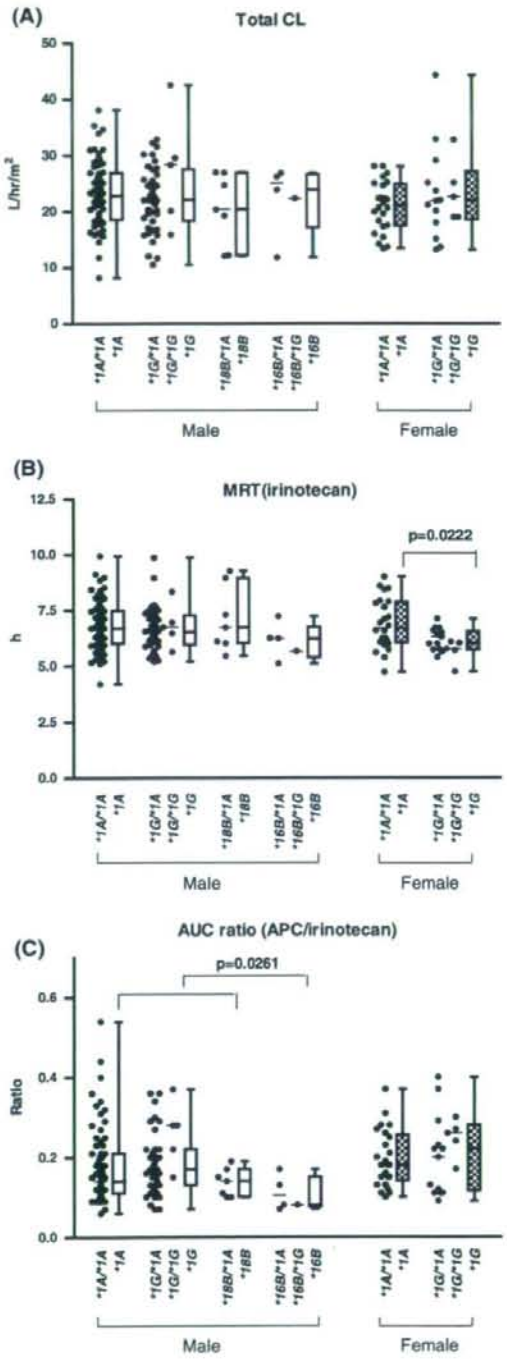

◀ **Fig. 2** Association of *CYP3A4* genotypes with irinotecan pharmacokinetics in Japanese cancer patients. The values of mean residence time (MRT) of irinotecan in female patients were significantly lower in those with **1G* than those with the wild-type (**1A/*1A*) ($P = 0.0222$, Mann–Whitney test). The levels of the AUC ratio (APC/irinotecan), a parameter of CYP3A4 activity, in male patients were significantly lower in those with **16B* than those without **16B* ($P = 0.0261$, Mann–Whitney test)

differences in C_{max}/dose for irinotecan among the genotypes were observed in both males and females (data not shown). Regarding the AUC ratio (APC/irinotecan) in males, a significantly lower median value (50%) was observed in patients with **16B* than patients without **16B* (i.e., *non-*16B* patients) ($P = 0.0261$, Mann–Whitney test) (Fig. 2c). In contrast, no significant changes in the AUC ratio (APC/irinotecan) were detected in the male **18B* heterozygotes. In both males and females, a higher median AUC ratio (20%), without statistical significance, was observed in **1G*-bearing patients (**1G/*1A* and **1G/*1G*) than wild-type patients (**1A/*1A*). As for C_{max}/dose of APC, similar trends were observed (without statistical significance): 35% decrease in the median value for **16B* compared with *non-*16B*; 10 and 20% increases in males and females, respectively, for **1G* compared with the wild type (data not shown).

Multivariate analysis of PK parameters

To further clarify contributions of the *CYP3A4* polymorphisms to APC generation, multivariate analysis was conducted on the AUC ratio (APC/irinotecan) data, where variables included patient backgrounds, irinotecan regimens, and *CYP3A4* (**1G*, **16B* and **18B*) and *UGT1A1* (**6* or **28*) haplotypes. Significant contributions of *CYP3A4*16B* (coefficient ± SE = -0.18 ± 0.077, $P = 0.021$) and **1G* (0.047 ± 0.021, $P = 0.029$) to the AUC ratio (APC/irinotecan) were confirmed, in addition to the contributions of two patient background factors, sex (female) and hepatic function (serum GOT and ALP) (Table 4). No significant associations were observed between the *CYP3A4* polymorphisms and total clearance or MRT of irinotecan (data not shown).

Associations of *CYP3A4* genotypes with toxicities

Severe irinotecan toxicities, grade 3 diarrhea and grade 3 or 4 neutropenia, were monitored in 176 patients during 2 months after starting irinotecan therapy. Since incidences of severe toxicities depended on the irinotecan regimens used and a higher incidence of severe neutropenia with comedication was evident [22], associations of the *CYP3A4*

Table 4 Multivariate analysis of AUC ratio (APC/irinotecan)

Variable	Coefficient	SE	*P* value
Female	0.040	0.016	0.0132
Serum GOT and ALP[a]	0.110	0.021	<0.0001
Serum creatinine[b]	0.132	0.071	0.0651
*CYP3A4*16B*	−0.180	0.077	0.0213
*CYP3A4*1G*	0.047	0.021	0.0291

The values after logarithmic conversion were used

R^2 0.225; Intercept −0.794; *N* 176

[a] Grade 1 or greater scores in both serum GOT and ALP before irinotecan treatment

[b] The absolute value (mg/dl) before irinotecan treatment

haplotypes with toxicities were evaluated in patients who received irinotecan monotherapy. Because there was no sex difference in the incidences of severe toxicities, the patients with irinotecan monotherapy were not stratified by sex. Furthermore, significant contributions of *UGT1A1*6* and **28* to neutropenia were previously demonstrated [22]. Therefore, the incidence of severe neutropenia was also evaluated among the wild-type patients without *UGT1A1*6 or *28* (*UGT −/−*). No significant differences in the incidences of severe diarrhea and neutropenia were observed among the *CYP3A4* diplotypes of all or *UGT −/−* patients with irinotecan monotherapy (Table 5). It must be noted that the **16B*-bearing patient ($N = 1$) treated with irinotecan monotherapy did not experience either toxicity. Similarly, for **1G* and **18B*, no statistically significant change in the neutropenia or diarrhea incidence was observed. Multivariate analysis also revealed no significant contribution of the *CYP3A4* polymorphisms to severe diarrhea (logistic model) or absolute neutrophil count nadir (data not shown).

Table 5 Association of *CYP3A4* genotypes with severe toxicities in irinotecan monotherapy

Diplotype	Diarrhea[a]/total (%)	Neutropenia[b]/total (%)	
	All	All	UGT-/-[c]
**1A/*1A*	3/27 (11.1)	5/27 (18.5)	2/11 (18.2)
**1G/*1A*	2/20 (10.0)	5/20 (25.0)	1/9 (11.1)
**1G/*1G*	0/3 (0.0)	2/3 (66.7)	0/0 (–)
**16B/*1A*	0/1 (0.0)	0/1 (0.0)	0/0 (–)
**18B/*1A*	1/4 (25.0)	2/4 (50.0)	0/1 (0.0)
P value[d]	0.8571	0.289	

[a] Grade 3

[b] Grade 3 or 4

[c] Wild type without *UGT1A1 *6 or *28*

[d] Chi-square test

Discussion

In the current study, the higher in vivo CYP3A4 activity in females than in males [24, 32] was suggested from the CYP3A4-mediated APC formation. Since correlations between in vivo CYP3A4 activity and irinotecan PK parameters have been reported [14, 19, 21], clinical impact of *CYP3A4* polymorphisms on irinotecan PK has been presumed. In this study, we demonstrated for the first time a role of *CYP3A4*16B* [554C > G (Thr185Ser) and IVS10 + 12G > A] in reduced APC generation (Fig. 2; Table 4). This finding is concordant with the findings of our previous studies showing a reduced in vitro activity of CYP3A4 by **16* [23] and altered AUC ratios of metabolite/paclitaxel in paclitaxel-administered Japanese patients bearing **16B* [24]. These findings indicate that *CYP3A4*16* could modulate pharmacokinetics of other drugs which are metabolized by CYP3A4. On the contrary, **18B* [878T > C (Leu293Pro) and IVS10 + 12G > A] did not alter the AUC ratios (APC/irinotecan) in irinotecan-administered patients. This also coincides with our previous finding that showed no clinical impact of **18B* on the metabolite/paclitaxel AUC ratio [24].

In the current study, an increasing trend in the AUC ratios (APC/irinotecan) by **1G* (IVS10 + 12G > A) was detected in both males and females, although their increases were small (20% in the median values). In accordance with this tendency, significant reduction in MRT of irinotecan by **1G* was observed in females, whereas this was not significant in males. At present, the reason of this sex-difference in MRT is not clear. Our previous haplotype analysis of the *CYP3A4* and *CYP3A5* regions revealed that *CYP3A4*1G* is mostly linked to *CYP3A5*1* but rarely to *CYP3A5*3* [3] which is a defective allele [10, 16, 17, 33]. Therefore, there is a possibility that *CYP3A5* polymorphisms rather than *CYP3A4*1G* contribute to irinotecan PK. However, this speculation is unlikely because CYP3A5 produces only a very minor metabolite of irinotecan, a de-ethylated product [27]. Since the effect of **1G* was relatively small and was not shown in case of paclitaxel [23], the clinical importance of **1G* should be further evaluated in pharmacogenetic studies on other drugs.

Contrary to the clear reduction in APC production, changes in the PK parameters for the parent compound, i.e., total clearance and Cmax of irinotecan, were not affected by the *CYP3A4* haplotypes. Furthermore, multivariate analysis revealed no associations of the *CYP3A4* haplotypes with the AUC ratio of (SN-38 + SN-38G)/irinotecan, an in vivo parameter for CES activity, and with the AUC ratio of SN-38 (SN-38/irinotecan) (data not shown). We previously observed that the total clearance of irinotecan was affected by other non-genetic factors, such as age, smoking, hepatic and renal functions, and co-administered drugs

(unpublished data), and that the plasma level of SN-38 was largely influenced by *UGT1A1*6* and **28* [22]. Therefore, it is likely that the contribution of CYP3A4 to irinotecan clearance is rather small as compared with other genetic and non-genetic factors.

