maximum of two dose reductions was allowed for defined adverse events of grade 3 or 4; the minimum dose for *nab*-paclitaxel was 50 mg/m^2 and that for carboplatin was an AUC of 3. All patients underwent comprehensive baseline assessments including clinical laboratory tests and imaging studies. Patients also received follow-up assessments and monitoring at regular intervals. Toxicity evaluations were based on CTCAE v3.0. Objective response was determined according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0.

Pharmacokinetics

Blood samples were collected on days 1 and 15 of cycle 1 (before as well as 0.5, 1, 1.5, 2, 4, 6, 8, 24, 48, and 72 h after dosing of *nab*-paclitaxel; before as well as 0.5, 1.0, 1.5, 3.5, 5.5, 7.5, and 23.5 h after dosing of carboplatin) and centrifuged, and the plasma supernatants were stored at −20°C until analysis. The plasma concentration of paclitaxel was measured by validated high-performance liquid chromatography and tandem mass spectrometry, with the lower limit of quantification being 1.00 ng/mL. The plasma concentration of free platinum derived from carboplatin was determined by validated inductively coupled plasma mass spectrometry, with the lower limit of quantification also being 1.00 ng/mL.

The maximum observed concentration (C_{max}) was determined directly from the observed plasma concentrations. The apparent terminal elimination rate constant (λz) was estimated by linear regression analysis of the decline from individual plasma concentration–time data. At least three points that resulted in the highest correlation coefficient were used for the λz calculation. The terminal elimination half-life ($t_{1/2}$) was calculated as $t_{1/2}=\ln(2)/\lambda z$ for each patient. The area under the plasma concentration–time curve from time 0 to the last measurable time (AUC_{0-t}) was calculated by the trapezoidal method. Individual AUCs extrapolated to infinity (AUC_{inf}) were calculated from the last measurable concentration (C_{last}) according to the formula $AUC_{inf}=AUC_{0-t}+C_{last}/\lambda z$. Individual area under the plasma concentration–time curves for free platinum were estimated from the concentration data. All pharmacokinetic parameters for paclitaxel and free platinum were calculated by noncompartmental techniques with the use of WinNonlin software (Professional Network version 5.2; Pharsight, Mountain View, CA).

Results

Patients

Eighteen chemotherapy-naïve patients with advanced NSCLC were enrolled in the study (Table 1). Four patients were female and 14 were male, and the median age was 64 years (range, 37 to 72). Histological analysis revealed that 14 patients had adenocarcinoma and three had squamous cell carcinoma; one patient who had unspecified NSCLC was classified as "other."

Table 1 Characteristics of the study patients

Number of patients	18
Median age, years (range)	64 (37–72)
Sex	
Male	14
Female	4
Performance status	
0	9
1	9
Disease stage	
IIIB	1
IV	17
Histology	
Adenocarcinoma	14
Squamous cell carcinoma	3
Other	1

Treatment delivery and safety

All 18 enrolled patients received at least one dose of the study treatment. A total of 82 cycles of treatment was delivered overall, with a median number of cycles per patient of 4 (range, 1 to 11). Dose reductions stipulated by the study protocol were instituted in 12 patients, mainly as

Table 2 Treatment-related toxicities

Adverse event	Toxicity grade			
	1	2	3	4
Hematologic				
Neutropenia	1	4	8	4
Anemia	3	9	4	0
Thrombocytopenia	5	6	0	0
Leukopenia	3	4	8	1
Nonhematologic				
Anorexia	4	5	3	0
Nausea	5	3	1	0
Vomiting	3	3	0	0
Fatigue	9	3	0	0
Arthralgia	8	1	0	0
Myalgia	10	1	0	0
Neuropathy: sensory	9	0	1	0
Alopecia	14	4	–	–
Febrile neutropenia	–	–	2	0

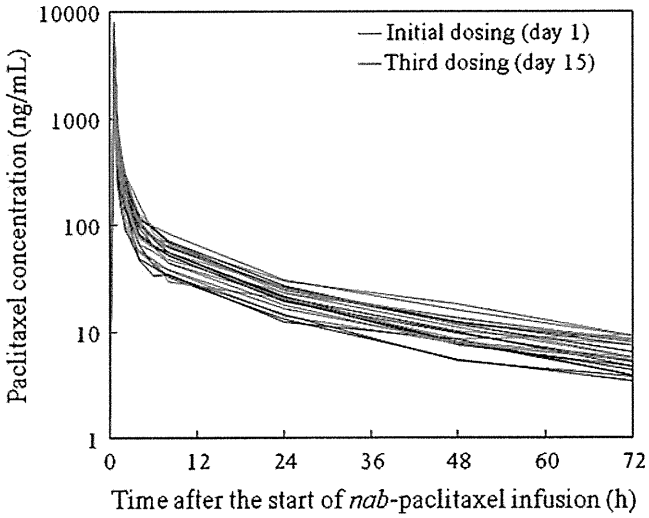

Fig. 1 Individual plasma paclitaxel concentration–time profiles for the initial (day 1) and third (day 15) dosings of *nab*-paclitaxel

a result of the development of neutropenia. The most common reason for treatment discontinuation was disease progression. Treatment was withdrawn because of adverse events (neuropathy or neutropenia) in two patients. All patients were evaluable for safety analysis. The major adverse events during the entire treatment period are shown in Table 2. Hematologic adverse events of grade ≥3 included neutropenia (67%), leukopenia (50%), and anemia (22%), with neutropenia of grade 4 being observed in four patients and leukopenia of grade 4 in one patient. In 12 patients with grade 3 or 4 neutropenia, the median time to neutrophil nadirs was 15 days and the median time from nadir to attaining recovery neutrophil level of 1500/mm^3 or more was 11 days. Nonhematologic toxicities of grade ≥3 included anorexia (17%), febrile neutropenia (11%), nausea (6%), and sensory neuropathy (6%). There were no treatment-related deaths. The adverse events observed in the present study were predictable from the safety profiles of *nab*-paclitaxel and carboplatin, and all events were well managed.

Pharmacokinetics

Twelve and nine patients were evaluable for paclitaxel pharmacokinetics analysis for the initial dosing of *nab*-paclitaxel administered with carboplatin (day 1 of cycle 1) and for the third dosing of *nab*-paclitaxel alone (day 15 of cycle 1), respectively. The individual paclitaxel concentration–time profiles are shown in Fig. 1. Paclitaxel pharmacokinetic profiles showed a multiphasic elimination and appeared similar for the initial and third dosings. A trace level of paclitaxel was detected in the trough samples obtained before the third dosing (Fig. 1), suggesting that paclitaxel accumulates in plasma after repeated administration of *nab*-paclitaxel (on days 1, 8, and 15). The C_{max}, AUC_{0-t}, AUC_{inf}, and $t_{1/2}$ values for paclitaxel were all ~20% higher after the third dosing (day 15) of *nab*-paclitaxel compared with those after the initial dosing on day 1 (Table 3).

Pharmacokinetic parameters for carboplatin were calculated from the free platinum concentration after the initial dosing of carboplatin following that of *nab*-paclitaxel (Table 3). The free platinum concentration–time profiles showed monophasic elimination with a $t_{1/2}$ of ~4 h. The C_{max} and AUC_{inf} for free platinum were 23,903 ng/mL and 3.89 mg·min/mL, respectively.

Tumor response

All 18 enrolled patients were evaluable for response. There were seven partial responses and no complete responses, yielding an overall response rate of 38.9% (95% confidence interval, 17.3 to 64.3).

Table 3 Pharmacokinetic parameters for paclitaxel and free platinum in plasma

Parameter		Initial dosing (day 1)		Third dosing (day 15)	
		Mean	SD	Mean	SD
Paclitaxel					
C_{max}	(ng/mL)	3460	905	4443	1827
AUC_{0-t}	(ng·h/mL)	3893	897	4565	1346
AUC_{inf}	(ng·h/mL)	4073	929	5060	1325
$t_{1/2}$	(h)	24.2	3.02	29.5	3.18
CL	(L/h/ m^2)	25.9	6.61	21.0	5.51
Vz	(L/m^2)	913	292	897	269
Free platinum					
C_{max}	(ng/mL)	23,903	3901		
AUC_{0-t}	(mg·min/mL)	3.86	0.35		
AUC_{inf}	(mg·min/mL)	3.89	0.36		
$t_{1/2}$	(h)	3.97	0.21		

CL total clearance; *Vz* volume of distribution

Discussion

We have evaluated the feasibility of administering *nab*-paclitaxel (100 mg/m^2) weekly as a 30-min uninterrupted intravenous infusion combined with q3w IV administration of carboplatin at an AUC of 6 in Japanese patients with advanced NSCLC. We found that this combination could be safely administered without steroid and antihistamine premedication to prevent the development of hypersensitivity reactions. With regard to nonhematologic toxicities, sensory neuropathy, arthralgia, and myalgia of grade 2 or 3 were each observed in only one patient (5.6%). These results compare favorably with the toxicity profiles described for the standard combination of carboplatin plus solvent-based paclitaxel in previous studies with NSCLC patients, in which higher frequencies (~20%) of sensory neuropathy, arthralgia, and myalgia of grade 2 or 3 were observed [13]. Our findings thus support the notion that *nab*-paclitaxel, a Cremophor EL–free formulation of paclitaxel, has an improved toxicity profile compared with that of conventional paclitaxel formulated with Cremophor EL. This difference in toxicity profiles is important because such toxicities can be debilitating in patients for whom symptom palliation is the primary therapeutic goal.

