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).

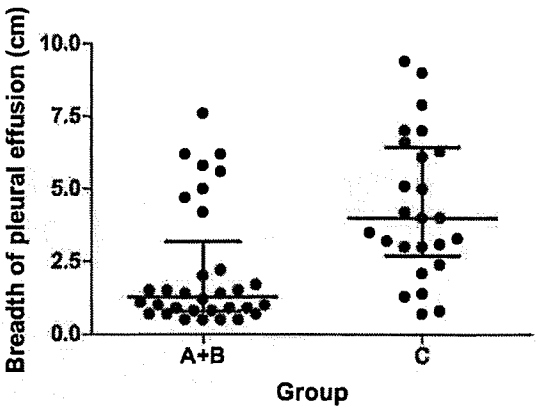

FIGURE 2. Breadth of pleural effusion in subgroup A + B, and C. Group A included patients who underwent chemotherapy and thoracic radiotherapy (TRT) (n = 26), group B included patients who did not undergo TRT in spite of the disappearance of pleural effusion after first-line chemotherapy (n = 8), and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

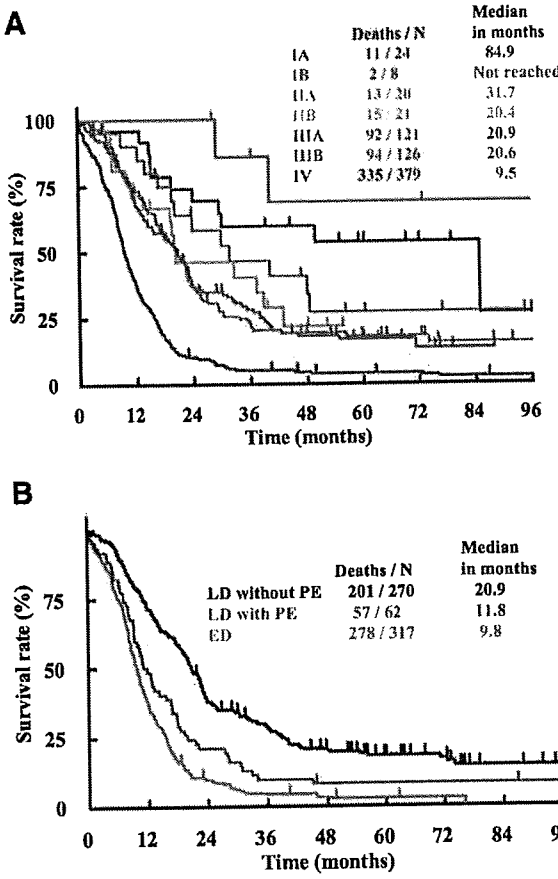

FIGURE 3. *A*, Overall survival in the all 699 patients with small cell lung cancer by the proposed seventh edition of the tumor, node, metastasis stage. *B*, Overall survival in the 649 patients who received chemotherapy as an initial treatment. LD, limited-disease; SCLC, small cell lung cancer; ED,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

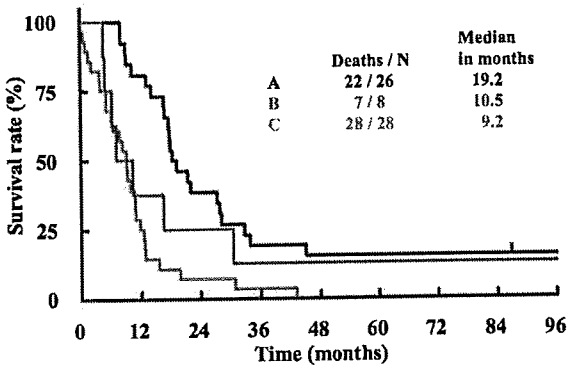

FIGURE 4. Overall survival in subgroups A, B, and C.

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

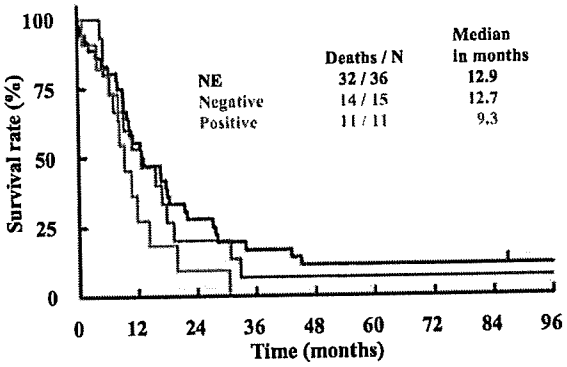

FIGURE 5. Overall survival according to the results of cytologic examination for ipsilateral pleural effusion. NE, not examined.