In accordance with the above observations, no significant associations were observed between the *CYP3A4* haplotypes and severe toxicities (grade 3 diarrhea and grade 3 or 4 neutropenia) in the patients with irinotecan monotherapy (Table 5). Similarly, we observed no significant effect of the *CYP3A4* haplotypes on incidence of the severe toxicities in the patients treated with both irinotecan and cisplatin (data not shown), although the numbers of patients bearing **16B* and **18B* were small. Taken together, the current study indicates that the influence of the *CYP3A4* genotypes on the activation pathway of irinotecan (generation of SN-38) might be small.

In conclusion, the current study suggested that *CYP3A4*16B* was associated with decreased metabolism of irinotecan to APC. However, impact of the *CYP3A4* haplotypes on total clearance of irinotecan and severe toxicities was not significant.

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Clinical Outcome of Chemoradiation Therapy in Patients with Limited-Disease Small Cell Lung Cancer with Ipsilateral Pleural Effusion

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Background: The indications for definitive thoracic radiotherapy (TRT) in limited-disease small cell lung cancer (LD-SCLC) and ipsilateral pleural effusion have not been thoroughly investigated. We retrospectively investigated the clinical outcome of LD-SCLC patients with ipsilateral pleural effusion.

Methods: The medical records of SCLC patients who received treatment at the National Cancer Center Hospital East between July 1992 and December 2006 were reviewed. Sixty-three of the 373 LD-SCLC patients (17%) had ipsilateral pleural effusion. Of these, 62 patients received chemotherapy as an initial treatment, and were included in this study. Since about 1998, definitive TRT was routinely performed if the patient's pleural effusion disappeared after induction chemotherapy. The 62 patients were divided into three subgroups: group A included patients who received chemotherapy and TRT ($n = 26$), group B included patients who did not receive TRT in spite of the disappearance of pleural effusion after first-line chemotherapy ($n = 8$), and group C included patients who did not receive TRT and whose pleural effusion persisted after first-line chemotherapy ($n = 28$).

Results: The response rate for first-line chemotherapy was 74%. Ipsilateral pleural effusion disappeared after first-line chemotherapy in 34 patients (55%). The median overall survival time was 11.8 months, and the 2 and 3-year survival rates were 21 and 10%, respectively. In groups A, B, and C, the median survival times were 19.2, 10.5, and 9.2 months, respectively, and the 2-year survival rates were 38, 25, and 7%, respectively.

Conclusion: Long-term survival was achieved by LD-SCLC patients with ipsilateral pleural effusion who successfully underwent chemoradiotherapy.

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Lung cancer is the leading cause of cancer-related deaths worldwide. In Japan, over 56,000 people died of lung cancer in 2003. Small cell lung cancer (SCLC) accounts for about 15% of all forms of lung cancer. SCLC has a more aggressive biologic behavior than non-small cell lung cancer. At the time of presentation, two-thirds of patients exhibit disseminated disease. SCLC is sensitive to chemotherapy, with a response rate of 70 to 80%. A clinical two-stage system proposed by the Veterans Administration Lung Study Group distinguishes limited-disease (LD) and extensive-disease (ED) in SCLC.[1] 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. The current standard care for LD-SCLC is a combination of chemotherapy and thoracic radiotherapy (TRT). On the other hand, 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, on the other hand, the classification of LD-SCLC includes bilateral hilar and/or supraclavicular nodal involvement and ipsilateral pleural effusion.[2] However, the indication for definitive TRT in patients with LD-SCLC and ipsilateral pleural effusion have not been thoroughly investigated. Recently, the IASLC proposed the seventh edition of the tumor, node, metastasis (TNM) classification for lung cancer. In the proposals, the presence of a pleural effusion is considered as M1 disease.[3–6]

Definitive TRT is contraindicated in lung cancer patients with malignant pleural effusion. We have sometimes treated SCLC cases in which the ipsilateral pleural effusion disappeared after induction chemotherapy. Should definitive TRT be indicated in SCLC patients if the ipsilateral pleural effusion disappears after induction chemotherapy? Since about 1998, we have routinely performed definitive TRT if the patient's pleural effusion disappeared after induction chemotherapy. In this retrospective study, we investigated the clinical course and outcome of LD-SCLC patients with ipsilateral pleural effusion and exam-

ined the overall survival in patients who received chemotherapy and TRT, comparing with that of ED-SCLC or LD-SCLC patients without ipsilateral pleural effusion. We also applied the proposed seventh edition of the TNM stage to our cohort.

PATIENTS AND METHODS

We retrospectively reviewed the medical records of lung cancer patients who received treatment at the National Cancer Center Hospital East between July 1992 and December 2006. During this period 699 patients were newly diagnosed as having SCLC. Three-hundred and seventy-three patients were diagnosed as having LD-SCLC, and 326 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. 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.[2] Sixty-three of the 373 LD-SCLC patients (17, 95% confidence interval (CI): 13–21%) had ipsilateral pleural effusion. Thirty-seven SCLC patients underwent surgical resection as an initial treatment, and 13 patients received only TRT and/or best supportive care. Remaining 649 patients received chemotherapy as an initial treatment. Of these, 62 LD-SCLC patients had ipsilateral pleural effusion, and were included in this study. The patient characteristics are shown in Table 1. The breadth of the pleural effusion was measured using a CT scan of the chest (Figure 1). Cytologic examination of the pleural effusion prior to treatment was performed in 26 patients. Eleven patients had cytologically positive effusion. Ten patients also had pericardial effusion. Three patients had solid pleural tumor and pleural effusion detected on CT scan. Twenty-six patients had atelectasis. Of these, 14 patients received cytologic examination of the pleural effusion, and four patients had cytologically positive effusion.

We collected clinical data on the patients from their medical records; this data included the chemotherapy regimen that was received, the response to first-line chemotherapy, whether pleural effusion disappeared after first-line chemotherapy, and whether the patient underwent definitive TRT. The World Health Organization's response criteria were used.[7]

Overall survival was defined as the interval between the start of treatment and death or the final follow-up visit. Median overall survival was estimated using the Kaplan-Meier analysis method.[8] Survival data was compared among groups using a log-rank test. The breadth of pleural effusion was compared using the Mann-Whitney U test. All reported p values are two-sided.

RESULTS

The induction chemotherapy regimens were shown in Table 2. Most common regimen was cisplatin or carboplatin plus etoposide. In LD patients with ipsilateral pleural effusion, there were three complete responses, 43 partial responses, seven no changes, and six progressive diseases. Response was not evaluated in three patients because of early death. The response rate was 74% (95% CI: 62–84%). Ipsilateral pleural effusion disappeared after first-line chemotherapy in 34 patients (55, 95% CI: 42–68%).

TABLE 1. Patient Characteristics

	LD-SCLC without Ipsilateral Pleural Effusion	LD-SCLC with Ipsilateral Pleural Effusion	ED-SCLC
No. of patients	270	62	317
Sex			
Male	226	50	262
Female	44	12	55
Age, yr			
Median	66	67	66
Range	38–87	46–79	28–85
Performance status			
0	71	2	20
1	178	45	203
2	14	10	59
3	6	5	28
4	1	0	7
Breadth of pleural effusion on CT scan, cm			
Median		2.3	
Range		0.5–9.4	
Cytology of pleural effusion			
Positive		11	
Negative		15	
Not examined		36	

Patients who received chemotherapy as an initial treatment were included.
LD, limited-disease; SCLC, small cell lung cancer; ED, extensive-disease; CT, computed tomography.

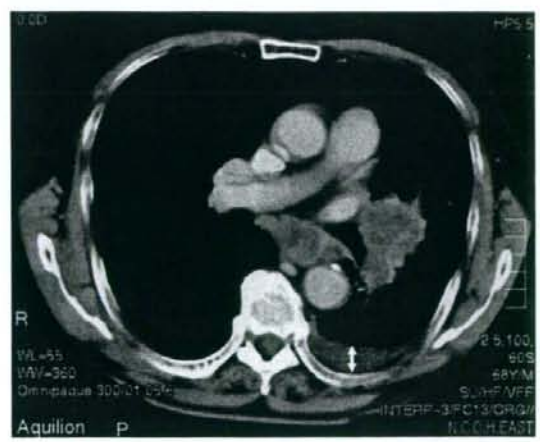

FIGURE 1. Ipsilateral pleural effusion. The arrow indicates the breadth of pleural effusion.

TABLE 2. Induction Chemotherapy Regimens and Response

	LD-SCLC without Ipsilateral Pleural Effusion	LD-SCLC with Ipsilateral Pleural Effusion	ED-SCLC
Chemotherapy regimens			
Platinum + ETP	252	54	154
Cisplatin and irinotecan containing regimens	10	2	92*
CODE	7	5	52
CAV/PE	1	1	11
Other	0	0	8
Response			
CR	64	3	28
PR	189	43	213
NC	8	7	37
PD	5	6	18
NE	4	3	21
Response rate (%) (95% CI)	94 (90–96)	74 (62–84)	76 (71–81)

*Nine patients received chemotherapy of cisplatin and topotecan.

LD, limited-disease; SCLC, small cell lung cancer; ED, extensive-disease; ETP, etoposide; CODE, weekly cisplatin, vincristine, doxorubicin, plus etoposide; CAV/PE, cyclophosphamide, doxorubicin, plus etoposide alternating with cisplatin plus etoposide; CR, complete response; PR, partial response; NC, no change; PD, progressive disease; NE, not evaluable; CI, confidence interval.