Although no effect of the sequence of *nab*-paclitaxel and carboplatin administration on the pharmacokinetics of paclitaxel has been described previously [14]. possible interactions of *nab*-paclitaxel and concomitantly administered carboplatin have not been specifically investigated. In the present study, the effect of carboplatin coadministration on the pharmacokinetics of paclitaxel was examined in similar patients treated with carboplatin and weekly *nab*-paclitaxel. The pharmacokinetic parameters of paclitaxel after *nab*-paclitaxel administration with or without carboplatin were similar to those described after single administration of *nab*-paclitaxel at 100 mg/m^2 in a previous study [7]. Whereas the AUC and C_{max} values of paclitaxel were increased ~20% after the third dosing (day 15) of *nab*-paclitaxel compared with those after the first dosing, these increases were likely due to the accumulation of paclitaxel after repeated *nab*-paclitaxel administration because a trace level of paclitaxel in plasma was detected immediately before the third dosing of *nab*-paclitaxel. The pharmacokinetics of carboplatin revealed that the AUC_{inf} calculated from the free platinum concentration was 3.89±0.36 mg·min/mL, corresponding to a range of 24.5 to 45.3% below the target AUC of 6. This finding is consistent with previous results showing that the measured AUC of carboplatin was 30% lower than the target AUC when a modified Calvert formula with creatinine clearance was substituted for glomerular filtration rate [15, 16]. Together, the present data suggest that concomitant administration of *nab*-paclitaxel and carboplatin according to the selected treatment schedule had no substantial impact on the pharmacokinetics of either drug. However, pharmacokinetic findings remain to be verified in a crossover study designed to examine drug-drug interactions.

The physical nature of the Cremophor EL–paclitaxel suspension may limit access of paclitaxel to tumor cells. Preclinical studies have shown that the Cremophor EL–free formulation of paclitaxel (*nab*-paclitaxel) yielded higher intratumoral levels of paclitaxel, as a result of albumin transportation into tumor cells, as well as higher antitumor activity [7, 8]. Although tumor evaluation was not the primary objective of the present study and the small sample size precluded any definitive conclusion regarding treatment efficacy, the combination of *nab*-paclitaxel and carboplatin yielded promising results, with seven partial responses observed among the 18 evaluable patients, for a response rate of 38.9%. A previous study of patients with advanced NSCLC showed that first-line treatment with weekly *nab*-paclitaxel (100 mg/m^2) plus carboplatin (according to the same schedule as that in the present study) similarly obtained a response rate of 48% (95% confidence interval, 28 to 68) [12]. Given its favorable safety profile and promising antitumor activity, this drug combination is currently under evaluation in a large randomized phase III trial (n=1050) in comparison with a standard dose of solvent-based paclitaxel plus carboplatin.

In conclusion, *nab*-paclitaxel administered weekly at 100 mg/m^2 in combination with carboplatin given q3w at an AUC of 6 was found to be well tolerated in Japanese patients with advanced NSCLC. No clinically relevant pharmacokinetic interaction of the two therapeutic agents was detected, and the observed antitumor activity merits further clinical investigation.

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Conflicts of interest H. Yamaya, K. Ono have been full-time employees of Taiho Pharmaceutical Co. Ltd.

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Clinical Outcome of Small Cell Lung Cancer with Pericardial Effusion but without Distant Metastasis

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Background: Pericardial effusion is defined as M1a in the Union Internationale Contre le Cancer seventh tumor, node, metastasis edition for lung cancer. The clinical course of small cell lung cancer (SCLC) with pericardial effusion but without distant metastasis (M1a) has not been adequately investigated.

Methods: The medical records of patients with SCLC treated at the National Cancer Center Hospital East between July 1992 and December 2007 were reviewed. During this period, 766 patients were newly diagnosed as having SCLC. Thirty-three of the 416 patients with limited disease (LD) SCLC (8%) had pericardial effusion. Seventy-nine patients with LD-SCLC (19%) had ipsilateral pleural effusion or dissemination. Of these, 16 patients had both pericardial and ipsilateral pleural effusion. We divided the 96 M1a patients into two subgroups: group A ($n = 33$) included patients with pericardial effusion, and group B ($n = 63$) included patients with ipsilateral pleural effusion or disseminated pleural nodules but without pericardial effusion.

Results: The median survival time among the patients with LD-M1a was 13.4 months (95% confidence interval: 10.7–16.6 months), and the 1-, 2-, 3-, and 5-year survival rates were 56%, 18%, 9%, and 8%, respectively. The survival of the patients with LD-M1a was intermediate between those of the patients with LD-M0 and patients with extensive disease M1b ($p < 0.0001$). The overall survival period was not statistically different between groups A and B ($p = 0.5182$). Nineteen patients in group A received chemoradiotherapy, but only two patients survived for more than 2 years (2- and 5-year survival rate: 11% both). Twenty-six patients in group B received chemoradiotherapy, and four patients survived for more than 5 years (5-year survival rate: 18%).

Conclusions: Long-term survival was achieved among patients with SCLC with pericardial effusion but without distant metastasis who successfully underwent chemoradiotherapy, although 5-year survival rate in these patients was relatively lower than in patients with SCLC with ipsilateral pleural effusion but without pericardial effusion or distant metastasis.

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Disclosure: The authors declare no conflicts of interest.

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Lung cancer is the leading cause of cancer-related deaths worldwide. Small cell lung cancer (SCLC) accounts for approximately 15% of all forms of lung cancer. Compared with non-SCLC, SCLC grows rapidly, quickly disseminates to the regional lymph nodes and distant sites, and is sensitive to chemotherapy with a response rate of 70 to 80%. The Veterans Administration Lung Study Group proposed a clinical two-stage system for SCLC that distinguishes limited disease (LD) and extensive disease (ED). LD is defined as being limited to one hemithorax, including mediastinal, contralateral hilar, and ipsilateral supraclavicular lymph nodes, whereas ED represents tumor spread beyond these regions.[1] The current standard care for LD-SCLC is a combination of chemotherapy and thoracic radiotherapy (TRT). Conversely, ED-SCLC is treated with chemotherapy alone. The original definition of LD was a tumor volume that could be encompassed by a reasonable radiotherapy plan. According to the International Association for the Study of Lung Cancer (IASLC)'s consensus report, however, the classification of LD-SCLC includes bilateral hilar or supraclavicular nodal involvement and ipsilateral pleural effusion, regardless of whether the cytological findings are positive or negative.[2] Pericardial effusion has not been defined precisely.

In 2007, the IASLC proposed a new tumor, node, metastasis (TNM) classification for lung cancer,[3–6] and the Union Internationale Contre le Cancer (UICC) seventh TNM edition has been available since 2009. According to the UICC seventh TNM edition, malignant pleural or pericardial effusion and tumor with pleural nodules are defined as M1a, leading to stage IV. An analysis of 12,620 patients with SCLC in the IASLC database demonstrated that patients who have ipsilateral pleural effusion without extrathoracic metastases (M1a) have a survival that is intermediate between stages I and III without effusion and stage IV. Nevertheless, no information regarding the presence of pericardial effusion is available in the IASLC database.[7]

Our previous retrospective analysis also demonstrated that the survival of patients with LD-SCLC with ipsilateral pleural effusion was intermediate between those of patients with LD without ipsilateral pleural effusion and patients with

ED, and long-term survival was achieved by patients with LD-SCLC who successfully underwent definitive TRT after their ipsilateral pleural effusion had disappeared after induction chemotherapy.[8] In this retrospective study, we investigated the clinical course and overall survival among patients with LD-SCLC with pericardial effusion, compared with those among patients with ED-SCLC or LD-SCLC with or without ipsilateral pleural effusion.

PATIENTS AND METHODS

In this study, LD-SCLC was defined as disease limited to one hemithorax, including mediastinal, contralateral hilar, and supraclavicular lymph nodes, ipsilateral pleural effusion, and pericardial effusion; ED-SCLC was defined as tumor spread beyond these manifestations.

We retrospectively reviewed the medical records of patients with lung cancer treated at the National Cancer Center Hospital East between July 1992 and December 2007.

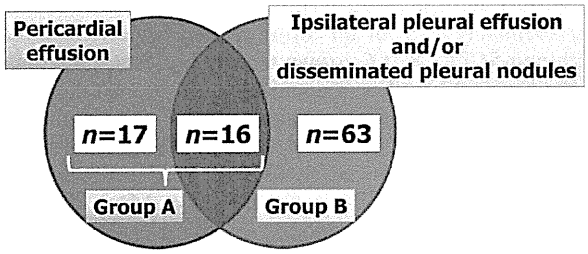

FIGURE 1. Patients with small cell lung cancer with M1a. Group A included patients with pericardial effusion, and group B included patients with ipsilateral pleural effusion or disseminated pleural nodules, but without pericardial effusion.