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

Yuichiro Ohe,[1] Yukito Ichinose,[2] Kazuhiko Nakagawa,[3] Tomohide Tamura,[1] Kaoru Kubota,[4] Nobuyuki Yamamoto,[5] Susumu Adachi,[6] Yoshihiro Nambu,[7] Toshio Fujimoto,[7] Yutaka Nishiwaki,[4] Nagahiro Saijo,[4] and Masahiro Fukuoka[3]

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

Authors' Affiliations: [1]Department of Internal Medicine, National Cancer Center Hospital, Tokyo, Japan; [2]National Kyushu Cancer Center, Fukuoka, Japan; [3]Kinki University School of Medicine, Osakasayama, Japan; [4]National Cancer Center Hospital East, Kashiwa, Japan; [5]Shizuoka Cancer Center Hospital, Shizuoka, Japan; [6]Eli Lilly and Company, Oncology Platform Team, Indianapolis, Indiana; and [7]Eli Lilly Japan K.K., Lilly Research Laboratories Japan, Kobe, Japan

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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.

Requests for reprints: Yuichiro Ohe, Department of Internal Medicine, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. Phone: 81-3-3542-2511; Fax: 81-3-3542-7006; E-mail: yohe@ncc.go.jp.

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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 chemotheraples		
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

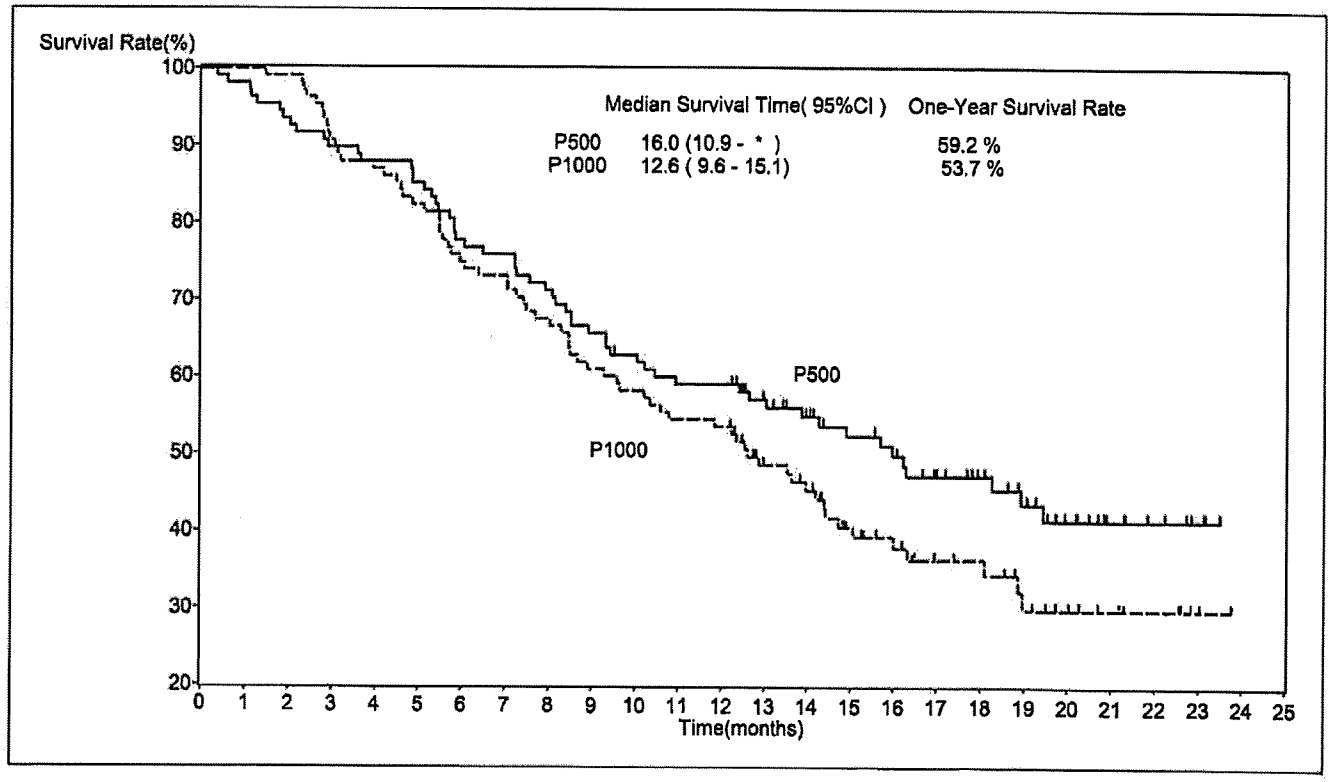

Fig. 1. Kaplan-Meier curve showing the overall survival for each arm. *Asterisk,* upper limit could not be calculated because of the censoring at the end of study period.