Since about 1998, definitive TRT to the primary lesion and mediastinum was routinely performed in patients whose pleural effusion disappeared after chemotherapy. We divided the 62 patients in this study into three subgroups: group A included patients who received chemotherapy and TRT (n = 26), group B included patients who did not receive TRT in spite of the disappearance of pleural effusion after first-line chemotherapy (n = 8), and group C included patients who did not receive TRT and whose pleural effusion persisted after first-line chemotherapy (n = 28).

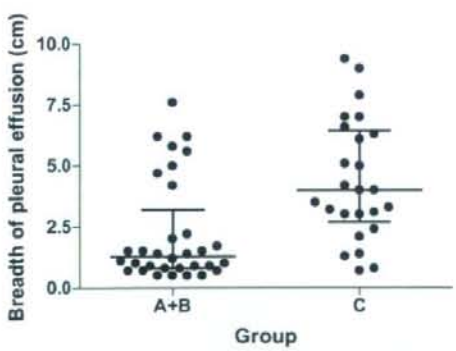

FIGURE 2. Breadth of pleural effusion in subgroup A + B, and C. Group A included patients who underwent chemotherapy and thoracic radiotherapy (TRT) (n = 26), group B included patients who did not undergo TRT in spite of the disappearance of pleural effusion after first-line chemotherapy (n = 8), and group C included patients who did not undergo TRT and whose pleural effusion persisted after first-line chemotherapy (n = 28). The line represents the median with the interquartile range.

The median (range) breadth of pleural effusion was 11.2 cm (0.5–7.6 cm) in group A, 1.8 cm (0.5–5 cm) in group B, and 4 cm (0.7–9 cm) in group C. Combining group A and B, the median breadth of pleural effusion was 1.3 cm, which was significantly lower than that of group C (p = 0.0007) (Figure 2).

In group A, all but two patients received platinum-based chemotherapy. One patient received weekly cisplatin, vincristine, doxorubicin, plus etoposide (PE) therapy, and the other patient received cyclophosphamide, doxorubicin, PE alternating with cisplatin PE therapy. Three of the 26 patients in group A underwent TRT (twice daily, 45 Gy in total) concurrently with the first course of chemotherapy. The breadths of pleural effusion in those three patients were 0.7, 0.8, and 1.0 cm. Two, seven, and one patient underwent TRT (once daily, 50 Gy in total) concurrently with the second, third, and fourth courses of chemotherapy, respectively. Thirteen patients underwent TRT (once daily, 50 Gy in total) sequentially after chemotherapy. Six patients received prophylactic cranial irradiation (PCI) of 25 Gy.

Figure 3*A* showed the survival of the all 699 SCLC patients by the proposed seventh edition of TNM stage. Figure 3*B* showed the survival of the 649 SCLC patients who received chemotherapy as an initial treatment. The survival of LD patients with ipsilateral pleural effusion was intermediate between those of LD patients without effusion and ED patients ($p < 0.0001$). The median survival time in LD patients with ipsilateral pleural effusion was 11.8 months (95% CI: 9.2–16.6), and the 1, 2, 3 and 5-year survival rates were 48, 21, 10 and 8%, respectively. Four patients have survived for over 5 years. One patient had a cytologically negative pleural effusion, and cytologic examinations were not performed for the remaining three patients. Breadth of pleural effusion of these four patients ranged from 1.0 to 1.5 cm. Two of these four patients have not shown any progression for more than 5 years. One patient who received only chemotherapy as an initial treatment developed a local recurrence 3 years after the first-line treatment. This patient received concurrent chemoradiotherapy and achieved a complete response. Unfortunately, he developed brain metastasis 9 years after the first-line chemotherapy and received whole brain radiotherapy. The other patient developed cervicular and inguinal node metastases 8 months after the initiation of first-line chemotherapy and concurrent TRT with three courses of chemotherapy. This patient received second, third, and fourth-line chemotherapy, radiotherapy to the cervicular and inguinal node metastases, and surgical resection of the recurrent inguinal node metastasis. He has not shown any signs of progression for 3 years and 3 months after the final surgical resection of the metastatic inguinal node. All three patients who had solid pleural tumor died within 31 months.

Survival analyses for the subgroups in LD patients with ipsilateral pleural effusion are shown in Figures 4, 5 and Table 3. In group A, the median survival time was 19.2 months (95% CI: 16.7–27.9) and the 1 and 2-year survival rates were 81 and

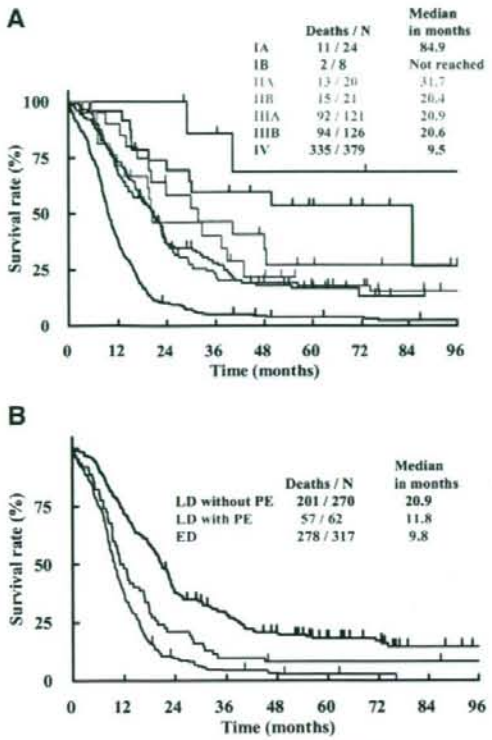

FIGURE 3. *A*, Overall survival in the all 699 patients with small cell lung cancer by the proposed seventh edition of the tumor, node, metastasis stage. *B*, Overall survival in the 649 patients who received chemotherapy as an initial treatment. LD, limited-disease; SCLC, small cell lung cancer; ED, extensive-disease.

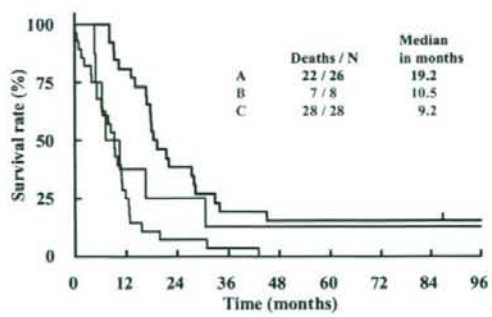

FIGURE 4. Overall survival in subgroups A, B, and C.

38%, respectively. The median survival time of patients with cytologically positive and negative pleural effusion were 9.3 months (95% CI: 3.8–14.2) and 12.7 months (95% CI: 5.1–17.9), respectively. The median survival time of those patients

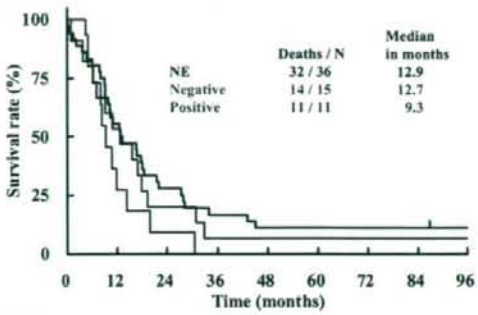

FIGURE 5. Overall survival according to the results of cytologic examination for ipsilateral pleural effusion. NE, not examined.

whose pleural effusions were not examined cytologically was 12.9 months (95% CI: 9.2–18.4). This difference was not statistically significant ($p = 0.1959$).

Disease progression was confirmed in 21 of the 26 patients in group A. The sites of first disease progression included the brain ($n = 10$), regional lymph nodes ($n = 5$), primary lesion ($n = 3$), distal lymph nodes ($n = 2$), liver ($n = 1$), adrenal gland ($n = 1$), and bone ($n = 1$). Twelve (57%) were distant, seven (33%) were local-regional, and two (10%) were both local-regional and distant. Brain metastasis was the only site of recurrence in nine patients. These nine patients had not received PCI. At the time of disease progression, ipsilateral pleural effusion recurred in 10 of the 18 patients.

DISCUSSION

LD-SCLC with ipsilateral pleural effusion accounted for 9% of all the patients with SCLC (63 of 669 patients) and 17% of all the patients with LD-SCLC (63 of 373 patients). Twenty-six (41%) of the LD-SCLC patients with ipsilateral pleural effusion received chemotherapy and definitive TRT. The median survival time of these patients was 19.2 months (95% CI: 16.7–27.9), and the 1 and 2-year survival rates were 81 and 38%, respectively. This overall survival time was comparable to that of LD patients without ipsilateral pleural effusion.

Among the LD-SCLC patients with ipsilateral pleural effusion, the median survival time was 11.8 months (95% CI: 9.2–16.6), and the 1 and 2-year survival rates were 48 and 21%, respectively. This survival was intermediate between those of LD patients without ipsilateral pleural effusion and ED patients. An analysis of 2,580 patients treated in the Southwest Oncology Group trials demonstrated that the survival of patients with LD-SCLC and ipsilateral pleural effusion was not significantly different from that of patients with ED-SCLC and a single metastatic lesion. The median survival times were 13.0 and 12.0 months ($p = 0.85$), respectively.[9] Thus, our data was compatible with that of the Southwest Oncology Group trials. Another analysis of 5,758 patients with SCLC from the IASLC database also demonstrated consistent results.[10]

According to the proposed seventh edition of the TNM classification for lung cancer, LD patients with ipsilateral

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 (%)
ED	317	9.8 (8.8–10.6)	37	10	4
LD without ipsilateral pleural effusion	270	20.9 (19.1–22.7)	72	38	29
LD with ipsilateral pleural effusion	62	11.8 (9.2–16.6)	48	21	10
Receiving TRT	26	19.2 (16.7–27.9)	81	38	19
Not receiving TRT	36	9.1 (6.0–10.8)	28	11	6
Not receiving TRT in spite of disappearance of pleural effusion	8	10.5 (4.5–30.6)	38	25	13
Not receiving TRT and persistent pleural effusion after chemotherapy	28	9.2 (5.1–10.8)	25	7	4
Cytologically positive pleural effusion	11	9.3 (3.8–14.2)	27	9	0
Cytologically negative pleural effusion	15	12.7 (5.1–17.9)	53	20	7
Without cytological examination	36	12.9 (9.2–18.4)	56	28	17

CI, confidence interval; ED, extensive-disease; SCLC, small cell lung cancer; LD, limited-disease; TRT, thoracic radiotherapy.

pleural effusion will be classified as stage IV.[3–6] However, prognosis of LD patients with ipsilateral effusion is better than that of ED patients with distant metastasis. If surgical cases such as clinical stage I cases were excluded, the simple staging system, LD or ED, seemed to be sufficient to select treatment strategy.