During this period, 766 patients were newly diagnosed as having SCLC. Four hundred sixteen patients were diagnosed as having LD-SCLC and 350 were diagnosed as having ED-SCLC using conventional staging procedures, including a medical history and physical examination, chest radiography, computed tomography (CT) scan of the chest, CT scan or ultrasound of the abdomen, bone scan, and CT scan or magnetic resonance imaging of the brain. Thirty-three of the 416 patients with LD-SCLC (8%, 95% confidence interval [CI]: 6–11%) had pericardial effusion and were included in this study. Seventy-nine of the 416 patients with LD-SCLC (19%, 95% CI: 15–23%) had ipsilateral pleural effusion or dissemination. Four patients had a disseminated mass without pleural effusion detected using CT scan. Sixteen patients with LD-SCLC had both pericardial and ipsilateral pleural effusion. Therefore, 63 patients with LD-SCLC had ipsilateral pleural effusion or dissemination without pericardial effusion. We divided the 96 M1a patients into two subgroups: group A included patients with pericardial effusion, and group B included patients without pericardial effusion. Group B patients had ipsilateral pleural effusion or disseminated pleural nodules (Figure 1).

The overall survival time was defined as the interval between the start of treatment and death or the final follow-up visit. The median overall survival time was estimated using the Kaplan-Meier analysis method.[9] Survival data were compared among the groups using a log-rank test. This study was approved by an institutional review board.

RESULTS

The patient characteristics are listed in Table 1. Eighty-three percent of the patients were male, and 81% had a performance status of 0 or 1. Fifty-four percent of the patients

TABLE 1. Patient Characteristics

	ED-SCLC (M1b)	LD-SCLC with Pericardial Effusion (M1a) (Group A)	LD-SCLC with Ipsilateral Pleural Effusion but without Pericardial Effusion (M1a) (Group B)	LD-SCLC (M0)
No. of patients	350	33	63	320
Sex				
Male	291	29	50	262
Female	59	4	13	58
Age (yr)				
Median	66	67	68	66
Range	28–85	37–82	46–83	22–87
Performance status				
0	22	0	4	108
1	224	25	47	190
2	63	6	9	15
3–4	41	2	3	7
Treatment delivered				
Chemotherapy	316	14	36	50
Chemoradiotherapy	25	19	26	224
Surgery + chemotherapy	0	0	0	33
Surgery alone	0	0	0	10
Best supportive care	9	0	1	3

LD, limited disease; SCLC, small cell lung cancer; ED, extensive disease.

TABLE 2. Timing of Thoracic Radiotherapy in Patients with M1a Small Cell Lung Cancer

Timing of Thoracic Radiotherapy	LD-SCLC with Pericardial Effusion (M1a) (Group A, n = 19)	LD-SCLC with Ipsilateral Pleural Effusion but without Pericardial Effusion (M1a) (Group B, n = 26)
Concurrently with the first course of chemotherapy	0	3
Concurrently with the second course of chemotherapy	0	4
Concurrently with the third course of chemotherapy	8	5
Concurrently with the fourth course of chemotherapy	4	0
Sequentially after chemotherapy	7	14

LD, limited disease; SCLC, small cell lung cancer.

received chemotherapy, and 38% received chemoradiotherapy. Six percent of the patients underwent surgical resection with or without adjuvant chemotherapy. Among the 96 patients with LD-M1a, all but one patient received chemotherapy (n = 50) or chemoradiotherapy (n = 45). Three patients underwent TRT (twice daily, 45 Gy in total) concurrently with the first course of chemotherapy. Four, 13, and four patients underwent TRT (once daily, 50 Gy in total) concurrently with the second, third, and fourth courses of chemotherapy, respectively. Twenty-one patients underwent TRT (once daily, 50 Gy in total) sequentially after chemotherapy. Among the group A patients, 12 patients underwent TRT concurrently with the third or fourth course of chemotherapy, and seven patients underwent TRT sequentially after chemotherapy. TRT was conducted if the pericardial effusion disappeared after induction chemotherapy. Among the group B patients, 12 patients underwent TRT concurrently with chemotherapy, and 14 patients underwent TRT sequentially (Table 2). Thirteen patients received prophylactic cranial irradiation of 25 Gy (seven patients in group A and six patients in group B).

Figure 2 shows the survival of all 766 patients with SCLC belonging to category M. The survival of patients with LD-M1a was intermediate between those of patients with LD-M0 and ED-M1b ($p < 0.0001$). Six hundred eighty-two patients have died. The median follow-up time was 65.8 months, ranging from 3.2 to 160.1 months. The median survival time among the patients with LD-M1a was 13.4 months (95% CI: 10.7–16.6 months), and the 1-, 2-, 3-, and 5-year survival rates were 56%, 18%, 9%, and 8%, respectively.

Survival analyses for the subgroup of patients with LD-M1a (n = 96) are shown in Figures 3, 4 and Table 3. Overall survival was not statistically different between groups A and B (p = 0.5182). All 14 patients who received chemotherapy in group A died within 3 years. One patient in

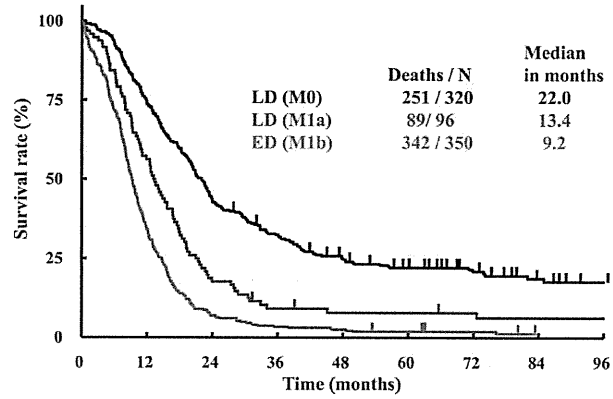

FIGURE 2. Overall survival among all 766 patients with M-category small cell lung cancer. LD, limited disease; ED, extensive disease.

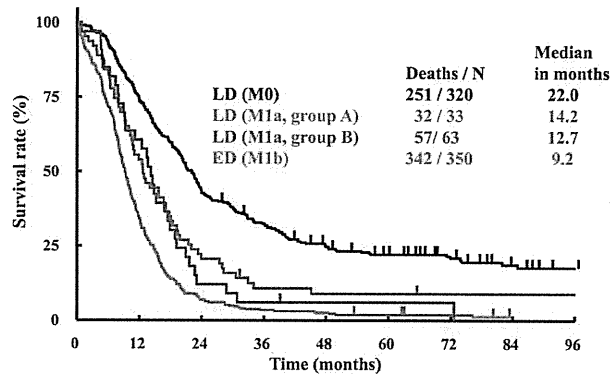

FIGURE 3. Overall survival among patients with M-category small cell lung cancer, subgroups A and B. LD, limited disease; ED, extensive disease.

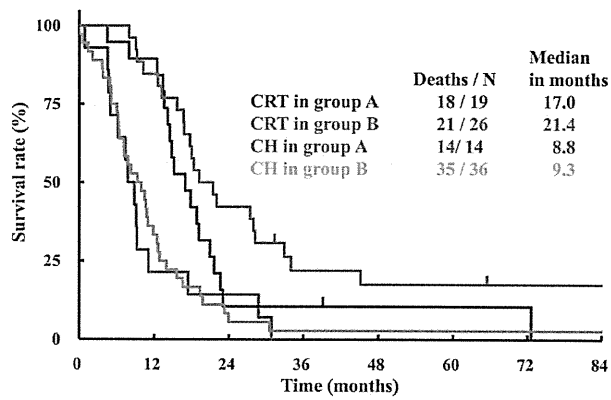

FIGURE 4. Overall survival among M1a patients with small cell lung cancer according to subgroups A, B, and initial treatment delivered. CRT, chemoradiotherapy; CH, chemotherapy.

group B who received chemotherapy as an initial treatment survived for more than 5 years, but this patient received chemoradiotherapy as a second-line treatment after a local

TABLE 3. Survival Data

Subgroup	No. of Patients	Median Survival Time (mo) (95% CI)	1-yr Survival Rate (%)	2-yr Survival Rate (%)	3-yr Survival Rate (%)	5-yr Survival Rate (%)
ED (M1b)	350	9.2 (8.5–10.0)	34	7	3	2
LD (M0)	320	22.0 (20.0–23.5)	74	43	33	22
LD with pericardial effusion (group A)	33	14.2 (9.1–17.5)	61	12	6	6
Receiving CRT	19	17.0 (13.6–21.0)	89	11	11	11
Receiving Chemotherapy	14	8.8 (4.7–11.1)	21	14	0	0
LD with ipsilateral pleural effusion but without pericardial effusion (group B)	63	12.7 (10.2–16.7)	54	21	11	9
Receiving CRT	26	21.4 (16.7–28.2)	85	42	22	18
Receiving chemotherapy	36	9.3 (6.3–11.8)	33	6	3	3

CI, confidence interval; ED, extensive disease; LD, limited disease; CRT, chemoradiotherapy.

TABLE 4. Six Patients with M1a Small Cell Lung Cancer who Survived for More Than 5 yr

Age (yr)	Sex	Group	Initial Treatment	Survival Time (mo)	State
64	M	A	Chemoradiotherapy	72.6	Dead
70	F	B	Chemoradiotherapy	146.5	Alive
53	M	B	Chemotherapy[a]	140.4	Alive
73	F	B	Chemoradiotherapy	138.0	Alive
72	M	B	Chemoradiotherapy	117.0	Alive
68	M	B	Chemoradiotherapy	65.5	Alive

[a] This patient received chemoradiotherapy as a second-line treatment after a local recurrence. Therefore, all six patients received chemoradiotherapy and achieved long-term survival for more than 5 yr.