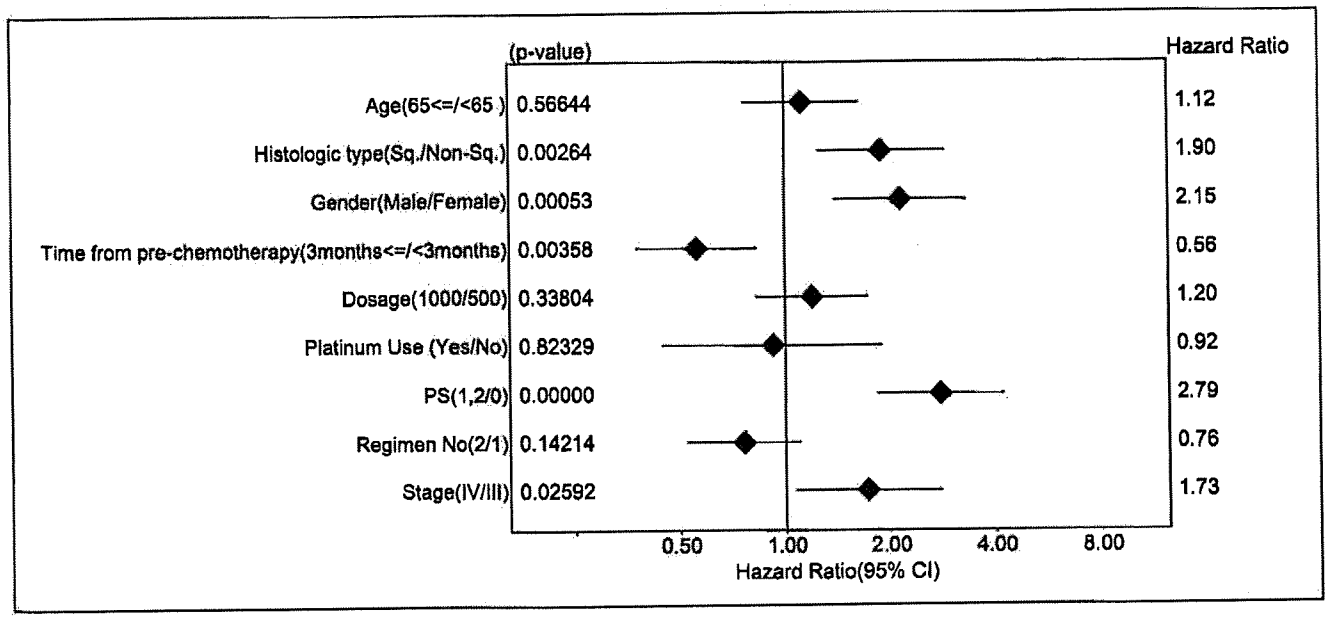

Fig. 2. Forest plot. Cox multiple regression analysis was done on all evaluable patients from two combined arms to identify significant prognostic factors for survival. Covariates evaluated were pemetrexed dose, gender, age, PS, disease stage, histology, interval from prior chemotherapy to registration 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

Yoichi Naito, Kaoru Kubota,* Keiji Nihei,† Tomonori Fujii,* Kiyotaka Yoh,* Seiji Niho,* Koichi Goto,* Hironobu Ohmatsu,* Nagahiro Saijo,* and Yutaka Nishiwaki**

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-

*Thoracic Oncology Division, and †Radiation Oncology Division, National Cancer Center Hospital East, Kashiwa, Japan.

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Address for correspondence: Yutaka Nishiwaki, Thoracic Oncology Division, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, Chiba, 277-8577, Japan. E-mail: ynishiwa@east.ncc.go.jp

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

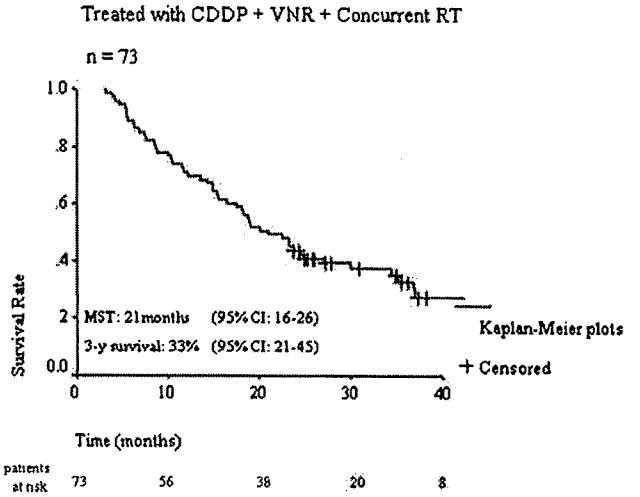

FIGURE 1. Overall survival of patients treated with CDDP + VNR + concurrent RT. CDDP, cisplatin; VNR, vinorelbine; RT, radiotherapy; MST, median survival time; 3-year survival, survival rate at 3 years.