In our study, four LD patients with ipsilateral pleural effusion have survived for more than 5 years. Three patients received chemotherapy and TRT as an initial treatment. The remaining one patient received only chemotherapy as an initial treatment but received chemotherapy and TRT after a local recurrence. TRT probably contributed to local control and long-term survival in those LD-SCLC patients with ipsilateral pleural effusion. A previous systematic review demonstrated that an early timing of TRT contributed to a significant improvement in long-term survival, compared with a late timing.[11] In patients whose ipsilateral pleural effusion disappears after chemotherapy, definitive TRT should be considered as early as possible.

Disease progression was confirmed in 21 out 26 patients (81%) who received chemotherapy and definitive TRT. The most common site of first failure was the brain. Nine of the 10 patients had not received PCI. In these nine patients, brain metastasis was the only site of recurrence. In LD-SCLC patients with ipsilateral pleural effusion who undergo chemotherapy and definitive TRT, PCI may further improve treatment outcome.

Cytologic examinations of the pleural effusion before treatment were only performed in 26 patients (42%). These cytologic results did not significantly affect overall survival. However, all nine patients with cytologically positive pleural effusion died within 31 months. A similar observation was reported in a cohort of IASLC database.[10]

Chemotherapy regimens were heterogeneous between LD and ED patients. More patients with ED received cisplatin and irinotecan containing regimens. However, response rates were similar between LD with ipsilateral pleural effusion and ED patients (74 and 76%).

In conclusion, long-term survival was achieved by LD-SCLC patients who underwent definitive TRT after their ipsilateral pleural effusion disappeared after induction chemotherapy. A prospective randomized trial is warranted to compare chemotherapy alone with chemoradiotherapy in LD-SCLC patients with ipsilateral pleural effusion. This work was supported in part by a Grant from the Ministry of Health, Labor, and Welfare for the 3rd term Comprehensive Strategy for Cancer Control and a Grant-in-Aid for Cancer Research from the Ministry of Health, Labor, and Welfare, Japan.

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Efficacy and Safety of Two Doses of Pemetrexed Supplemented with Folic Acid and Vitamin B_{12} in Previously Treated Patients with Non-Small Cell Lung Cancer

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Abstract **Purpose:** The objective of this study was to evaluate the efficacy and safety of two doses of pemetrexed supplemented with folic acid and vitamin B_{12} in pretreated Japanese patients with advanced non-small cell lung cancer (NSCLC).

Experimental Design: Patients with an Eastern Cooperative Oncology Group performance status 0 to 2, stage III or IV, and who received previously one or two chemotherapy regimens were randomized to receive 500 mg/m^2 pemetrexed (P500) or 1,000 mg/m^2 pemetrexed (P1000) on day 1 every 3 weeks. The primary endpoint was response rate.

Results: Of the 216 patients evaluable for efficacy (108 in each arm), response rates were 18.5% (90% confidence interval, 12.6-25.8%) and 14.8% (90% confidence interval, 9.5-21.6%), median survival times were 16.0 and 12.6 months, 1-year survival rates were 59.2% and 53.7%, and median progression-free survival were 3.0 and 2.5 months for the P500 and P1000, respectively. Cox multiple regression analysis indicated that pemetrexed dose was not a significant prognostic factor. Drug-related toxicity was generally tolerable for both doses; however, the safety profile of P500 showed generally milder toxicity. Main adverse drug reactions of severity grade 3 or 4 were neutrophil count decreased (20.2%) and alanine aminotransferase (glutamine pyruvic transaminase) increased (15.8%) in P500 and neutrophil count decreased (24.3%), WBC count decreased (20.7%), and lymphocyte count decreased (18.0%) in P1000. One drug-related death from interstitial lung disease occurred in the P500.

Conclusion: P500 and P1000 are similarly active with promising efficacy and acceptable safety outcomes in pretreated patients with NSCLC. These results support the use of P500 as a second- and third-line treatment of NSCLC.

Pemetrexed (LY231514; Alimta), a multitargeted antifolate, has shown antitumor activity as a single agent or in combination with other anticancer agents (1, 2). Pemetrexed at doses of 500 or 600 mg/m^2 has been evaluated in various clinical settings in a broad range of tumors including lung (non-small cell and mesothelioma), colorectal, gastric, pancreatic, head and neck, bladder, cervical, and breast cancers (3-13). In a randomized phase III trial that compared 3-week regimens of single-agent 500 mg/m^2 pemetrexed versus 75 mg/m^2 docetaxel in pretreated patients with non-small cell lung cancer (NSCLC), respective response rates (9.1% versus 8.8%) and median survival times (MST; 8.3 versus 7.9 months) did not differ between pemetrexed and docetaxel. However, fewer hematologic adverse effects, such as grade 3 or 4 neutropenia, febrile neutropenia, and neutropenic fever, were observed in patients treated with pemetrexed (3).

Myelosuppression is the predominant dose-limiting toxicity of pemetrexed as reported in phase I studies (14-16). A multivariate analysis identified the correlation between poor folate status (as indicated by elevated plasma homocysteine levels) and increased toxicity to pemetrexed, which led to the requirement that patients in all pemetrexed studies receive folic acid and vitamin B_{12} supplementation (2, 17). This has been shown to decrease toxicity to pemetrexed without compromising efficacy (18). Without supplementation, the maximum tolerated dose of pemetrexed, given every 3 weeks, has been shown to be 600 mg/m^2 in heavily pretreated patients (14); however, with supplementation, higher pemetrexed doses have been given without limiting side effects. In a Japanese phase I

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Note: The results of this study have been reported at American Society of Clinical Oncology, World Conference on Lung Cancer, and European Cancer Conference in 2007.

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study of pemetrexed that included folic acid and vitamin B_{12} supplementation, the maximum tolerated dose of pemetrexed was 1,200 mg/m^2 and recommended dose was 1,000 mg/m^2 given every 3 weeks (19). Pemetrexed pharmacokinetics in Japanese patients was not overtly different from those observed in Caucasian patients.

In view of these data, we conducted a randomized, phase II study that confirmed the efficacy and safety of a standard dose of pemetrexed (500 mg/m^2; P500) with that of a higher dose (1,000 mg/m^2; P1000), including folic acid and vitamin B_{12} supplementation, in previously treated NSCLC patients. The primary endpoint was evaluation of response rate. Secondary endpoints were assessments of response duration, progression-free survival (PFS), 1-year survival rate, MST, quality of life (QoL), and adverse events.

Materials and Methods

Patient selection. Men and women, between 20 and 75 years old, with a life expectancy of at least 12 weeks and histologically and/or cytologically confirmed advanced NSCLC were eligible for the study. In addition, all patients met the following inclusion criteria: stage III or IV disease, at least one target lesion, one or two prior chemotherapeutic regimens, an Eastern Cooperative Oncology Group performance status (PS) of 0 to 2, adequate bone marrow function (neutrophils ≥2,000/mm^3, platelets ≥100,000/mm^3, and hemoglobin ≥9.0 g/dL), hepatic function [total bilirubin within 1.5 times the upper normal limit, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) within 2.5 times the upper normal limit, and serum albumin ≥2.5 g/dL], renal function (serum creatinine ≤1.2 mg/dL and creatinine clearance ≥45 mL/min), and pulmonary function (functional oxygen saturation ≥92%).

Patients were excluded from the study for radiographic signs of interstitial pneumonitis or pulmonary fibrosis, serious or uncontrolled concomitant systemic disorders, active infections, the need for chronic administration of systemic corticosteroids, active double cancer and/or brain metastases, treatment with third-space fluid collections within 2 weeks of signing the informed consent or the need of such treatment, grade 3 or 4 toxicity, peripheral sensory neuropathy, previous pemetrexed therapy, unable or unwilling to take folic acid or vitamin B_{12} supplementation, or pregnant or breast-feeding.

This study was conducted in compliance with the guidelines of good clinical practice and the principles of the Declaration of Helsinki, and it was approved by the local institutional review boards. All patients gave written informed consent before study entry.

Study design and sample size. This open-label multicenter study had response rate as the primary objective, and 244 patients were enrolled and 226 were allocated to either 500 mg/m^2 (P500) or 1,000 mg/m^2 (P1000) randomly.

The sample size was calculated to ensure that the response rate in each group exceeded 5%. Based on the results from previous study, assuming a 13% true response rate, 5% one-sided significance level for the test with exact probability based on binomial distribution, and 90% power, at least 107 patients in each treatment arm (total of 214) were necessary. Assuming a 10% dropout rate, 240 patients were planned for the study (actual: 244 patients).

The randomization was done by an independent registration center and was dynamically balanced for PS, previous platinum chemotherapy, disease stage, gender, time from prior chemotherapy to the enrollment, and hospital. Patients were balanced with respect to the study drug in each stratum for each prognostic factor using the minimization method.

Treatment plan. Pemetrexed was administered as an i.v., 10-min infusion on day 1 of a 21-day cycle. Patients were instructed to take orally 1 g/d of a multivitamin containing 500 μg folic acid from 1 week before day 1 of course 1 until 22 days after the last administration of pemetrexed. Vitamin B_{12} (1000 μg) was injected i.m. 1 week before day 1 of course 1 and repeated every 9 weeks until 22 days after the last administration of pemetrexed. Patients were discontinued from the study for disease progression, unacceptable adverse events, inadvertent enrollment, use of excluded concomitant therapy, a cycle delay of >42 days, or if the patient requested to discontinue the study.