M, male; F, female.

recurrence. Four of the 26 patients who received chemoradiotherapy in group B survived for more than 5 years (Table 4). Conversely, only 2 of the 19 patients who received chemoradiotherapy in group A survived for more than 2 years. One patient developed a local recurrence at 4 years and 10 months after the initiation of first-line chemoradiotherapy and died of lung cancer 14 months later. The remaining patient also developed a local recurrence at 2 years and 9 months after the initiation of first-line chemoradiotherapy and received second-line chemotherapy. This patient was still alive at the time of the data cutoff.

DISCUSSION

This retrospective analysis demonstrated that the survival of patients with SCLC and ipsilateral pleural or pericardial effusion (M1a) was intermediate between those of M0 and M1b patients. It is suitable that patients with ipsilateral pleural effusion or pericardial effusion belong to M1a category in the UICC seventh TNM edition. No statistically significant difference in the overall survival between M1a patients with pericardial effusion (group A) and those with ipsilateral pleural effusion but without pericardial effusion (group B) was observed. Among the patients who successfully underwent chemoradiotherapy, the patients in group B had 2-, 3-, and 5-year survival rates of 42%, 22%, and 18%, respectively, whereas the patients in group A had a 2-year survival rate of only 11%. Our previous retrospective analyses demonstrated that the median survival time of patients with cytologically positive and cytologically negative pleural effusion were 9.3 and 12.7 months, respectively. Furthermore, all 11 patients with cytologically positive pleural effusion died within 3 years.[8] Long-term survival for more than 5 years was achieved only by patients with cytologically negative pleural effusion. We speculate that an inflammatory process, such as atelectasis, causes ipsilateral pleural effusion in some patients. Conversely, most pericardial effusion is believed to be malignant. Therefore, long-term survival was seldom achieved by patients with pericardial effusion, even if they received chemoradiotherapy.

Recently, the applicability of the UICC seventh TNM edition for SCLC was investigated using the California Cancer Registry database. This database included 108 and 1518 M1a patients with pericardial effusion and pleural dissemination, respectively. No significant difference in overall survival was observed among patients with pleural or pericardial effusion (median survival time: 7 versus 7 months, 2-year survival rate: 16.7% versus 9.7%, respectively).[10] These data were comparable with our results. Nevertheless, no information regarding the treatment performed for the M1a patients was included in the previous article.

Our retrospective analysis has several limitations. First, the number of M1a patients with pericardial effusion was only 33, because only 8% of the patients with LD-SCLC exhibited pericardial effusion. Second, we did not conduct a cytological examination of the pericardial effusion. Pericardial puncture or drainage is usually performed in patients with cardiac tamponade. None of the patients in group A had cardiac tamponade; therefore, a pericardial puncture was technically difficult. Third, examination period was more than 15 years, from 1992 to 2007. Irinotecan, active for SCLC, has been commonly used from 2000 in Japan. Patients in this study were treated with a potential range of different chemotherapeutic agents during the period, which was not controlled.

Only 2 of 19 patients (11%) who received chemoradiotherapy in group A survived for more than 3 years. Con-

versely, all 14 patients who did not receive chemoradiotherapy in group A died within 3 years. TRT probably improves local control and achieves long-term survival in some patients. Definitive TRT is recommended in M1a patients with SCLC, if ipsilateral pleural or pericardial effusion has disappeared after induction chemotherapy.

In conclusion, the survival of patients with SCLC and ipsilateral pleural or pericardial effusion (M1a) is intermediate between those of M0 and M1b patients. No statistically significant difference in the overall survival of M1a patients with pericardial effusion and those with ipsilateral pleural effusion but without pericardial effusion was observed. Long-term survival was achieved among M1a patients with pericardial effusion who successfully underwent chemoradiotherapy, although 5-year survival rate in these patients was relatively lower than in M1a patients with ipsilateral pleural effusion but without pericardial effusion.

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INTERNAL MEDICINE

□ CASE REPORT □

Development of Cushing's Syndrome During Effective Chemotherapy for Small Cell Lung Cancer

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Abstract

Paraneoplastic Cushing's syndrome caused by ectopic adrenocorticotropin (ACTH) production has been reported. However, most cases of this syndrome are diagnosed before first-line chemotherapy or at the time of disease recurrence. Here, we present a 53-year-old man who gradually developed the symptoms of Cushing's syndrome during effective chemotherapy for small cell lung cancer. His symptoms were controlled using mitotane, but his primary cancer progressed and he died 5 months after the start of chemotherapy. This very rare case of Cushing's syndrome associated with small cell lung cancer during effective chemotherapy is presented here.

Key words: Cushing's syndrome, ACTH, lung cancer, chemotherapy

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Introduction

Paraneoplastic Cushing's syndrome caused by ectopic adrenocorticotropin (ACTH) production has been reported. However, most cases of this syndrome are diagnosed before first-line chemotherapy or at the time of disease recurrence. A few reports have described the gradual emergence of the symptoms of Cushing's syndrome during effective treatment for lung cancer. Identifying the symptoms of Cushing's syndrome at an early stage is important from the perspective of early diagnosis. Here, we present a case of paraneoplastic Cushing's syndrome that emerged gradually during effective chemotherapy for small cell lung cancer.

Case Report

A 53-year-old man presented with a cough, sputum, and dyspnea lasting for about two months. A plain chest radiograph at another hospital showed an abnormal shadow in a hilum of the left lung. A bronchoscopy revealed a small cell lung cancer (SCLC). He was referred to our hospital for treatment.

The patient had smoked 30 cigarettes a day for 32 years. Computed tomography (CT) of the chest revealed a mass in the left hilum of the lung and mediastinal lymph node swelling (Fig. 1A). No tumors other than those in the left thorax and no enlarged lymph nodes except those were found. His laboratory findings, including the serum potassium level, were almost normal. Regarding serum tumor markers, squamous cell carcinoma-related antigen and carcinoma-related antigen were not detected, but the serum neuron-specific enolase (NSE) level was 32.1 ng/mL (normal, <16.3 ng/mL) and the serum Pro-GRP level was 473 pg/mL (normal, <46 pg/mL). The clinical stage was T2N3M0, indicating limited SCLC.

At the time of hospitalization, the physical findings were not characteristic of a Cushingoid appearance. Because of the large radiation field, chemotherapy using cisplatin and etoposide was first performed (Fig. 2). After two cycles of chemotherapy, a tumor reduction was confirmed using CT (Fig. 1B). Thereafter, the patient began to complain of chest pain. We consulted a cardiologist, and three stenosed lesions were discovered in his coronary arteries. Percutaneus transluminal coronary angioplasty was performed for one lesion. Thereafter, we reinitiated chemotherapy after changing cisplatin to carboplatin to reduce the cardiac burden. Prior to the fourth round of chemotherapy, he developed hypoka-

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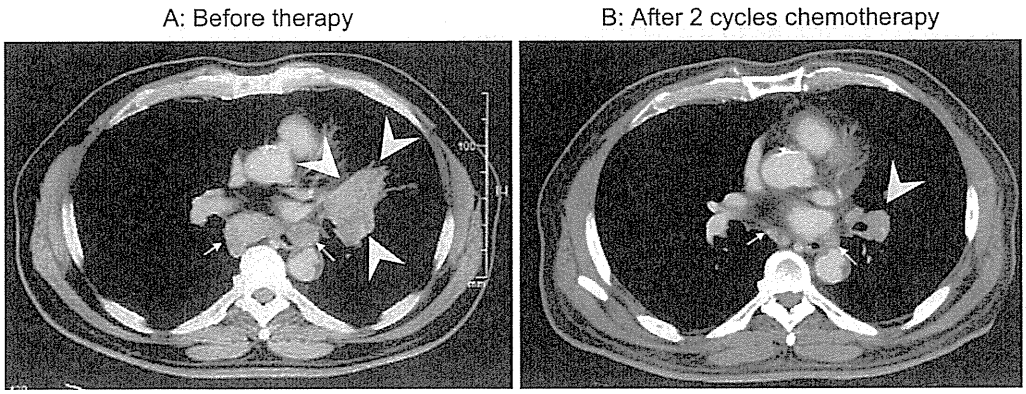
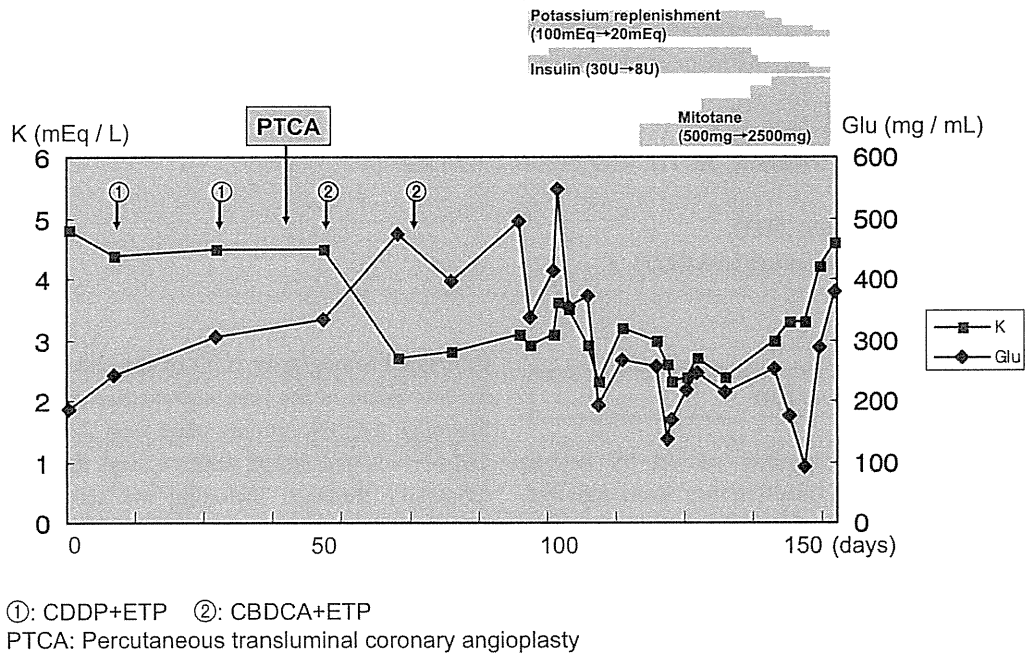