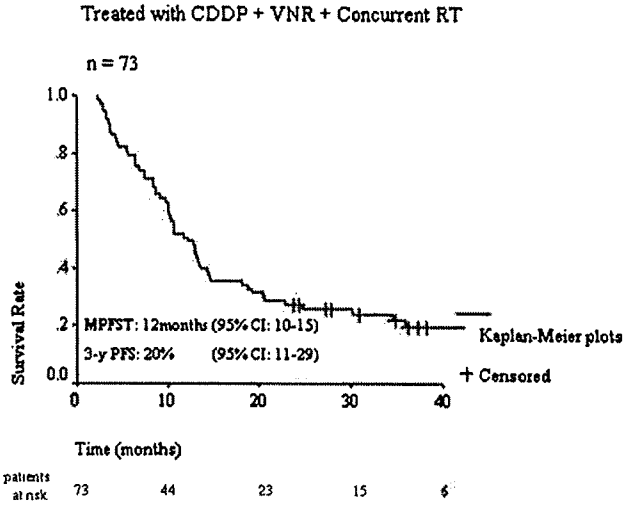

FIGURE 2. Progression-free survival of patients treated with CDDP + VNR + concurrent RT. CDDP, cisplatin; VNR, vinorelbine; RT, radiotherapy; MPFST, median progression-free survival time; 3-year survival, progression-free survival rate at 3 years.

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.

out the treatment course, and toxicity data were recorded on medical records in detail. It should be confirmed by a prospective study.

Taxanes are also investigated widely in patient with unresectable stage III NSCLC. Weekly administration with carboplatin (CBDCA) plus paclitaxel (PTX) and concurrent RT was reported in multiinstitutional phase II study. Reported MST was promising, with 20.5 months.[25] Nevertheless, recently reported phase III trial compared induction chemotherapy plus CRT with CRT alone, which employed weekly CBDCA and PTX, showed disappointing results, with MST of 14 months and 12 months, respectively.[26] The authors concluded that the routine use of weekly CBDCA and PTX with simultaneous TRT should be re-examined. Chemotherapy with docetaxel (DOC) plus CDDP and concurrent TRT was also reported in a phase I/II study.[21] The result was promising, with MST of 23 months, and phase III trial comparing DOC and CDDP to CDDP, VDS, and mitomycin is currently underway.

Local recurrence was observed in 21 patients (29%), and the brain was also a major site of treatment failure (16 patients, 22%). These results are comparable to the literature.[21] On the basis of these observations, other radiation approaches such as hyperfractionated radiotherapy or high-dose thoracic radiation to improve local control should be considered.[27–31] Moreover, whether prophylactic cranial irradiation reduces the incidence of brain metastases should be confirmed.

Advanced age did not correlate with worse prognosis and it is compatible with literature.[32] Gender, tumor size, body weight loss, smoking status did not significantly correlate with shorter overall survival, and it may be due to the small sample size of our study.

We excluded 33 patients who participated in the trial evaluated consolidation docetaxel after concurrent CRT with CDDP and VNR.[14] Sekine and colleagues reported that majority of patients could not continue with consolidation docetaxel after concurrent CRT with CDDP and VNR because of pulmonary toxicity. Although consolidation therapy using docetaxel seems to be highly effective in SWOG phase II study,[33] randomized phase III trial failed to demonstrate that addition of consolidation docetaxel improves survival.[34]

Two patients did not receive full dose of radiotherapy. Nevertheless, these two patients were treated initially with curative intent. Therefore we included these two patients in this analysis. Moreover, exclusion of these two patients did not alter the results (data not shown).

In conclusion, chemoradiotherapy with CDDP and VNR was promising and well tolerated. This regimen could be used as a control arm in future trial for stage III NSCLC.

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Meeting Report

Report from the second Japanese Urological Association–Japanese Society of Medical Oncology joint conference, 2007: 'Diagnosis and treatment of urological malignant tumors: How can we promote subspecialists?'

Nagahiro Saijo,* Tsuneharu Miki,* Yoshinobu Kubota,* Seiji Naito,* Hideyuki Akaza,* Shunji Takahashi* and Hironobu Minami*

Preface: The second Japanese Urological Association–Japanese Society of Medical Oncology joint conference was held on 25 October 2007. The theme of this year's conference was 'Diagnosis and treatment of urological malignant tumors: How can we promote subspecialists?' This Meeting Report briefly discusses the themes of uro-oncology education; collaboration of urologists and medical oncologists for treatment of advanced renal cell carcinoma; the role of urologists in treatment of urological cancer; the role of the medical oncologist in therapy, and collaboration between the JUA and the JSMO.

Program

Moderators:	**Nagahiro Saijo**	Deputy Director, National Cancer Center Hospital East
	Tsuneharu Miki	Professor, Kyoto Prefectural University of Medicine

1. EDUCATION OF URO-ONCOLOGY IN THE JAPANESE UROLOGICAL ASSOCIATION

Presenter:	**Yoshinobu Kubota**	Professor, Yokohama City University

2. INVOLVEMENT OF UROLOGISTS AND MEDICAL ONCOLOGISTS IN THE TREATMENT OF ADVANCED RENAL CELL CARCINOMA

Presenter:	**Seiji Naito**	Professor, Kyushu University

3. THE POSITION OF THE UROLOGIST IN THE TREATMENT OF UROLOGICAL CANCER

Presenter:	**Hideyuki Akaza**	Professor, University of Tsukuba

4. THE ROLE OF THE MEDICAL ONCOLOGIST IN THERAPY FOR UROLOGICAL MALIGNANCY IN JAPAN

Presenter:	**Shunji Takahashi**	Chief, Cancer Institute Hospital

5. COLLABORATION BETWEEN THE JAPANESE SOCIETY OF MEDICAL ONCOLOGY AND THE JAPANESE UROLOGICAL ASSOCIATION FOR DEVELOPING TRAINING SYSTEMS FOR MEDICAL ONCOLOGISTS