Administration of pemetrexed was delayed if patients met any of the following criteria: neutrophils <2,000/mm^3, hemoglobin <9.0 g/dL, platelets <100,000/mm^3, AST/ALT >2.5 times the upper normal limit, total bilirubin >1.5 times the upper normal limit, serum creatinine >1.2 mg/dL, PS 3 or 4, or grade ≥3 nonhematologic toxicity (except for anorexia, nausea, vomiting, and fatigue). The dose of pemetrexed was decreased to 400 mg/m^2 in the P500 arm and to 800 mg/m^2 in the P1000 arm, if any of the following events occurred in the previous course: grade 4 leukopenia or neutropenia, grade ≥3 febrile neutropenia, thrombocytopenia, or platelet transfusion, grade ≥3 nonhematologic toxicity (except for grade 3 anorexia, nausea, vomiting, and fatigue), or AST/ALT increased. The pemetrexed dose was similarly reduced if initiation of the next course was postponed after day 29 due to drug-related adverse events. Patients who continued to show evidence of toxicity after reducing the pemetrexed dose were discontinued from the study.

Baseline and treatment assessments. Pretreatment assessments included chest X-ray, electrocardiogram, blood chemistry, urinalysis, pregnancy test, creatinine clearance, functional oxygen saturation, vital signs, PS, body weight, and use of prior therapies. Tumor size was examined using X-ray, computer tomography, or magnetic resonance imaging done within 28 days before the planned day of the first treatment. This was repeated about every 4 weeks after the first examination.

Tumor response rate was assessed as the percentage of patients in whom complete response (CR) and partial response (PR) were confirmed based on the best overall response of the tumor response evaluation. Response was evaluated according to the Response Evaluation Criteria in Solid Tumors (20). Objective tumor responses in all responding patients were evaluated by an external review committee given no information on the treatment groups.

Duration of overall response (CR + PR) was measured from the date of the first objective assessment of CR or PR until the date of progressive disease. PFS was measured from the date of registration (for the initiation of course 1) until the date of progressive disease or death. One-year survival rate was defined as the percentage of patients who survived for 1 year from the registration date. Survival was measured from the registration date to the date of death (regardless of cause).

QoL was assessed by the QoL Questionnaire for Cancer Patients Treated with Anticancer Drugs and the Functional Assessment of Cancer Therapy for Lung Cancer (Japanese version; refs. 21–23).

Assessments of QoL were done before treatment, before the second and third courses of chemotherapy, and 3 months after the start of treatment.

Adverse events were recorded throughout the study and after the last drug administration until signs of recovery were evident. All such events were evaluated according to the Common Terminology Criteria for Adverse Events version 3.0.

Statistical analysis. Efficacy measurements were done according to the guidelines for clinical evaluation methods of anticancer drugs. Efficacy analysis was done on patients who met all selection criteria and received at least one dose of pemetrexed. Safety analysis was done on patients who received at least one dose of pemetrexed.

Statistical tests were done to establish a pemetrexed response rate of >5%; 90% confidence intervals (CI) for the objective response rate were constructed for each arm. All survival curves for time-to-event variables were created using the Kaplan-Meier method; 95% CIs were calculated for each arm. Response rate, response duration, and PFS were compared between the two arms using the χ^2 test. Cox multiple regression analysis was done on all evaluable patients from two combined arms to

identify significant prognostic factors for survival. Covariates evaluated were pemetrexed dose, gender, age, PS, disease stage, histology, interval from prior chemotherapy to registration for the first treatment course, the number of prior chemotherapeutic regimens, and use of prior platinum chemotherapy. For the QoL analysis, distributions of subscales were summarized for each arm using descriptive statistics (mean, SD, minimum, median, and maximum). As a retrospective analysis for safety, major grade 3 to 4 drug-related adverse events were compared between the two arms using the χ^2 test.

Results

Patient disposition and characteristics. From October 2004 to October 2005, a total of 244 Japanese patients with advanced NSCLC were enrolled at 28 centers. Of the 244 patients enrolled, 226 were randomly assigned (114 to the P500 arm and 112 to the P1000 arm) at least 1 week before treatment after receiving folic acid and vitamin B_{12} supplementation. A total of 225 patients (114 in the P500 arm and 111 in P1000 arm) were evaluable for safety. Of these patients, 216 (108 in each arm) were evaluable for efficacy. Gender, age, PS, histology, stage, and prior platinum chemotherapy were well balanced across the two arms (Table 1).

Efficacy evaluation. Objective tumor response rates and durations of overall response are shown in Table 2. Of the 108 patients evaluable for efficacy in the P500 arm, 20 achieved PR for an objective response rate of 18.5% (90% CI, 12.6-25.8%); the median duration of response was 4.9 months (95% CI, 3.8-8.7 months). Of the 108 patients evaluable for efficacy in the P1000 arm, 16 achieved PR for an objective response rate of 14.8% (90% CI, 9.5-21.6%); the median duration of response was 3.0 months (95% CI, 2.8-6.1 months). As seen above, the lower limits of the 90% CI in both arms were >5%, showing a statistically significant objective response rate >5% in each of the arms. The differences between arms in response rate and response duration were not statistically significant (P = 0.5839 and 0.1740).

By October 2006, 125 of the 216 evaluable patients had died. The MST and 1-year survival rate were 16.0 months and 59.2% in the P500 arm and 12.6 months and 53.7% in the P1000 arm (P = 0.1463, log-rank test for survival; Fig. 1). Median PFS was 3.0 months (95% CI, 2.0-3.5 months) in the P500 arm and 2.5 months (95% CI, 1.8-3.2 months) in the P1000 arm (P = 0.7139, log-rank test).

Cox multiple regression analysis indicated that pemetrexed dose was not a significant prognostic factor; however, gender (female), PS (0), disease stage (III), histologic type (non-squamous cell carcinoma), and longer intervals from prior chemotherapy were shown to be good prognostic factors (Fig. 2). Of note, patients with non-squamous cell carcinoma had a longer MST compared with those with other histologic types (16.0 versus 9.3 months; P = 0.00264, Cox regression analysis). Pretreatment QoL assessments in both arms were relatively high and showed neither worsening nor improvement following pemetrexed treatment (Table 3).

Safety evaluation. A total of 225 patients (114 for P500 and 111 for P1000) were evaluable for safety. Leukopenia, neutropenia, lymphopenia, anemia, elevation of AST/ALT, lactate dehydrogenase, and rash were commonly reported; however, no grade 4 leukopenia or febrile neutropenia was observed (Table 4). Other grade 4 toxicities were uncommon. Gastrointestinal toxicities such as nausea, vomiting, and anorexia were mostly mild and more frequently reported in the P1000 arm. As a retrospective analysis for safety, major grade 3 to 4 drug-related adverse events were compared

Table 1. Patient characteristics

Variable	P500	P1000
Patients who were given at least one dose of pemetrexed	114	111
Gender		
Male	72	71
Female	42	40
Age, median (range)	61.0 (37-74)	62.0 (26-74)
Eastern Cooperative Oncology Group PS		
0	45	37
1	63	68
2	6	6
Histology		
Adenocarcinoma	79	82
Squamous cell carcinoma	25	26
Others	10	3
Disease stage		
III	22	22
IV	92	88
No. prior chemotherapies		
1	44	53
2	67	57
3	3	1
Prior platinum chemotherapy		
Yes	108	104
No	6	7
Interval from prior chemotherapy to registration for the first course starts (mo)		
<3	72	66
3	42	45

Table 2. Objective tumor response and median response duration

Variable	P500 (n = 108)	P1000 (n = 108)
Objective tumor response		
CR	0	0
PR	20	16
Stable disease	40	34
Progressive disease	48	58
Response rate (90% CI), %	18.50 (12.6-25.8)	14.80 (9.5-21.6)
Median response duration (95% CI), mo	4.9 (3.8-8.7)	3.0 (2.8-6.1)

between the two arms using the χ^2 test. Grade 3 or 4 anorexia was reported more frequently in the P1000 arm (10.8% versus 2.6%; P = 0.0284). Drug-related rash was observed in 67.5% and 80.2% of the patients treated with P500 and P1000, respectively. However, all severities were grade 1 or 2. Five of the P500 patients and 3 of the P1000 patients developed interstitial lung disease related to pemetrexed treatment that resulted in the death of one patient (P500 arm). The other 7 patients recovered from their illness after discontinuing the study drug. A total 16 (14.0%) patients in the P500 arm and 26 (23.4%) patients in the P1000 arm discontinued the treatment because of drug-related adverse events.

Dose administration. The median number of treatment courses completed in both arms was 3 (range, 1-24+). Eleven percent of patients in the P500 arm and 8% in the P1000 arm completed at least 10 courses. Dose reduction occurred in 20 (17.5%) patients in the P500 arm and 27 (24.3%) patients in the P1000 arm. The most frequent cause of dose reduction was ALT elevation. Relative dose intensities were 89.6% in the P500 group and 89.8% in the P1000 group.