Figure 1. A: Computed tomography (CT) image obtained before chemotherapy. A chest CT revealed a mass in the left hilum of the lung (arrowhead) and mediastinal lymph node swelling (arrow). B: CT image obtained after 2 cycles of chemotherapy. The main tumor and swollen lymph node show signs of reduction.



①: CDDP+ETP ②: CBDCA+ETP
PTCA: Percutaneous transluminal coronary angioplasty

Figure 2. Clinical course.

lemia. His blood glucose level also gradually began to increase. Because these symptoms were not severe, we continued the chemotherapy. The serum tumor marker kept decreasing (NSE: max 50.3 ng/mL→21.5 ng/mL, Pro-GRP: max 1172 pg/mL→695 pg/mL) during the chemotherapy period. After completing 4 cycles of chemotherapy, he had developed severe hypokalemia, diabetes, hypertension and a depressive state (Fig. 2). He also exhibited centripetal obesity and a buffalo hump. We started the administration of potassium and insulin. However, no response to treatment was observed. The NSE and pro-GRP levels, which had been declining, began to rise. We speculated that these findings were consistent with Cushing's syndrome. The plasma ACTH concentration was 481.0 pg/mL (normal range, 7.2-63.3 pg/mL) and the plasma cortisol concentration was 144.0 μg/dL (normal range, 4.0-18.3 μg/dL). The serum ACTH concentration failed to be suppressed after treatment with 1 mg of dexamethasone overnight. It also was not suppressed after metyrapone loading. Magnetic resonance imaging (MRI) did not reveal a pituitary mass. These results suggested that the patient's Cushing's syndrome was caused by ectopic ACTH production associated with the SCLC.

The patient was treated with mitotane (500 mg/day). We gradually increased the amount of mitotane, reaching a final dosage of 2500 mg/day. After the start of mitotane treatment, his hypokalemia and hyperglycemia gradually improved. The amount of required potassium and insulin also decreased (Fig. 2). The plasma ACTH and cortisol concentration also decreased (ACTH: 481 pg/mL→329.0 pg/mL, cortisol: 144.0 μg/dL→89.0 μg/dL). However, his primary

lung cancer was progressing. Second-line chemotherapy could not be started because of the patient's uncontrollable symptoms, poor performance status, and the refusal of the patient to undergo chemotherapy. He died 5 months after the start of the initial chemotherapy.

Discussion

A previous retrospective study demonstrated that the incidence of paraneoplastic Cushing's syndrome is 5% or less among all SCLC patients (1). In the recent literature, the incidence of SCLC associated with paraneoplastic syndrome has seemed to decrease (2). A possible explanation for this trend might be the recent improvements in diagnosis, chemotherapy, and radiotherapy. However, SCLC patients who develop paraneoplastic syndrome still have a poor prognosis because of various complications. Reportedly, 43% of SCLC patients with ectopic ACTH production experienced severe infections that contributed significantly to their eventual deaths (1). Another study reported a high rate of fatal infections (about 28%) and nonfatal infections in Cushing's syndrome (3). The cause of such infections might be hypercortisolism. The early diagnosis of Cushing's syndrome is very important for improving patient survival.

As shown in the case presentation, the chemotherapy was considered to have been effective. However, the patient gradually developed the symptoms of Cushing's syndrome. Most cases of Cushing's syndrome reportedly develop at the time of the initial presentation or the relapse of SCLC (1). Patients who develop Cushing's syndrome often have a poor outcome because of chemoresistance. The worsening of Cushing's syndrome during effective chemotherapy is thought to be very rare. One possible reason for the poor outcome in the present case is that chemoresistant cell clones might have produced the ACTH. In other words, cell clones that survived the chemotherapy might have begun to proliferate rapidly after chemotherapy. Thus, "the chemoresistant cancer cell clones that produced ACTH" might have contributed to the poor outcome of the present patient with SCLC who developed ectopic ACTH syndrome. Vanhees et al reported a case of syndrome of inappropriate antidiuretic hormone (SIADH) associated with effective chemotherapy in SCLC (4). They hypothesized that the release of ADH from the malignant cells during the early tumor breakdown from chemotherapy resulted in SIADH. As well as this hypothesis, the present case might have had the possibility of developing Cushing's syndrome from the release of ACTH from malignant cells in the period of rapid cell necrosis due to effective chemotherapy.

Once Cushing's syndrome is suspected, a differential diagnosis must be made by performing an overnight dexamethasone test and metyrapone test. If no ectopic ACTH production is present, the serum ACTH level should be greatly suppressed after the administration of 1 mg dexamethasone and should increase after the administration of metyrapone. If pituitary Cushing's disease is present, the serum ACTH level should also increase after the administration of metyrapone. The ACTH level in the present patient did not respond to the administration of dexamethasone and metyrapone. These results indicated that the patient had ectopic ACTH production; in this manner, a final diagnosis of Cushing's syndrome as a result of SCLC was confirmed. He was treated with mitotane to counteract the ectopic ACTH production. Mitotane, or o,p'DDD, can block the adrenocortical steroid synthesis by inhibition of cholesterol side-chain cleavage and 11β-hydroxylase. This inhibition affects extra-adrenal cortisol disposition by inducing its hepatic clearance, reducing hormone production, and ameliorating the symptoms of hormone excess (5). A recent study from a single center showed the ideal therapeutic control of the ectopic ACTH secretion syndrome by using mitotane (6). In that study, 20 of the 23 patients showed clinical improvement of Cushing's syndrome manifestations. The present patient's symptoms arising from Cushing's syndrome began to improve by using mitotane, but his SCLC also began to progress and could not be stopped, mainly because treatment of the cancer itself could not be resumed.

We could not perform an immunohistochemical study for ACTH using primary or metastatic tumor specimens for the diagnosis of ectopic ACTH secretion. ACTH produced from neoplasms is said to have a different structure than that of wild-type ACTH, and conventional immunohistochemical staining using a polyclonal anti-ACTH antibody may not be useful in tumor cells (7). The predominant form of ACTH in tumor extracts is reportedly a large ACTH molecule that cannot be detected using the usual immunohistochemical staining (8).

In summary, we have described a rare case of Cushing's syndrome that progressed even during effective chemotherapy for SCLC. The clinical symptoms of Cushing's syndrome must be kept in mind when treating patients with lung cancer, since early detection and appropriate treatment can overcome the otherwise poor prognosis.

The authors state that they have no Conflict of Interest (COI).

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CLINICAL INVESTIGATION **Thoracic Cancer**

PHASE I STUDY OF CONCURRENT HIGH-DOSE THREE-DIMENSIONAL CONFORMAL RADIOTHERAPY WITH CHEMOTHERAPY USING CISPLATIN AND VINORELBINE FOR UNRESECTABLE STAGE III NON-SMALL-CELL LUNG CANCER

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Purpose: To determine the maximum tolerated dose in concurrent three-dimensional conformal radiotherapy (3D-CRT) with chemotherapy for unresectable Stage III non–small-cell lung cancer (NSCLC).

Patients and Methods: Eligible patients with unresectable Stage III NSCLC, age ≥20 years, performance status 0–1, percent of volume of normal lung receiving 20 GY or more (V_{20}) ≤30% received three to four cycles of cisplatin (80 mg/m^2 Day 1) and vinorelbine (20 mg/m^2 Days 1 and 8) repeated every 4 weeks. The doses of 3D-CRT were 66 Gy, 72 Gy, and 78 Gy at dose levels 1 to 3, respectively.

Results: Of the 17, 16, and 24 patients assessed for eligibility, 13 (76%), 12 (75%), and 6 (25%) were enrolled at dose levels 1 to 3, respectively. The main reasons for exclusion were V_{20} >30% (n = 10) and overdose to the esophagus (n = 8) and brachial plexus (n = 2). There were 26 men and 5 women, with a median age of 60 years (range, 41–75). The full planned dose of radiotherapy could be administered to all the patients. Grade 3–4 neutropenia and febrile neutropenia were noted in 24 (77%) and 5 (16%) of the 31 patients, respectively. Grade 4 infection, Grade 3 esophagitis, and Grade 3 pulmonary toxicity were noted in 1 patient, 2 patients, and 1 patient, respectively. The dose-limiting toxicity was noted in 17% of the patients at each dose level. The median survival and 3-year and 4-year survival rates were 41.9 months, 72.3%, and 49.2%, respectively.