Presenter:	**Hironobu Minami**	Professor, Kobe University

DISCUSSION

Summary of second Japanese Urological Association–Japanese Society of Medical Oncology joint conference

Moderators

Nagahiro Saijo MD
Deputy Director
National Cancer Center Hospital East
Tsuneharu Miki MD
Professor
Department of Urology
Kyoto Prefectural University of Medicine

The second Japanese Urological Association–Japanese Society of Medical Oncology (JUA–JSMO) joint conference was held on 25 October 2007, at the National Kyoto International Congress Center from 18:00 to 20:00 hours. The meeting was sponsored by the JUA and the JSMO and was cosponsored by Takada Pharmaceutical Company. The theme of this year's conference was 'Diagnosis and treatment of urological malignant tumors: How can we promote subspecialists?' The session was chaired by Tsuneharu Miki, a professor at Kyoto Prefectural University of Medicine, and Nagahiro Saijo, Deputy Director of the National Cancer Center Hospital East. Three and two speakers were invited from the JUA and the JSMO, respectively.

Yoshinobu Kubota, a professor at Yokohama City University School of Medicine, talked about current educational programs in urology at universities and through the Japanese Urology Association. He reported that the study of urology in Japan covers molecular biology, diagnosis, surgery and chemotherapy, including palliative care of the kidneys, urinary tract and male genital organs. He stressed the need for a Society of Uro-oncology as a subspecialty of urology and bidirectional communication between the JUA–JSMO and the Japanese Association of Radiation Oncology (JASTRO) through joint symposiums and educational seminars.

Seiji Naito, a professor at the Graduate School of Medical Sciences, Kyushu University, talked about the recent development of new molecular target drugs in the field of urology. The development of new drugs like Sorafenib and Sunitinib in Japan has depended solely on clinical trials

* Presenters in order of Program.

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conducted by urologists. He stressed that the quality of these clinical trials for oncology drugs was high, even though the trials were conducted by urologists. He also mentioned that surgery will remain an important treatment modality in the field of uro-oncology and emphasized the importance of collaborations between the JUA and the JSMO, the JASTRO and the Japanese Society of Palliative Care.

Hideyuki Akaza, a professor at the University of Tsukuba, criticized the situation of Gan Shinryo Renkei Kyoten Byoin, nominated by the Ministry of Health, Labour and Welfare, because it lacks fundamental functions requested by the government. He also criticized the functions of two National Cancer Center Hospitals, Tsukiji and Kashiwa, because essential key elements do not exist for the integration of Gan Shinryo Renkei Kyoten Byoin. He stressed that neither of the National Cancer Center Hospitals function as medical centers, since Cancer Centers should be connected with all other branches of medicine. He concluded that bidirectional education and efforts will be essential to establish the field of uro-oncology in Japan.

Shunji Takahashi, Chief of Ariake Ganken Hospital, talked about the current situation of the Cancer Board for the treatment of urogenital tumors at his hospital. Ariake Ganken Hospital organizes a Cancer Board for each tumor type and cares for their cancer patients using a multidisciplinary specialist team consisting of surgeons, medical oncologists, radiation oncologists and nurses. At this moment, their model represents the ideal situation for taking care of cancer patients in Japan.

Hironobu Minami, a professor at Kobe University Graduate School of Medicine and the executive director of the Japanese Society of Medical Oncology, talked about the missions, strategic plans and visions of the JSMO. The JSMO began certifying medical oncologists in 2005 and presently has 205 certified medical oncologists. They have subspecialties for thoracic oncology, hematology/oncology, gastrointestinal oncology, breast cancer, and other areas. Unfortunately, there is only one specialist in uro-oncology. More specialists are essential for optimizing the care of patients with urogenital tumors. The JUA and the JSMO should collaborate with regard to the education of urologists and medical oncologists.

Although the meeting was scheduled to last from 18:00 to 20:00 hours, more than 100 participants attended and many productive discussions were held. The next joint meeting will be scheduled in conjunction with the JUA or the JSMO Annual Meeting.

Education of uro-oncology in Japanese Urological Association

Presenter

Yoshinobu Kubota MD
Professor
Department of Urology, Yokohama City University School of Medicine

Urology in Japan covers diagnoses and treatments including surgeries and molecular therapeutics of a broad range of diseases in urogenital organs. This wide field of urology is different from the urology in the USA which is mainly urological surgery. Thus, Japanese urologists have required wide knowledge, technical skills and experience in several therapeutic modalities including chemotherapy for urogenital cancers. Chemotherapy for urological cancers is therefore a familiar subject of urology in Japan.