Discussion

This phase II, randomized study is the first report on the efficacy and safety of a higher dose of pemetrexed (1,000 mg/m^2) in pretreated Japanese patients with NSCLC. Most patients (>50%) received two courses of prior chemotherapy, and the vast majority or patients (>90%) received prior platinum-based chemotherapy. The response data indicate promising tumor reduction activity and are noteworthy in pretreated patients. The survival data are also promising and better than those reported in second- and third-line settings and comparable with those reported in first-line settings (3, 24, 25). In the phase III study (3) comparing pemetrexed with docetaxel, the response

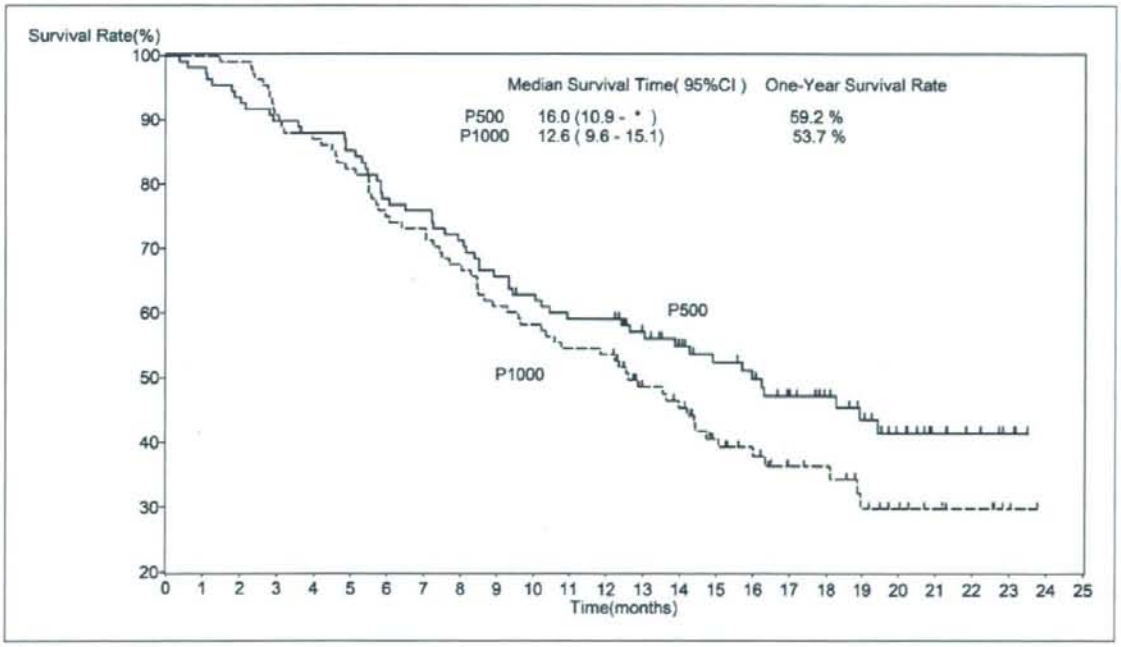

Fig. 1. Kaplan-Meier curve showing the overall survival for each arm. *Asterisk*, upper limit could not be calculated because of the censoring at the end of study period.

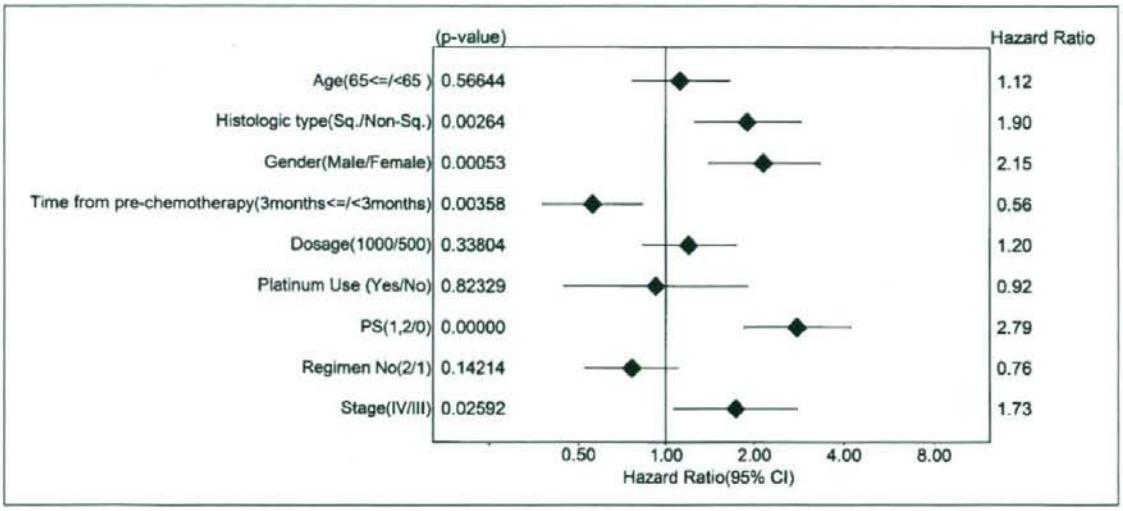

Fig. 2. Forest plot. Cox multiple regression analysis was done on all evaluable patients from two combined arms to identify significant prognostic factors for survival. Covariates evaluated were pemetrexed dose, gender, age, PS, disease stage, histology, interval from prior chemotherapy to registration for the first treatment course, the number of prior chemotherapeutic regimens, and use of prior platinum chemotherapy.

rate and median survival in the pemetrexed arm were 9.1% and 8.3 months, respectively.

Both P500 and P1000 with folic acid and vitamin B_{12} supplementation were similarly active in previously treated patients with NSCLC. All efficacy measures were similar in both arms as shown by the response rate, survival, and PFS, suggesting that doubling the standard dose of pemetrexed does not show superior efficacy. In addition, Cox multiple regression analysis showed that the difference of pemetrexed dose did not influence survival. Overall, toxicity was more frequent at the higher dose, although toxicity in both arms was mild.

Cullen et al. reported a randomized trial of 500 versus 900 mg/m^2 pemetrexed in patients with advanced NSCLC treated previously with platinum-based chemotherapy (26). The response rate, median PFS, and median survival were 7.1%, 2.6 months, and 6.7 months in patients treated with 500 mg/m^2 and 4.3%, 2.8 months, and 6.9 months in patients treated with 900 mg/m^2 pemetrexed, respectively. The higher dose did not improve survival more than the lower dose.

Dose intensification is not always accompanied by higher efficacy, such as in the case of docetaxel and cisplatin. One possible explanation for this in pemetrexed is that either the intracellular transport of pemetrexed is maximal at 500 mg/m^2 or the inhibition of target enzymes is saturated above this dose; however, there are as yet no *in vitro* data to support either mechanism. Although the mechanism still needs to be elucidated, the wide therapeutic window of pemetrexed makes it unique and safe for patients.

Of interest, our subgroup analysis identified some prognostic factors. The subgroups that were identified as good prognostic factors, gender (female), good PS, early-stage disease, and longer intervals from prior chemotherapy are well known as good prognostic factors for NSCLC. Of particular note, the MST

Table 3. Summary for Functional Assessment of Cancer Therapy for Lung Cancer Lung Cancer Subscale

	n	Mean (SD)	Min	Med	Max
P500 (*n* = 108)					
Before course 1	107	71.5 (18.81)	32.1	71.4	100
Before course 2	101	74.3 (16.68)	39.3	75	100
Before course 3	84	74.3 (18.08)	35.7	78.6	100
Registration of course 1 + 3 mo*	59	76.3 (18.1)	32.1	78.6	100
P1000 (*n* = 108)					
Before course 1	107	69.6 (18.52)	25	67.9	100
Before course 2	98	73.5 (17.21)	32.1	75	100
Before course 3	72	71.4 (18.4)	28.6	71.4	100
Registration of course 1 + 3 mo*	61	74.3 (18.62)	28.6	71.4	100

*Three months ±2 weeks after the day of registration for one course.

Table 4. Hematologic and nonhematologic toxicity evaluated by Common Terminology Criteria for Adverse Events version 3.0

	P500 (n = 114)				P1000 (n = 111)				P
	Grade (%)				Grade (%)				
	2	3	4	3/4/5	2	3	4	3/4/5	
Leukopenia	32.5	14.9	0	14.9	38.7	21.6	0	21.6	0.2582
Neutropenia	25.4	17.5	3.5	21.1	27.9	19.8	4.5	24.3	0.6695
Lymphopenia	28.9	9.6	2.6	12.3	30.6	16.2	1.8	18	0.31
Anemia	19.3	7	0.9	7.9	34.2	9	0.9	9.9	0.7667
Thrombocytopenia	0	0	0	0	8.1	0.9	0	0.9	NA
Febrile neutropenia	*	0	0	0	*	0	0	0	NA
Nausea	14	0	0	0	14.4	2.7	0	2.7	NA
Vomiting	7	0	0	0	11.7	1.8	0	1.8	NA
Anorexia	16.7	2.6	0	2.6	15.3	10.8	0	10.8	0.0284
Fatigue	3.5	0	0	0	1.8	0.9	0	0.9	NA
Diarrhea	2.6	0.9	0	0.9	1.8	1.8	0	1.8	0.9815
Constipation	1.8	0.9	0	0.9	5.4	0	0	0	NA
Rash	49.1	2.6	0	2.6	63.1	4.5	0	4.5	0.6903
Alopecia	0	*	*	*	0	*	*	*	NA
Pneumonitis	1.8	1.8	0	2.6†	0	2.7	0	2.7	1
AST	21.9	7.9	0	7.9	25.2	4.5	0	4.5	0.4375
ALT	17.5	16.7	0	16.7	32.4	7.2	0.9	8.1	0.8143

NOTE: Major grade 3 to 4 drug-related adverse events were compared between two arms using χ^2 test.
*Not indicated in Common Terminology Criteria for Adverse Events version 3.0.
†One patient died of drug-induced pneumonitis.

of patients with non-squamous cell carcinoma was significantly longer compared with that in patients with squamous cell carcinoma (16.0 versus 9.3 months; $P = 0.00264$). Pemetrexed induces its antitumor activity by inhibiting key enzymes related to the folate metabolism, such as thymidylate synthase. Studies of the tumor histology of adenocarcinoma progressive disease have reported lower-level expression of thymidylate synthase than squamous cell carcinoma (27). Good survival benefit in patients with non-squamous cell carcinoma by pemetrexed may be explained by lower levels of thymidylate synthase. Because MST was the subject of a subgroup analysis and survival was not a primary endpoint of this study, this finding should be considered exploratory requiring independent confirmation. However, if this finding of superior effectiveness in non-squamous cell carcinoma could be substantiated in future studies, it would be very useful. Indeed, histology could be a simple means of tailoring chemotherapy treatment.

In conclusion, although the recommended dose is P1000 with folic acid and vitamin B_{12} supplementation for Japanese patients, it has similar efficacy and safety with P500, the recommend dosage in rest of the world. These results support the use of P500 as a second- or third-line treatment of NSCLC.