Conclusions: 72 Gy was the maximum dose that could be achieved in most patients, given the predetermined normal tissue constraints. © 2012 Elsevier Inc.

Lung cancer, Chemotherapy, Radiotherapy, High dose, Conformal.

INTRODUCTION

Approximately one third of patients with non–small-cell lung cancer (NSCLC) present with locally advanced Stage III disease at the initial diagnosis (1). Of this category, Stage IIIA disease with bulky N2 and Stage IIIB disease without pleural effusion are characterized by a large primary lesion and/or involvement of the mediastinal or supraclavicular lymph nodes. In addition, the majority of these patients have occult systemic micrometastases. Concurrent thoracic radiotherapy and chemotherapy has been the standard care for these patients with unresectable disease (2, 3). A platinum doublet with a third-generation anticancer agent combined with thoracic radiotherapy was reported to yield a median overall survival time (OS) of more than 2 years and long-term survivors (4–6), but the effect of platinum-based chemotherapy has reached a plateau.

The failure pattern in patients with Stage III NSCLC treated by concurrent chemoradiotherapy was roughly local recurrence alone in one third of the patients, both local and distant recurrence in another third of patients, and distant metastasis without local failure in the remaining third of patients (2, 5).

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Thus, improvement of local control and suppression of distant metastasis are essential for prolongation of patient survival.

The conventional total dose of thoracic radiotherapy in patients with inoperable NSCLC has been 60 Gy administered in 30 fractions. This dose was established in 1987 by randomized Radiation Therapy Oncology Group trials that demonstrated better 3-year survival with a radiation dose of 60 Gy than with lower doses (7). In these trials, two-dimensional treatment planning was used, wherein the tumor volume was defined on kilovoltage radiographs (7). Thereafter, the standard initial target volume included the primary tumor, metastatic lymph nodes, and adjacent uninvolved ipsilateral hilar and mediastinal regions (elective nodal irradiation: ENI). Except for selected patients, excessive toxicity hampered an increase of the total dose to over 60 Gy in patients with locally advanced NSCLC.

It is, however, time now to reconsider the optimal dose of thoracic radiotherapy using new techniques in patients with locally advanced NSCLC, for the following reasons. First, positron emission tomography (PET) provides more accurate diagnosis of mediastinal lymph node metastases (8) and more accurate quantification of the tumor volumes, especially when atelectasis is present (9). Second, three-dimensional conformal radiation therapy (3D-CRT) enables radiation oncologists to delineate the tumor and adjacent normal tissue more sharply and to choose beam angles to maximize tumor coverage with minimum irradiation of normal tissues (10). Third, omission of the ENI resulted in improvement of radiation-associated toxicity without worsening the local control rate of the tumor (11, 12). Thus, by use of these new techniques, the optimal dose of thoracic radiation could exceed the conventional 60 Gy.

Two dose escalation studies in patients with locally advanced NSCLC showed that the total dose of thoracic radiotherapy could be increased up to 90 Gy in concurrent chemoradiotherapy using the 3D-CRT technique combined with weekly carboplatin and paclitaxel chemotherapy (13, 14). In these trials, chemoradiotherapy was administered after induction chemotherapy. However, it remained unclear whether these doses could be delivered safely to the majority of patients with locally advanced NSCLC, because it is not known how many patients were screened for the trials and how many of them were actually registered, and because some of the registered patients were excluded from the chemoradiotherapy phase after induction chemotherapy. The total number of patients evaluated in the two trials was also limited. Furthermore, chemotherapy other than weekly carboplatin and paclitaxel has not been evaluated in the setting of combined chemotherapy with high-dose thoracic radiotherapy, to our knowledge. The objectives of the current study were (1) to evaluate the toxicity of concurrent high-dose 3D-CRT without ENI with cisplatin and vinorelbine for unresectable Stage III NSCLC, (2) to determine the maximum tolerated dose (MTD) of thoracic radiotherapy, and (3) to observe the antitumor effects of this regimen.

PATIENTS AND METHODS

Study design

This study was designed as a Phase I study at the National Cancer Center Hospital. The protocol and consent form were approved by the Institutional Review Board of the National Cancer Center on July 28, 2005. We planned to treat 12 patients at a dose level and follow them up at least 6 months, and then escalate to the next level if 67% of the patients did not experience dose-limiting toxicity (DLT). We followed widely accepted normal tissue dose constraints. Patients with percent volume of the normal lung receiving 20 Gy or more (V_{20}) of greater than 30% were excluded and treated outside the study. Other dosimetric constraints were applied at the discretion of the treating radiation oncologist. Maximum doses exceeding 50 Gy to the spinal cord, 66 Gy to the esophagus, or 66 Gy to the brachial plexus were generally excluded.

Patient selection

Previously untreated patients with locally advanced NSCLC without effusion were screened for entry into this study. The eligibility criteria were (1) histologically or cytologically proven NSCLC, (2) unresectable Stage IIIA or IIIB disease confirmed by both computed tomography (CT) and PET, (3) no previous treatment, (4) measurable disease, (5) $V_{20} \leq 30\%$, (6) age ≥ 20 years, (7) Eastern Cooperative Oncology Group performance status (PS) of 0 or 1, and (8) adequate bone marrow function (white blood cell [WBC] count $\geq 4.0 \times 10^9$/L, hemoglobin ≥ 9.5 g/dL, and platelet count $\geq 100 \times 10^9$/L), liver function (total bilirubin ≤ 1.5 mg/dL and transaminase ≤ 80 IU/L), renal function (serum creatinine ≤ 1.5 mg/dL), and pulmonary function ($PaO_2 \geq 70$ Torr under room air). Patients were excluded if (1) they had malignant pleural or pericardial effusion or (2) they had a concomitant serious illness such as uncontrolled angina pectoris, myocardial infarction in the previous 3 months, heart failure, uncontrolled diabetes mellitus, uncontrolled hypertension, interstitial pneumonitis or lung fibrosis identified by a chest x-ray, infection, or other diseases contraindicating chemotherapy or radiotherapy, or (3) they were pregnant 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 CT scan, brain CT scan or magnetic resonance imaging, abdominal CT, and PET.

Treatment schedule

Chemotherapy consisted of cisplatin 80 mg/m^2 on Day 1 and vinorelbine 20 mg/m^2 on Days 1 and 8, repeated every 4 weeks for three to four cycles. Cisplatin was administered by intravenous infusion for 60 minutes with 2,500 to 3,000 mL of intravenous fluid for hydration and prophylactic antiemetic therapy consisting of a 5-hydroxytriptamine-3 antagonist on Day 1 and a corticosteroid on Days 1 to 5. Vinorelbine, diluted in 50 mL of normal saline, was administered intravenously.

Radiation therapy started on Day 1 of the first cycle of chemotherapy and was delivered with megavoltage equipment (6–10 MV) once daily for 5 days a week. The total dose was 66 Gy in 33 fractions at level 1, 72 Gy in 36 fractions at level 2, and 78 Gy in 39 fractions at level 3. All patients underwent a 3D treatment planning CT 3 to 7 days before the start of the treatment, and the eligibility was finally confirmed based on evaluation using the

dose–volume histogram (DVH). The gross tumor volume (GTV) was defined as the primary tumor delineated on pulmonary windows of the chest CT or on the diagnostic PET scans. Atelectasis or secondary changes in the peripheral lung region of the primary tumor were not included. Metastatic lymph nodes defined as nodes of 1 cm or larger visualized on mediastinal windows of the CT images or PET-positive lymph nodes were also included in the GTV. The clinical target volume (CTV) was equivalent to the GTV. Uninvolved mediastinum or supraclavicular fossae were not included in the CTV. The planning target volume (PTV) was determined as the CTV plus 1.0 cm for the anterior, posterior, medial, and lateral margins and a 1.0 to 2.0 cm for the superior and inferior margins, taking account of setup variations and internal organ motion. The spinal cord dose was typically limited to 44 Gy, but a maximum of 50 Gy was allowed. The lung V_{20} was limited to 30% in all patients. The maximum dose to the brachial plexus and esophagus did not exceed 66 Gy. The 100% dose was prescribed to the reference point located in the central part of the PTV, and the entire PTV was covered with 95–107% of the prescribed dose principally, but variation of ±10% was allowed. Lung heterogeneity corrections using the equivalent path length algorithm were applied in all patients.

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. Toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE v3.0). The lung toxicity grade was defined as the highest grade among cough, dyspnea, obstruction/stenosis of airways, pneumonitis/pulmonary infiltrates, and pulmonary fibrosis in the pulmonary/upper respiratory section (15).