Recently, cancer chemotherapy has progressed to be one of the key tools of the treatment for solid cancers such as urogenital cancer. And the JUA has been involved in developing several subspecialties in collaboration with other associated scientific and medical societies.

Considering these situations, there are two key issues for the JUA regarding education on chemotherapy for urogenital cancers. One is education on cancer chemotherapy for urologists and trainees. The other is to train uro-oncologists, especially specialists in chemotherapy for urogenital cancer. In each educational issue, collaboration with medical oncology and urology is essential.

The establishment of a society for the subspecialty of urological oncology, in collaboration with both the JSMO and the JUA is important (Fig. 1). Also, closer communication between the JSMO and the JUA is recommended for further developing and promoting new chemotherapies which are effective against urogenital cancer.

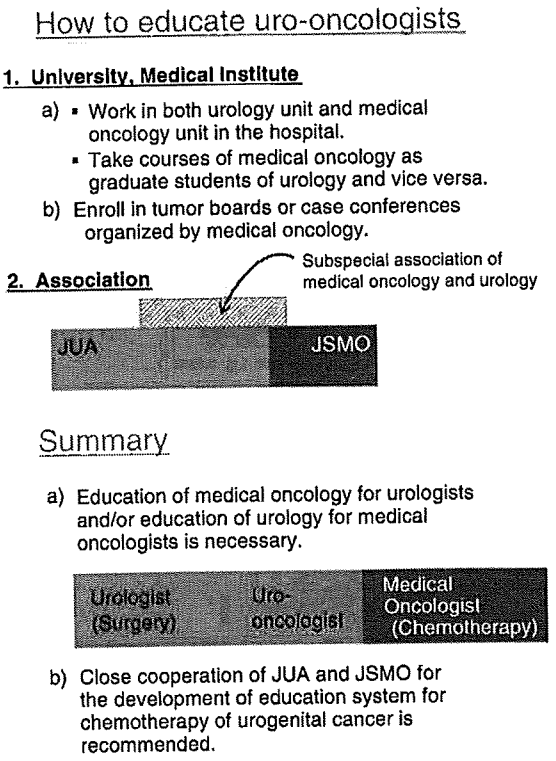

Fig. 1 How to educate the uro-oncologist.

Involvement of urologists and medical oncologists in the treatment of advanced renal cell carcinoma

Presenter

Seiji Naito MD
Professor
Department of Urology, Graduate School of Medical Sciences, Kyushu University

Cytokine therapy, mainly using IFN-α or IL2, has been conventionally adopted as a drug therapy for advanced renal cell carcinoma. Cytokine therapy has demonstrated a low response rate (approximately 15%) and a limited duration of response (6–10 months) so it is not considered to be a satisfactory treatment. Recently, several molecular-targeted drugs, which exert their therapeutic effects by inhibiting intracellular signal transduction involved in tumor cell proliferation or angiogenesis, have been developed. The beneficial effects of these drugs on renal cell

carcinoma have been reported and so the therapeutic strategy has dramatically changed recently. In Europe and the USA, sunitinib, which is an orally available, multitargeted receptor tyrosine kinase inhibitor of vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR), is now being positioned as a first line treatment for metastatic renal cell carcinoma. Furthermore, sorafenib, which is an orally available multikinase inhibitor active on Raf-1, and receptor tyrosine kinases including VEGFR-1, -2, -3, PDGFR-β, c-Kit, Flt-3 and RET, are being positioned as second line treatment for cytokine refractory metastatic renal cell carcinoma. Temsirolimus, which is an inhibitor of the kinase m-TOR (mammalian target of rapamycin), is being positioned as a first line treatment for poor-risk patients with metastatic renal cell carcinoma. In Japan, the phase II studies of sunitinib and sorafenib have been completed and applications for the approval of these drugs have been submitted to the Health, Labour and Welfare Ministry. They will soon be approved for use in the clinical setting. The dosage of sorafenib used in the Japanese phase II study was equivalent to the dosage used in the clinical studies in Europe and the USA. However, the response rate and the incidence of adverse drug reactions such as hand–foot skin reaction and hypertension obtained in the Japanese study were higher than those observed in other clinical studies in Europe and the USA. It is difficult to make an accurate comparison without careful consideration, but the possible effect of ethnicity on the response and adverse drug reactions can not be ruled out. Considering the possibility of the long-term administration of these drugs, adverse drug reactions may be encountered which have not yet been predicted. The postmarketing collection and broad distribution of data on adverse drug reactions and therapeutic effects from registered patients treated at specified medical facilities, at least for some time, are indispensable to preserve patient safety, validate the efficacy of these drugs and educate urologists in charge of treatment. In order to deal with such a situation, urologists should promote close cooperation with physicians who specialize in medical oncology, radiation oncology, psychotherapy, palliative therapy, dermatology, cardiovascular diseases, respiratory diseases, etc. (Fig. 2).