Disclosure of Potential Conflicts of Interest

Authors have conflicts with Eli Lilly and company.

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Concurrent Chemoradiotherapy with Cisplatin and Vinorelbine for Stage III Non-small Cell Lung Cancer

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Introduction: Concurrent chemoradiotherapy with full doses of cisplatin-based chemotherapy is standard treatment for inoperable stage III non-small cell lung cancer (NSCLC). Although many platinum-based two drug combinations with third-generation agents are difficult to combine fully with thoracic radiotherapy (TRT), a phase I study reported a full dose of cisplatin (CDDP) plus 80% dose of vinorelbine (VNR) was successfully combined with concurrent TRT.

Methods: Between October 2000 and October 2004, 73 patients with inoperable stage III NSCLC treated with CDDP, VNR, and concurrent TRT were retrospectively analyzed. Patients were treated with CDDP 80 mg/m^2 on day 1 and VNR 20 mg/m^2 on days 1 and 8 every 4 weeks. Radiotherapy was administered concurrently in cycle 1. The total radiation dose was 60 Gy in 30 fractions. Common Terminology Criteria for Adverse Events version 3.0 were used to assess treatment-related adverse events.

Results: Median age was 63 years (40–78). Twenty-nine patients had adenocarcinoma, 63 were male, 47 ECOG PS 1, and 47 stage IIIB. Median chemotherapy cycle was 2.0. Objective response rate was 93% and median survival time was 21 months. Three-year overall survival rate was 33%. Infield control rate was 71%. The most common grade 3 or 4 adverse event was leukocytopenia (67%). Only 3 patients (4%) experienced grade 3 esophagitis. One patient died of radiation pneumonitis 87 days after completion of chemoradiotherapy.

Conclusions: Concurrent chemoradiotherapy with CDDP and VNR was highly active and well-tolerated. This regimen could be used as a control arm in future trial for stage III NSCLC.

Key Words: Concurrent chemoradiotherapy, Non-small cell lung cancer, Cisplatin, Vinorelbine.

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Lung cancer is the leading cause of cancer-related deaths throughout the world, including Japan.[1] Stage III inoperable non-small cell lung cancer (NSCLC) constitutes approximately 30% of all newly diagnosed cases of NSCLC.[2] Historically, patients with stage III NSCLC were treated with thoracic radiotherapy (TRT) alone. Nevertheless, the survival of patients treated with TRT alone was poor, with a 5-year survival rate of approximately 5%.[3] As the treatment option of chemoradiotherapy (CRT) has developed, the survival of patients with stage III NSCLC has improved, with 3-year survival of approximately 15–20% and median survival time (MST) of 15–20 months.[4,5] Several randomized trials have demonstrated that concurrent CRT using full dose of cisplatin-based chemotherapy improves long-term survival compared with sequential CRT.[6–9] Although two-drug combinations with cisplatin (CDDP) and third-generation agents including vinorelbine (VNR), docetaxel, paclitaxel, gemcitabine, and irinotecan are standard chemotherapy regimens for stage IV NSCLC[10–12], it is difficult to deliver full doses of these regimens and concurrent TRT because of excessive toxicity.

Recently a phase I trial of CDDP, VNR, and concurrent RT was reported.[13] The recommended doses were CDDP 80 mg/m^2 on day 1 and VNR 20 mg/m^2 on days 1 and 8. Although this was a phase I study, an encouraging survival rate of 50% at 3 years was reported. On the basis of this result, we have treated inoperable stage III NSCLC patients with CDDP, VNR, and concurrent RT in clinical practice at the National Cancer Center Hospital East, Japan. Herein is our review of the efficacy and tolerability of CRT with CDDP and VNR.

MATERIALS AND METHODS

The objective of this retrospective analysis was to evaluate the efficacy and tolerability of concurrent CRT using CDDP and VNR.

Patient Selection

We reviewed consecutive 106 inoperable stage III NSCLC patients who were treated with CDDP, VNR, and concurrent TRT at the National Cancer Center Hospital East, Japan, between October 2000 and October 2004. Clinically apparent or histologically/cytologically proven N2/N3 disease or T4 otherwise pulmonary metastasis in the same lobe was considered "inoperable." Chest CT, abdominal CT/ultrasonography, bone scintigram or FDG-PET, and brain MRI/CT were performed in all patients. In general, lymph nodes that were larger than 1.0 cm in minor axis were considered as metastatic. Lymph nodes that were involved in multiple stations were considered 'clinically apparent N2/3.' To con-

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firm N2 disease, which was detected in chest CT and considered 'not apparent,' FDG-PET and/or mediastinoscopy was performed. FDG-PET (or PET/CT) was performed in 18 patients. Mediastinoscopy was performed in ten patients. In addition, there were 5 histologically/cytologically confirmed N3 (supraclavicular lymph nodes) diseases. Thirty-three patients were excluded because they participated in a clinical trial that evaluated CDDP plus VNR followed by docetaxel,[14] therefore 73 patients were evaluated in the present analysis. Data of survival, recurrence, and treatments after failure were obtained from medical records. All patients were evaluated at weekly case conference in which radiation oncologists and medical oncologists who had special expertise in thoracic oncology made treatment decisions. Inclusion criteria for CRT in our institution were generally as follows; white blood cell count $>3.0 \times 10^9$/liter, platelet count $>10.0 \times 10^9$/liter, serum creatinine <1.5 mg/dl, total bilirubin <1.5 mg/dl, and transaminase less that twice the upper limit of the normal value. Exclusion criteria were pulmonary fibrosis identified by a chest x-ray, malignant pleural or pericardial effusion, and a concomitant serious illness, such as uncontrolled angina pectoris, myocardial infarction in the previous 3 months, heart failure, uncontrolled diabetes mellitus, *severe respiratory failure* and uncontrolled hypertension. All patients gave informed consent before CRT.

Chemotherapy

Chemotherapy consisted of CDDP (80 mg/m^2 on day 1) and VNR (20 mg/m^2 days on 1 and 8). Treatment cycles were repeated every 4 weeks with a maximum of 3 cycles administered. Cisplatin and VNR were administered by intravenous infusion. All patients received prophylactic antiemetic therapy consisting of 5-HT3 antagonist, metoclopramide, and dexamethasone. If a patient experienced excessive adverse events, dose reduction of both drugs was implemented during the subsequent treatment cycle. When leukocyte or platelet counts were inappropriate, or if infection developed at day 8, VNR was withheld.

Radiotherapy

TRT was administered concurrently in cycle 1. A CT-scan based treatment planning was used in all patients. The clinical target volume (CTV) for the primary tumor was defined as the gross tumor volume plus 0.5–0.8 cm margin taking account of subclinical extension. The CTV for metastatic lymph nodes were the same as the gross tumor volume for metastatic lymph nodes. Metastatic lymph nodes were defined as the lymph nodes that were larger than 1.0 cm in minor axis. Regional lymph nodes (mainly #3, #4, #7), excluding the contralateral hilar and supraclavicular lymph nodes, were included in the CTV for elective nodal irradiation. The planning target volume for the primary tumor, the metastatic lymph nodes, and regional lymph nodes was determined as CTVs plus setup margin (0.5 cm) and internal margins according to the respiratory motion on fluoroscopy (circumferential 0.5 cm, cranial 0.5 cm, and caudal 1.0–1.5 cm). Lung heterogeneity corrections were not used, and the doses were prescribed to the center of planning target volume. Principally, the initial radiation field was planned not to exceed 50% of ipsilateral lung volume on chest radiograph, or since August 2003, V20 of the normal lung (the percent volume of normal lung receiving 20 Gy or more) was planned not to exceed 35%. The total radiotherapy dose was 60 Gy in 30 fractions (5 fractions per week) delivered over 6 weeks. Radiation therapy was delivered with megavoltage equipment (6 mV) using parallel opposed fields up to 40 Gy in 20 fractions including primary tumor, the metastatic lymph nodes, and the regional lymph nodes. A booster dose of 20 Gy in 10 fractions was given to the primary tumor and the metastatic lymph nodes according to the CT obtained after initial 40 Gy radiation, using opposed oblique fields to avoid excessive dose to the spinal cord.

Evaluation of Efficacy and Adverse Events

Overall survival was defined as time from start of chemoradiotherapy to death of any cause. Progression-free survival was defined as time from start of chemoradiotherapy to the first documented disease progression or death. Disease progression was subdivided into infield relapse or not. Chest CT was used to asses if the relapse was within the initial radiation field. Response Evaluation Criteria in Solid Tumor criteria were used to assess the best tumor response. Chest CT was reviewed independently by a radiologist. The response rate was calculated as the total percentage of patients with a complete or partial response. In principle, the chest CT was taken 2 and 4 months after starting chemoradiotherapy and as needed to evaluate the response and toxicity. Treatment-related adverse events were evaluated using the Common Terminology Criteria for Adverse Events Version 3.0. Late toxicities were scored according to the European Organization for Research and Treatment of Cancer/Radiation Therapy Oncology Group late radiation morbidity scoring scheme.

Statistical Analyses

Multivariate analyses were performed using Cox regression models. Expected prognostic factors included age (<70 years versus >70), gender (male versus female), Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1), clinical stage (IIIA versus IIIB), smoking history (<30 pack-year versus >30), histology (adenocarcinoma versus others), tumor size (<5 cm versus >5 cm), stage (IIIA versus IIIB), and weight loss (<5% versus >5%). Kaplan–Meier methods were used to graphically describe the distribution of survival. All statistical analyses were performed using SPSS II for Windows version 11.0.1J.

RESULTS

Patients' characteristics are shown in Table 1. Median number of chemotherapy cycles were 2.0 (mean 2.4, ranges 1–3). Dose reduction of chemotherapy was implemented in 11 patients mainly due to grade 4 leukocytopenia. Two patients did not receive full dose of radiotherapy. In one patient, radiotherapy was discontinued at the dose of 40 Gy because the tumor was located nearby the spinal cord, and in the other patient because of declined PS.