Vinorelbine administration on Day 8 was omitted if any of the following were noted: WBC count $<3.0 \times 10^9$/L, neutrophil count $<1.5 \times 10^9$/L, platelet count $<100 \times 10^9$/L, Grade 2–3 elevation of the serum hepatic transaminase level or total serum bilirubin levels, Grade 2–3 infection, Grade 2–3 pneumonitis, other ≥Grade 3 nonhematologic toxicity, body temperature ≥38°C, or PS of 2–3. Subsequent cycles of cisplatin and vinorelbine chemotherapy were delayed if any of the following toxicities were noted on Day 1: WBC count $<3.0 \times 10^9$/L, neutrophil count $<1.5 \times 10^9$/L, platelet count $<100 \times 10^9$/L, serum creatinine level ≥1.6 mg/dL, Grade 2–3 elevation of the serum hepatic transaminase level or total serum bilirubin levels, Grade 2–3 infection, Grade 2–3 pneumonitis, other ≥Grade 3 nonhematologic toxicity, body temperature ≥38°C, or PS of 2–3. If these toxicities did not recover within 6 weeks from Day 1 of the previous cycle of chemotherapy, subsequent cycles of chemotherapy were stopped. The dose of cisplatin was reduced by 25% in all subsequent cycles if the serum creatinine level rose to 2.0 mg/dL or higher. The dose of vinorelbine was reduced by 25% in all subsequent cycles if any of the following toxicities were noted: WBC count $<1.0 \times 10^9$/L, platelet count $<25 \times 10^9$/L, or Grade 3 infection or liver dysfunction. Thoracic radiotherapy was suspended if any of the following were noted: body temperature ≥38°C, Grade 3 esophagitis, PS of 3, or suspected radiation pneumonitis. Thoracic radiotherapy was terminated if any of the following were noted: Grade 4 esophagitis, Grade 3 or 4 pneumonitis, PS of 4, or duration of radiotherapy of over 62 days (level 1), 67 days (level 2), or 70 days (level 3). Any protocol-defined treatments were terminated if Grade 4 nonhematologic toxicities other than transient electrolyte disturbances or a PS of 4 was noted.

Dose-limiting toxicity and maximum tolerated dose

The DLT was defined as the following toxicities observed during a 6-month period from the start of treatment: (1) Grade 3 esophagitis, lung toxicity, myelitis, dermatitis associated with radiation, and cardiac toxicity associated with radiation, (2) Grade 4 nonhematologic toxicity, or (3) treatment termination due to prolonged toxicity. Twelve patients were enrolled at each dose level. All patients were followed up for at least 6 months to evaluate DLT. During the period, if none to 4 of the 12 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. The recommended dose for Phase II trials was defined as the dose preceding the MTD.

Response evaluation

Objective tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.0 (16).

Follow-up

Patients who completed the protocol therapy were followed up to monitor toxicity, response, and recurrence. CT of the chest was performed every 2 to 4 months for 1 year, every 6 months for 2 years, and then yearly for 2 years. The relapse pattern was categorized into (1) local alone, including relapse from the primary site or the hilar, mediastinal, or supraclavicular lymph nodes, (2) distant metastasis alone, including pleural dissemination, pleural and pericardial effusions, and distant metastases, and (3) local and distant.

Statistical analyses

Progression-free survival time (PFS) and OS were estimated by the Kaplan-Meier method. The PFS was measured from the date of registration to the date of disease progression or death resulting from any cause or date of last follow-up. The OS was measured from the date of registration to the date of death resulting from any cause or date of last follow-up. Patients who were lost to follow-up without events were censored at the date of their last known follow-up. A confidence interval (CI) for the response rate was calculated by the method used for exact binomial CIs. The Dr. SPSS II 11.0 software package for Windows (SPSS Japan Inc., Tokyo, Japan) was used for the statistical analyses.

RESULTS

Registration and characteristics of the patients

From August 2005 to September 2008, 57 patients were deemed to initially be eligible. Of these, 3 patients were excluded because idiopathic interstitial pneumonitis (n = 1) and anemia (n = 2) developed. Explanation of the study using the consent form was given to 54 patients, and informed consent was obtained in 51 patients. The 51 patients underwent 3D treatment planning, and eligibility was finally confirmed in 31 patients. Those 31 were enrolled into this study. A total of 20 patients were excluded as a result of the DVH evaluation: because of V_{20} higher than 30% in 10 patients, overdose to the esophagus in 8 patients, and overdose to the brachial plexus in 2 patients. Eventually, of 17 patients assessed as to their eligibility for dose level 1, 16 patients for dose level 2, and 24 patients to dose level 3, 13 (76%), 12 (75%), and 6 (25%) patients were actually enrolled into levels 1 to 3, respectively (Fig. 1).

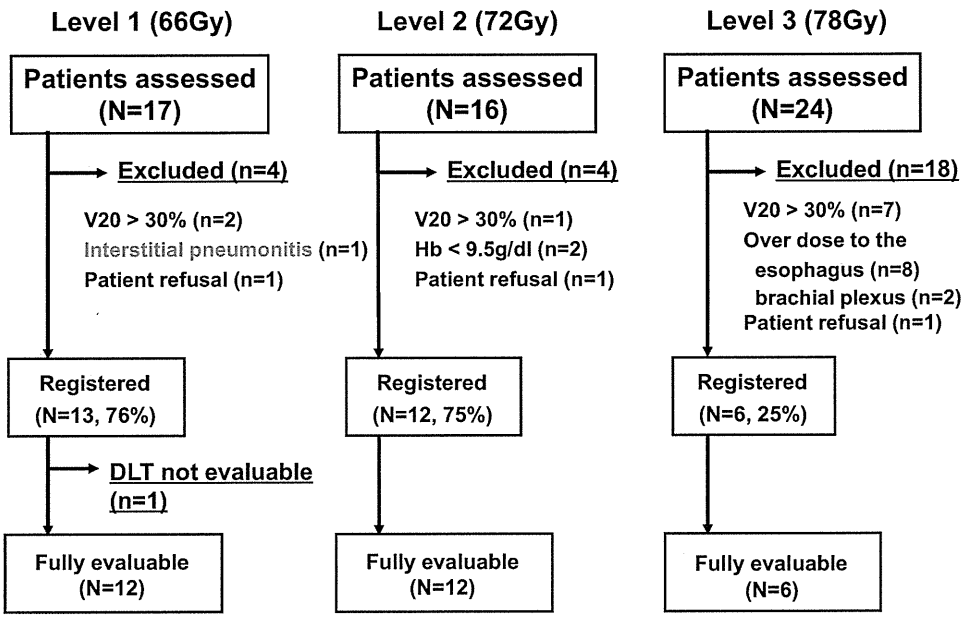

Fig. 1. Algorithm illustrating the flow of the patients. Of the 17, 16, and 24 patients assessed for eligibility, 13 (76%), 12 (75%), and 6 (25%) were actually enrolled at dose levels 1, 2, and 3, respectively.

The pretreatment characteristics of the patients enrolled in this trial are shown in Table 1. The majority of the patients were in good general condition, with a PS of 0 in 25 (81%) and no weight loss in 26 (84%) patients. Adenocarcinoma was the predominantly encountered histological characteristic, seen in 23 (74%) patients.

Treatment delivery

The treatment delivery to the patients was fairly good (Table 2). The planned dose of radiotherapy was administered to all patients of all the three dose levels. More than 80% of the patients received three to four cycles of chemotherapy without or with only one omission of vinorelbine on Day 8, regardless of the dose levels.

Toxicity and DLTs

The hematologic toxicity was comparable to that of other concurrent chemoradiotherapy (Table 3). Grade 4 septic shock was encountered during the fourth cycle of chemotherapy in 1 patient enrolled at dose level 1, but it was manageable by standard care with antibiotics. Other nonhematologic toxicities were mild and acceptable.

Table 1. Patient characteristics

Characteristic	*n*	(%)
Sex		
M	26	(84)
F	5	(16)
Age (y)		
Median (range)	60	(41–75)
Performance status		
0	25	(81)
1	6	(19)
Body weight loss (%)		
0	26	(84)
0.1–5.0	2	(6)
≤5.0	3	(10)
Histology		
Adenocarcinoma	23	(74)
Squamous cell carcinoma	4	(13)
NSCLC, not otherwise specified	4	(13)
Stage		
IIIA	20	(65)
IIIB	11	(35)

Abbreviation: NSCLC = non–small-cell lung cancer.

Table 2. Treatment delivery

	Level 1 (*n* = 13)	Level 2 (*n* = 12)	Level 3 (*n* = 6)
Radiotherapy			
Total dose (Gy)			
66	13 (100)	–	–
72	–	12 (100)	–
78	–	–	6 (100)
Delay (days)			
≤5	11 (85)	5 (42)	5 (83)
6–10	2 (15)	6 (50)	0
11–15	0	1 (8)	1 (17)
Chemotherapy			
No. of cycles			
4	6 (46)	6 (50)	4 (67)
3	6 (46)	4 (33)	2 (33)
2	0	1 (8)	0
1	1 (8)	1 (8)	0
No. of VNR omissions			
0	10 (77)	7 (58)	2 (33)
1	2 (15)	4 (33)	3 (50)
2	0	0	1 (17)
3	1 (8)	1 (8)	0

Abbreviation: VNR = vinorelbine administered on Day 8.