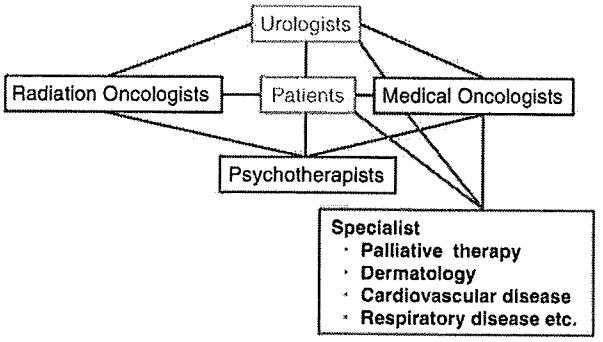

Fig. 2 Holistic medical care for patients with renal cell carcinoma by cooperation among urologists and other relevant physicians including medical oncologists.

Other promising new molecular-targeted drugs for renal cell carcinoma are also in the development phase. Various combination therapies, such as the concomitant use of molecular-targeted drugs, molecular-targeted drugs and cytokines, or the sequential use of molecular-targeted drugs are now being investigated, so the strategy of drug therapy for renal cell carcinoma may change in the near future. In principle, a nephrectomy has been recommended prior to cytokine therapy for patients with metastatic renal cell carcinoma. Whether or not a nephrectomy should also be recommended prior to molecular-targeted therapy still remains unknown. The timing of surgical treatment for metastatic sites during molecular-targeted therapy may also be an important issue in the future.

Urologists should be specialists that provide holistic medical care throughout the course of renal cell carcinoma. In the practical treatment of renal cell carcinoma, urologists are expected to organize a medical team, usually consisting of radiologists, physicians specializing in palliative therapy and those specializing in psychosomatic internal medicine, as well as medical oncologists depending on the patient's pathological condition.

In conclusion, since the advent of effective molecular-targeted drugs, the treatment strategy for metastatic renal cell carcinoma is dramatically changing. In order to practice effective holistic medical care, opportunities for exchanging expertise among physicians including urologists, medical oncologists and other relevant clinicians should be encouraged and increased to promote the development of urologists with comprehensive knowledge and experience regarding the treatment of renal cell carcinoma.

The position of the urologist in the treatment of urological cancer

Presenter

Hideyuki Akaza MD
Professor
Department of Urology, University of Tsukuba, Ibaraki, Japan

A significant number of patients with malignancies including urological cancer have systemic involvement such as metastasis at either a macroscopic or microscopic level. In addition, some patients have various complications at diagnosis. Thus, a treatment strategy should be developed not only for the cancer lesion itself but for other systemic conditions. In a total care system like this the role of the urologist is very important.

It is important in cancer care not to treat only cancer lesions but to care for the patient according to the comorbidity and complications that may occur during cancer treatment (Fig. 3).

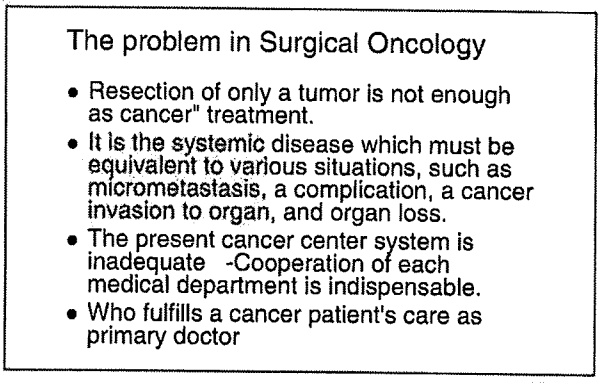

Fig. 3 The problems in surgical oncology.

It is crucial for cancer care to be carried out at an institution where all medical departments are ready, or in an environment where hospital to hospital cooperation is possible. A cancer control program act (Gann taisaku kihon-hou) was enacted in 2007 and the cancer base hospital

design (Gann kyoten byouinn) is progressing as one of the policies for the realization of 'the standardization of cancer therapy'.

The following provision is in guidelines for the maintenance of the cancer base hospital delivered by the Ministry of Health, Labour and Welfare on 1 February 2007:

> The National Cancer Center Central Hospital and Hospital East, regarded as the cancer base hospital, set these guidelines and decide to bear roles, such as support to other cancer base hospitals, particularly the training of a specialty medical practitioner.[1]

Are these organizations fully endowed with a central mechanism that unifies a cancer base hospital? Have they got the mechanism fully established to respond to a subspecialty (such as cardio-vascular, respiratory, or renal function, which affect cancer therapy occasionally and are indispensable to it in these institutions) a complication, or a multiorgan operation?

What has caused the 'cancer refugee' who has become the center of attention these days? For example, the extirpation of renal cell carcinoma with a tumor thrombus in the vena cava inferior or further upstream can not be done without cardio-vascular surgery or vascular surgery. In what kind of institution is this possible? Can the complications accompanying urinary dysfunction or sexual dysfunction associated with prostate cancer, or various problems during endocrine therapy be dealt with appropriately?

