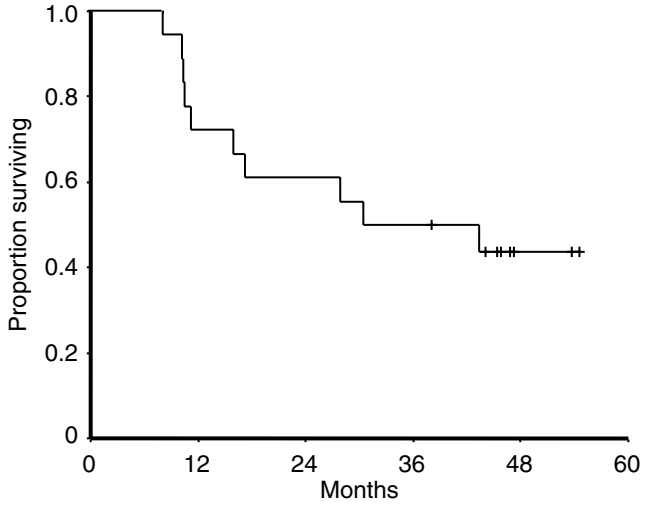

Fig. 1. Overall survival in 18 patients. The median (range) follow-up period of censored cases has been 35.4 (32.0–43.4) months, and the median overall survival time has not yet been reached.

Late lung toxicity associated with thoracic radiotherapy was grade 3 in 1 (6%) patient, grade 2 in 4 (22%) patients, and grade 1 in 8 (44%) patients. No late esophageal toxicity was noted.

Objective responses, relapse pattern, and survival. All patients were included in the analyses of tumor response and survival. No CR, 15 PRs, and 1 NC were noted, and the overall response rate (95% confidence interval) was 83% (59–96%). Relapse was noted in 12 (67%) of 18 patients. Initial relapse sites were locoregional alone in 5 (28%) patients, locoregional and distant in 3 (17%) patients, and distant alone in 4 (22%) patients. Brain metastasis was detected in 5 patients, and the brain was the most frequent site of distant metastasis. The median progression-free survival time was 15.6 months, and the median overall survival time was 30.4 months. The 1-year, 2-year, and 3-year survival rates were 72%, 61%, and 50%, respectively (Fig. 1).

Discussion

The combination of cisplatin, vindesine, and mitomycin with concurrent thoracic radiotherapy has been shown to yield an encouraging survival outcome, a median survival time of 17–19 months, and a 5-year survival rate of 16% in patients with unresectable stage III NSCLC.[5, 7, 8] A Japanese randomized trial revealed that replacement of vindesine by vinorelbine in combination with cisplatin and mitomycin yielded a promising response rate (57% versus 38%, P=0.025) and median survival time (15 months versus 11 months, P<0.01) in patients with stage IIIB or IV NSCLC.[13] Thus, the combination of cisplatin, vinorelbine, and mitomycin is a chemotherapy regimen with potential for combination with concurrent thoracic radiotherapy. The present study, however, showed that a DLT developed in 60% of patients who received cisplatin and vinorelbine 25 mg/m^2 days 1 and 8 (level 2), and since the DLTs were associated with myelosuppression, which is the major critical toxicity of mitomycin, we concluded that it would be impossible to incorporate mitomycin into this regimen.

The recommended doses of vinorelbine of 20 mg/m^2 on days 1 and 8 and cisplatin of 80 mg/m^2 on day 1 repeated every 4 weeks in this study are comparable to the doses used in the CALGB (vinorelbine 15 mg/m^2 on days 1 and 8 and cisplatin 80 mg/m^2 on day 1 repeated every 3 weeks),[19, 20] and the Czech Lung Cancer Cooperative Group (vinorelbine 12.5 mg/m^2 on days 1, 8, and 15 and cisplatin 80 mg/m^2 on day 1, repeated every 4 weeks),[21] but lower than in a Mexican study (vinorelbine at 25 mg/m^2 on days 1 and 8 and cisplatin 100 mg/m^2 on day 1, repeated every 3 weeks).[22] These recommended doses are also lower than expected when compared with the recommended vinorelbine dose combined with cisplatin for metastatic NSCLC (vinorelbine 30 mg/m^2 on days 1 and 8 and cisplatin 80 mg/m^2 on day 1, repeated every 3 weeks),[23] and when compared with the results of vindesine, cisplatin, and mitomycin combined with thoracic radiotherapy, where the full doses can be administered concurrently.[8] Thus, vinorelbine can be safely administered with cisplatin and concurrent thoracic radiotherapy at a maximum dose of two-thirds the optimal dose without radiotherapy.

The results for response and survival in this study, however, were very encouraging. This may have been attributable to patient selection bias, but the percentage of patients who had stage IIIB disease in this study was similar to the percentage in the CALGB randomized phase II study.[20] In addition, 33% of the patients in this study had ≥5% body weight loss, whereas only 7% of the patients did in that study.[20] The median survival time was 30.4 months and exceeded the results of concurrent

chemoradiotherapy with old drug combinations that yielded a median survival time of 15–19 months.[3–8] Thus, it could be argued that the combination of cisplatin and vinorelbine is more active for locally advanced NSCLC than the older drug combinations, although there have not been any randomized trials comparing this regimen with old drug combinations in combination with thoracic radiotherapy in patients with stage III NSCLC. Our results also seem better than those of other trials using concurrent cisplatin, vinorelbine, and thoracic radiotherapy, in which the median survival time was 13 to 18 months.[20, 22] Those trials used induction chemotherapy followed by chemoradiotherapy. Since the response rate to induction chemotherapy is no more than 40%, induction chemotherapy may be disadvantageous. This issue is being evaluated in an on-going CALGB phase III trial.

Severe esophagitis and pneumonitis have been DLTs in many trials of concurrent chemoradiotherapy, but neither was observed in this study. Nevertheless, since the occurrence of these non-hematological toxicities associated with thoracic radiotherapy is sporadic, the sample size in this study may have been too small to detect them. Thus, careful observation for these toxicities is needed in further phase II and phase III trials to definitely establish the safety profile of this regimen.

In conclusion, cisplatin and vinorelbine chemotherapy combined with concurrent full-dose thoracic radiotherapy is feasible, and the recommended dose of vinorelbine for phase II trials is 20 mg/m^2 on days 1 and 8 repeated every 4 weeks. This regimen was highly active in patients with stage III NSCLC.

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