All 73 patients were assessable for survival, time to progression, response rate, and adverse events. No patient achieved complete response. Partial response, stable disease,

TABLE 1. Patient Characteristics

	Patients (n = 73)	
	No.	%
Age		
Median (range) (yr)	63 (40–78)	
<70 yr	48	66
≥70 yr	25	34
Gender		
Female	10	14
Male	63	86
Histological diagnosis		
Adenocarcinoma	29	40
Squamous cell carcinoma	28	38
Others	16	22
Tumor size		
Median (range) (cm)	5.4 (1.5–12.0)	
<5 cm	33	45
≥5 cm	40	55
ECOG performance status		
0	26	36
1	47	64
Smoking history		
Never smoker	5	7
<30 pack-yr	11	15
≥30 pack-yr	57	78
Stage		
IIIA	26	36
T3N1	3	4
N2	23	32
IIIB	47	64
T4[a]	40	55
N3	12	16
Body weight loss (recent 6 mo)		
<5%	58	79
≥5%	15	21

[a] Six were T4N0, 3 were T4N1, and 5 were T4N3.

TABLE 2. Overall Objective Response

	Number	%
Number of patients evaluated	73	
Complete response (CR)	0	0
Partial response (PR)	68	93.2
Stable disease (SD)	5	7.8
Progressive disease (PD)	0	0
Response rate (95% CI)		93.2 (87.2–99.1)%

CI, confidence interval.

and progressive disease were observed in 68, 5, and 0 patient, respectively (Table 2). The response rate was 93.2% (95% confidence interval; 87.2–99.1%). Median progression free survival time was 12 months and median overall survival time was 21 months with median follow-up of 35 months (ranges 23.7–61.2). Two- and 3-year survival rate was 44 and 33%, respectively. The Kaplan–Meier plots of overall survival are shown in Figure 1; Figure 2 shows progression-free

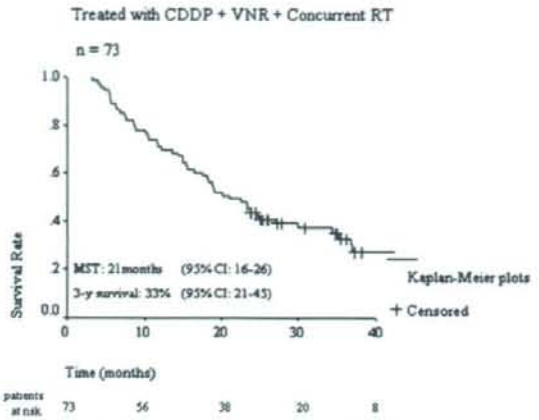

FIGURE 1. Overall survival of patients treated with CDDP + VNR + concurrent RT. CDDP, cisplatin; VNR, vinorelbine; RT, radiotherapy; MST, median survival time; 3-year survival, survival rate at 3 years.

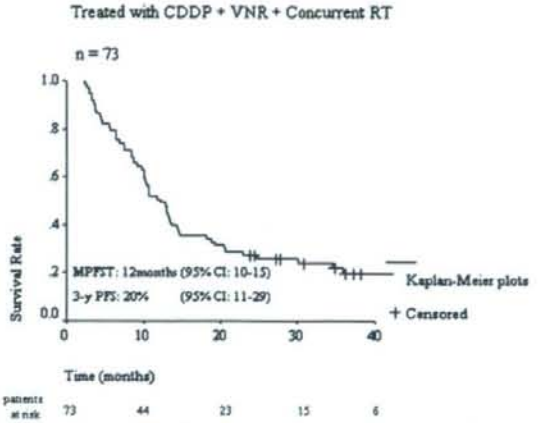

FIGURE 2. Progression-free survival of patients treated with CDDP + VNR + concurrent RT. CDDP, cisplatin; VNR, vinorelbine; RT, radiotherapy; MPFST, median progression-free survival time; 3-year survival, progression-free survival rate at 3 years.

survival. Multivariate analysis showed that no variables significantly affected the overall survival (Table 3).

There were 46 disease relapses and 50 deaths. Infield relapses were observed in 21 patients (11 without and 10 with relapse outside of the radiation fields); therefore infield control rate was 71%. Distant metastases were the first sites of the failure in 35 patients; brain (n = 16), bone (n = 10), adrenal gland (n = 5), liver (n = 3), and lung (n = 16). Seventeen patients received docetaxel and 12 received gefitinib as second line treatment. None responded to docetaxel and two patients (16%) responded to gefitinib (and 1 achieved partial response).

TABLE 3. Prognostic Factors Treated with CDDP + VNR + Concurrent TRT (n = 73)

Parameter	Hazard Ratio	95% CI	p
Age (<70 yr vs. ≥70)	1.787	0.941–3.394	0.076
Gender (male vs. female)	1.364	0.490–3.799	0.553
PS (0 vs. 1)	0.818	0.435–1.537	0.533
Clinical Stage (IIIA vs. IIIB)	1.109	0.588–2.093	0.749
Smoking (<30 pack-yr vs. ≥30)	0.698	0.321–1.519	0.365
Tumor size (< 5 cm vs. ≥5)	0.862	0.473–1.569	0.626
Histology (Ad vs. others)	1.565	0.766–3.198	0.219
Body weight loss (<5% vs. ≥5)	1.567	0.786–3.125	0.202

CI, confidence interval; Ad, adenocarcinoma.

The incidence of treatment-related adverse events is listed in Table 4. The most common grade 3 or 4 adverse event was leukocytopenia (67%). Grade 3 or 4 neutropenia was observed in 38 patients (52%). Grade 3 or 4 thrombocytopenia was not observed; grade 3 or 4 anemia occurred in 17 patients (23%). Only 3 patients (4%) experienced grade 3 esophagitis related to radiotherapy. Five patients (7%) developed grade 3 or 4 pneumonitis and one of them died of respiratory failure 87 days after completion of chemoradiotherapy. The autopsy revealed diffuse alveolar damage compatible with radiation pneumonitis and fibrosis. None of the 5 patients with grade 3 or 4 pneumonitis received second line chemotherapy. Another patient of them developed grade 3 pulmonary fibrosis, but no other severe late radiation morbidity was observed.

DISCUSSION

Chemoradiotherapy is standard treatment for patients with inoperable stage III NSCLC. Several trials indicate that concurrent CRT improves long-term survival compared with sequential CRT.[6–9] Nevertheless, the optimal regimen and dose of chemotherapy has not been determined yet. The efficacy of chemoradiotherapy with CDDP and vinca alkaloids or etoposide has been reported, and CDDP plus vindesine with or without mitomycin has been one of the standard chemotherapy regimens.[6,15–17]

VNR is a newer semi-synthetic vinca alkaloid and more active than vindesine against metastatic NSCLC.[18] Zatloukal et al.[8] reported the efficacy of CRT with CDDP and VNR in a randomized phase II trial, which randomized concurrent CRT or sequential. Concurrent arm was favored in overall survival (MST was 16.6 months in the concurrent arm and 12.9 months in the sequential arm). Vokes et al.[19] also reported the efficacy of CRT with CDDP and VNR in randomized phase II trial, which randomized 3 CDDP-based combination chemotherapies with third-generation agents. In this series, MST of all patients were 17 months and 3 year survival of VNR arm was 23%. With these results, concurrent CRT with CDDP and VNR could be considered one of the new standard regimens for stage III NSCLC, although the employed VNR doses in each phase II study were 12.5 mg/m^2 and 15 mg/m^2. Standard doses of CDDP plus VNR for metastatic NSCLC are 80 mg/m^2 of CDDP and 25 mg/m^2 of VNR. The doses of 20 mg/m^2, employed in the present study, are close to the standard. Moreover, 20 mg/m^2 of VNR alone has reported to be active in advanced NSCLC, with response rate of 21.7%.[20]

Results of the present study were encouraging, demonstrating MST of 21 months and a 3-year survival rate of 33%. Our study confirmed clinical usefulness of combination chemotherapy with CDDP, VNR, and simultaneous TRT.

The most common treatment-related adverse events were hematological (grade 3 or 4 leukocytopenia in 67%, neutropenia in 52%, and anemia in 23%), and these were well tolerated. There were 5 patients (7%) who developed grade 3 or more pneumonitis and only one patient (2%) died of radiation pneumonitis. The incidence and mortality of radiation pneumonitis was comparable with other reports.[6,8,9,19,21–24] Recently we have evaluated dose volume histogram and plan V20 not to exceed 35% in CRT, which may contribute to reducing severe radiation pneumonitis.

Low incidence of severe radiation-related esophagitis in our study deserves special mention. In the present study grade 3 esophagitis was developed in only 3 patients (4%), which is lower than other studies of concurrent chemoradiotherapy where radiation-related esophagitis was reported to be in the range of 12–46%,[21–23] with the exception of one study using CDDP, vindesine (VDS), and mitomycin.[6] In this report, the incidence of grade 3 or more radiation-related esophagitis was only 3%. The cause of this difference is still unknown; however, low incidence of esophagitis may correlate with the use of vinca alkaloids and Japanese studies. Further examination is warranted. We believe that highly conformal therapy could reduce the rate of esophagitis. Overall, chemoradiotherapy with CDDP and VNR were well tolerated.

Although the collection of toxicity data retrospectively is of concern, most patients were treated as inpatient through-

TABLE 4. Grade 3 or 4 Treatment-Related Adverse Events (NCI-CTC vs. 3.0, n = 73)

Adverse Event	Grade 3 (%)	Grade 4 (%)
Leukocytes	32	36
Neutrophiles/granulocytes	25	27
Hemoglobin	22	1
Platelets	1	0
Febrile neutropenia	14	0
Infection with grade 3 or 4 neutropenia	1	0
Infection without neutropenia	10	0
Pneumonitis/pulmonary infiltrates	5	1[a]
Radiation esophagitis	4	0
Radiation dermatitis	0	0
Anorexia	16	0
Nausea	8	0
Vomiting	5	0
Diarrhea	1	0
Creatinine	0	0
Supraventricular arrhythmia (atrial fibrillation)	1	0

[a] One patient died from radiation pneumonitis 87 d after completion of chemoradiotherapy.