At the first JUA-JSMO joint conference during the 44th Annual meeting of the Japanese Society of Clinical Cancer Oncology, the previous chairman of the European Organization of Research and Treatment of Cancer, Louis Denis made the following comments: 'In Europe most of the cancer centers are attached to hospitals as a separate section where they can be connected with all the other branches of medicine. Clinical trials of the last 30 years have forced cancer specialists into close collaboration'.[1] Is this what is lacking in cancer center design in Japan today? It is important in the treatment of urological cancer (at least for the time being until an ideal structure is established) to have efficient cooperation between the urological discipline and medical oncology.

Urologists should study medical oncology in general and medical oncologists should study urological oncology in order to become urological oncologists. These efforts should be bidirectional. Urological oncology in the USA is a specialty produced as a result of this bidirectional study.

The role of the medical oncologist in therapy for urological malignancy in Japan

Presenter

Shunji Takahashi MD
Chief
Department of Medical Oncology, Cancer Institute Hospital, Tokyo

In Japan, urological tumors have been treated by surgeons alone, including chemotherapy. However, recent demands for more specialized cancer treatment from patients and the development of molecular target therapy in the urological area have necessitated medical oncologists specializing in the urological tumor. There are very few medical oncologists participating in the treatment of urological tumors in Japan right now. How medical oncologists should participate in the treatment of urological tumors in Japan is discussed from the standpoint of our hospital.

The Cancer Institute Hospital moved to new buildings at Ariake, Koto-ku in Tokyo and the Department of Medical Oncology opened a new ward in June 2006. We started to participate in chemotherapy for urological tumors since the summer of 2006. First, at the 'Urological Cancer Board' once a week, surgeons, medical oncologists, pathologists, and nurses discussed cases of urological tumors treated with chemotherapy (Fig. 4). We are learning the diagnosis, standard treatment including surgery, and clinical courses of urological malignancies in the cancer board. In turn, we provided advice on oncological emergencies such as severe bone marrow suppression and electrolyte disturbances, or the new therapies for resistant cases.

During September 2006 we started to treat urological malignancy with second or third line chemotherapies, or phase I study in the new ward. We use irinotecan, taxanes, or other drugs for urothelial cancers or germ cell tumors, and started phase I study of new tyrosine kinase inhibitors for renal cell carcinoma (RCC) or urothelial cancer. Around five patients are always treated in the ward.

Most of the chemotherapy for urothelial cancer or germ cell tumor includes cisplatin, such as methotrexate, vinblastine, adriamycin, and cisplatin (MVAC) and bleomycin, etoposide and cisplatin (BEP). Most patients are hospitalized because of nausea and renal toxicity. Furthermore, MVAC is often associated with severe mucositis, and BEP is associated with severe bone marrow suppression, so many patients have been hospitalized for a long time. We first tried to decrease the length of hospitalization during cisplatin-containing therapy to 3 or 4 days by mucositis treatment and infection prevention. Then we started an outpatient treatment program of cisplatin-containing chemotherapy by clinical path including pre- and post chemotherapeutic hydration.

Molecular target therapy has recently been introduced into urological tumor treatment, especially for RCC. Molecular target drugs such as sunitinib, sorafenib, and bevacizumab are associated with a diverse range of adverse effects compared with conventional cytotoxic drugs. Bevacizumab (Avastin) was approved for colon cancer in Japan in April 2007. Grade 3–4 adverse effects with bevacizumab include hypertension (8–25%), bleeding (2–9%), arterial or venous thrombosis (1–20%), gastrointestinal perforation (1–2%), and proteinuria (1%). In the several months following the approval of bevacizumab, we experienced a few cases of deep vein thrombosis, GI perforation, and GI bleeding. To manage those adverse effects efficiently and safely, we needed a multidisciplinary approach (Fig. 5).

A few months before bevacizumab went on the market, we made 'Team Avastin', which consisted of doctors, pharmacists, nurses (of outpatient clinics, inpatient units, and an ambulatory treatment

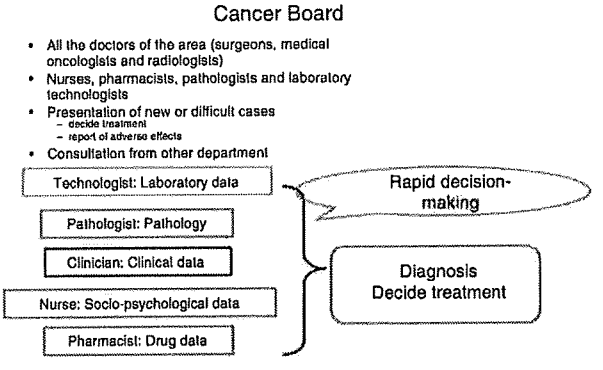

Fig. 4 Members and purposes of the 'Cancer board'.