Table 3. Toxicity

	Grade										
	Level 1			(*n* = 13)	Level 2			(*n* = 12)	Level 3			(*n* = 6)
Toxicity	2	3	4	(3+4 %)	2	3	4	(3+4 %)	2	3	4	(3+4 %)
Leukopenia	4	6	2	(62)	1	3	8	(92)	1	3	2	(83)
Neutropenia	4	4	4	(62)	0	1	10	(92)	1	3	2	(83)
Anemia	8	2	2	(31)	7	3	1	(33)	2	2	0	(50)
Thrombocytopenia	0	0	0	(0)	1	1	0	(8)	0	0	0	(0)
Febrile neutropenia	–	1	0	(8)	–	3	0	(25)	–	1	0	(17)
Infection	0	0	1	(8)	0	1	0	(8)	2	0	0	(0)
Esophagitis	1	1	0	(8)	2	1	0	(8)	0	0	0	(0)
Lung toxicity	2	0	0	(0)	0	0	0	(0)	0	1	0	(17)
Anorexia	3	0	0	(0)	2	2	0	(17)	0	0	0	(0)
Nausea	3	0	0	(0)	3	0	0	(0)	0	0	0	(0)
ALT elevation	1	1	0	(8)	0	0	0	(0)	1	0	0	(0)
CRN elevation	7	0	0	(0)	4	0	0	(0)	0	0	0	(0)

Abbreviations: ALT = alanine aminotransferase; CRN = creatinine.

Of the 13 patients at dose level 1, one was excluded from the analysis of the DLT because he received only one cycle of chemotherapy as a result of the development of cisplatin-induced renal toxicity. Two (17%) of the remaining 12 patients at this dose level developed DLT: Grade 3 esophagitis in 1 patient and Grade 4 septic shock in the other. At dose level 2, two (17%) DLTs were noted: Grade 3 esophagitis in 1 patient and treatment delay by more than 15 days in the other. One (17%) of the 6 patients at dose level 3 developed Grade 3 bronchial stenosis without local recurrence of the disease. This was considered to be a Grade 3 lung toxicity and was counted as DLT. No other DLTs were noted. Thus, inasmuch as the incidence of DLT was below 33% at all dose levels, MTD was not reached.

Preliminary efficacy results

Objective responses and survival were evaluated in the 31 patients. Two patients showed complete responses and 27 showed partial responses, which represented a response rate (95% CI) of 94% (79–99). Disease progression was noted in 23 patients, and the median PFS was 11.6 months with a median duration of follow-up of 30.5 (range, 9.0–49.5) (Fig. 2). The first relapse sites aresummarized in Table 4. Brain metastasis alone as the first relapse site was noted in 7 (23%) patients. The median OS was 41.9 months, and the 2-, 3-, and 4-year survival rates (95% CI) were 83.6% (65.0–92.8), 72.3% (51.9–85.2), and 49.2% (26.2–68.7), respectively (Fig. 3).

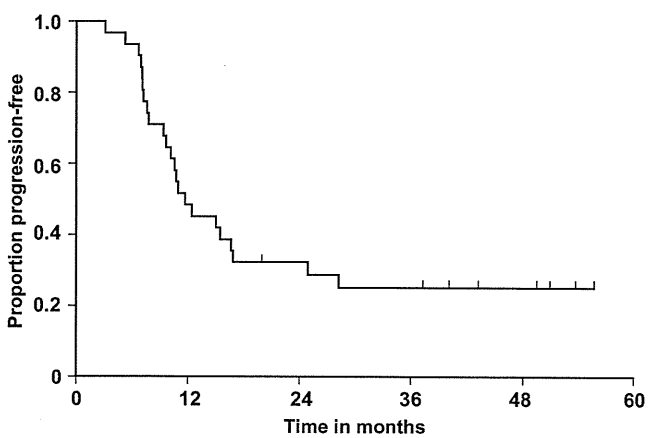

Fig. 2. Progression-free survival (*n* = 31). The median progression-free survival was 11.6 months, with a median duration of follow-up of 30.5 months (range, 9.0–49.5 months).

DISCUSSION

This study showed that concurrent 3D-CRT to the thorax with cisplatin plus vinorelbine chemotherapy was safe even up to 78 Gy in patients with unresectable Stage III NSCLC. This does not mean, however, that doses as high as 78 Gy can be given to all patients with this disease, because the safety in this study was shown only in highly selected patients by a PET/CT and DVH evaluation and by the standard staging procedure. Twenty-five of the 33 patients met the eligibility criteria for enrollment at dose levels 1 and 2, whereas only 6 of the 24 patients could be enrolled at dose level 3 in this study—that is, only one fourth of the patients could be treated with 78 Gy. Thus, this study showed that 72 Gy was the maximum dose that could be achieved in most patients given the predetermined normal tissue constraints, which forced three quarters of the enrolled patients at the 78-Gy level to not

Table 4. First relapse sites (*n* = 31)

Sites	*n*	(%)
Local recurrence alone	6	(19)
Local and distant metastasis	6	(19)
Distant metastasis alone	11	(35)
Brain alone	7	(23)
No relapse	8	(26)

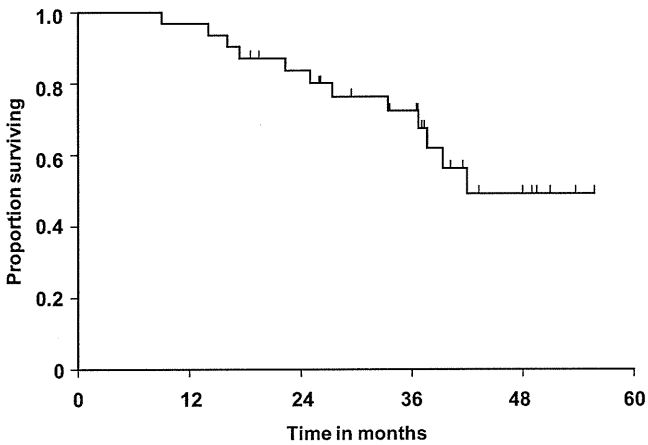

Fig. 3. The median overall survival was 41.9 months, and the 2-, 3-, and 4-year survival rates (95% CI) were 83.6% (65.0–92.8), 72.3% (51.9–85.2), and 49.2% (26.2–68.7), respectively.

be eligible on the basis of those normal tissue constraints, and that the maximum tolerated dose was not determined because of this issue.

One obstacle to enrolling patients at dose level 3 was that the lung V_{20} often exceeded 30% when the total dose was increased to 78 Gy. This lung V_{20} dose constraint might have been too strict. According to a recent review, it is prudent to limit V_{20} to ≤30–35% with conventional fractionation, but there is no sharp dose threshold below which there is no risk for severe radiation pneumonitis (17). This is partly because DVH-based parameters will change at specific phases of the respiratory cycle when CT images for DVH evaluation have been obtained, there is uncertainty regarding how much of the bronchus should be defined as lung, and the lung edges may vary with the CT window level setting. In addition, patient-associated factors such as age, smoking status, lung function, and preexisting lung damage may influence the incidence and severity of radiation pneumonitis (18). If the threshold of V_{20} were set at higher than 30% (*e.g.*, 35%), then more patients would meet the eligibility criteria, but safety might not be guaranteed. Given that the definite threshold cannot be determined, a strict constraint should be introduced. This study showed that the lung toxicity was acceptable when the V_{20} was kept within 30%; therefore, we decided to use this eligibility criterion for concurrent chemotherapy and high-dose radiotherapy for a subsequent Phase II study.

Another obstacle was overdose to the esophagus and brachial plexus, which were close to the subcarinal (No. 7) and supraclavicular lymph nodes, respectively, that were frequently involved in patients with advanced NSCLC; therefore, the volume of these serial organs were included, in part, in the PTV in many patients with Stage III disease. The radiation tolerance doses of these organs have been defined as no higher than 72 Gy when one third of the organs are included in the irradiation volume (19). However, few data are available on the radiation tolerance doses of normal organs in humans; therefore, whether or not radiation doses above 72 Gy may be tolerated is unknown, especially when only small percentages of the organs are actually included in the irradiation volume. Notwithstanding, we do not agree that the radiation dose can be increased close to the intolerable level, because serious radiation toxicity to these serial organs could be irreversible, frequently leaves severe sequelae, and is fatal in some cases.

The toxicity observed in this trial was comparable to that in our previous study of concurrent chemoradiotherapy with vinorelbine and cisplatin chemotherapy plus thoracic radiation at a total dose of 60 Gy administered in 30 fractions: Grade 3–4 neutropenia in 77% and 67% of patients, Grade 3–4 esophagitis in 6% and 12% of patients, and Grade 3–5 lung toxicity in 3% and 7% in the current and previous studies, respectively (5). This suggests that patient selection using PET/CT and DVH evaluation may be useful to keep the toxicity associated with high-dose thoracic radiation within the range of toxicity induced by conventional-dose thoracic radiation.

In this study, a remarkably high proportion (74%) of subjects had adenocarcinoma, which may provide an explanation for the high rate of subsequent brain metastases. Patient selection also affects the treatment efficacy considerably; therefore, it is difficult to compare it between the current and previous studies. However, the median PFS of 11.6 months and median OS of 41.9 months sound promising. We are conducting a Phase II study of concurrent 3D-CRT at a total dose of 72 Gy and chemotherapy with cisplatin and vinorelbine.

In conclusion, concurrent 3D-CRT with cisplatin and vinorelbine chemotherapy was feasible up to 72 Gy, in patients with unresectable Stage III NSCLC. At the level of 78 Gy, however, only 25% of the patients assessed for eligibility were found to be actually eligible. Thus, 72 Gy in 36 fractions was the maximum dose that could be achieved in most patients given the predetermined normal tissue constraints when administered concurrently with cisplatin and vinorelbine.

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