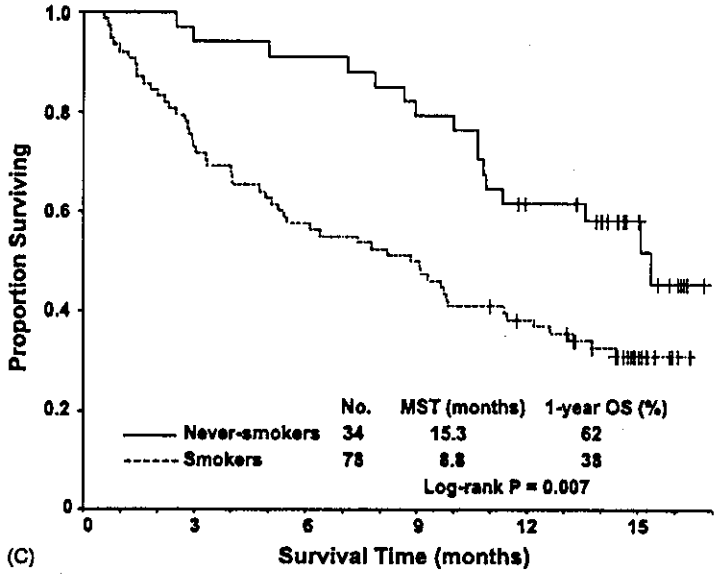

Fig. 2 (*Continued*).

as high as 5.4%. The risk of ILD appears to be around 2–5% if gefitinib is given to patients without careful risk assessment. We think that the incidence can be reduced by patient selection after a thorough risk assessment and that the proper use of gefitinib may enable great benefit, far exceeding its potential risks.

Our analysis of the risk factors for the development of ILD revealed pre-existing PF as a strong risk factor. Of the 112 patients in this study, 12 had PF at the start of gefitinib administration. Four (33%) of these patients subsequently developed ILD, 3 (25%) died as a result, and no response was seen in any of these 12 patients. A panel of experts convened by AstraZeneca Japan retrospectively analyzed 104 patients with NSCLC who developed ILD during gefitinib therapy in Japan and reported that 30 (29%) of them were diagnosed as pre-existing PF by chest X-rays or computed tomography scans taken before gefitinib administration [8]. The panel also noted that the patients with PF had a significantly higher mortality rate after the onset of ILD: it was 77% (23/30) among the patients with PF and 34% (25/74) among the patients without PF ($P < 0.001$) [8]. We conclude that gefitinib treatment may be harmful to patients with PF and recommend that gefitinib not be used if PF is apparent on the chest X-rays.

In our study, all patients were Japanese and a 33% response rate was observed. In the IDEAL 1 trial, 102 Japanese and 106 non-Japanese patients received gefitinib, and the response rate was 27.5% in the Japanese and 10.4% in the non-Japanese [5]. Whether this difference was attributable to ethnicity or an imbalance in other characteristics is unknown, but a high response rate in Japanese patients has been consistently observed in clinical practice.

Both the IDEAL 1 and 2 trials suggested "female gender" and "adenocarcinoma" as predictive factors for tumor response to gefitinib [5,6], and a retrospective analysis of gefitinib monotherapy for advanced NSCLC showed that "adenocarcinoma" (especially with bronchioloalveolar features) and "no history of smoking" were significantly correlated with response to gefitinib [9]. We observed the same tendency with a response rate of 53% in women, 38% in patients with adenocarcinoma, and 63% in never-smokers. "No history of smoking" was a significant predictive factor for response in multivariate analysis, and it was also a significant predictor of longer TTF and longer survival. Since both female gender and adenocarcinoma were significantly associated with no history of smoking, which of these characteristics are true predictive factors remains uncertain. It was also suggested that heavier smokers and male smokers specifically had a lower response rate among the patients with smoking history. Since heavier smokers tended to have a higher risk of ILD, we should carefully assess their risk-benefit ratio of gefitinib therapy before selecting therapeutic strategies.

There are some biological explanations for these clinical characteristics associated with response to gefitinib [10]. Although gefitinib inhibits the intracellular tyrosine kinase domain of EGFR, no correlation between expression of EGFR and response

has been demonstrated [11]. When EGFR and human epidermal growth factor receptor 2 (HER2) are coexpressed, HER2 is the preferred dimerization partner of EGFR, and EGFR-HER2 heterodimers have more signaling potency than EGFR homodimers [12]. Preclinical studies have indicated that tumor cell lines overexpressing HER2 or coexpressing EGFR and HER2 are sensitive to gefitinib [13–16]. Since EGFR/HER2-coexpression is more common in adenocarcinoma of the lung than in squamous cell carcinoma [13,17], the high response rate in adenocarcinoma may be attributable to it. In women, estrogens and estrogen receptors are involved in the development of NSCLC [18], and estrogens binding to its receptors upregulates EGFR and EGFR ligands [19]. The presence of estrogens and its receptors may impact EGFR signaling and the response of NSCLC to gefitinib in women. NSCLC in never-smokers may also have a different biology. Since several studies have indicated fewer mutations of the p53 and K-ras genes in never-smokers than in smokers [20,21], the relation between such tobacco-related mutations and gefitinib response should be investigated. Subgroups of patients who obtain a clinical benefit from gefitinib administration are needed to be identified more precisely, and molecular markers predictive of tumor response should be sought by using DNA microarrays and a proteomics-based approach.

Our analysis suggests that patients who suffer from skin toxicity, diarrhea, or liver toxicity have a greater clinical benefit from gefitinib treatment. A correlation between skin toxicity and survival has also been shown in a study of gefitinib for head and neck cancer [22] and in studies of erlotinib, another EGFR tyrosine kinase inhibitor [23]. Because these findings may be attributable to the responders having taken gefitinib for longer periods and the toxicities in these patients being evaluated more carefully, further studies are needed to confirm them. If the early onset of toxicities has predictive value for survival, it can be used for clinical decision making regarding continuation of gefitinib treatment.

5. Conclusion

When gefitinib is used to treat advanced NSCLC, it confers a higher risk of ILD on patients with PF and a greater clinical benefit on never-smokers, women, patients with adenocarcinoma, and patients with no history of thoracic radiotherapy. Gefitinib therapy is an important treatment option for patients with advanced NSCLC, but the proper use of it based on individual risk-benefit assessments is crucial.

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References

[1] Nakagawa K, Tamura T, Negoro S, et al. Phase I pharmacokinetic trial of the selective oral epidermal growth factor receptor tyrosine kinase inhibitor gefitinib ('Iressa', ZD1839) in Japanese patients with solid malignant tumors. Ann Oncol 2003;14:922–30.

[2] Ranson M, Hammond LA, Ferry D, et al. ZD1839, a selective oral epidermal growth factor receptor-tyrosine kinase inhibitor, is well tolerated and active in patients with solid, malignant tumors: results of a phase I trial. J Clin Oncol 2002;20:2240–50.

[3] Herbst RS, Maddox A-M, Rothenberg ML, et al. Selective oral epidermal growth factor receptor tyrosine kinase inhibitor ZD1839 is generally well-tolerated and has activity in non-small-cell lung cancer and other solid tumors: Results of a phase I trial. J Clin Oncol 2002;20:3815–25.

[4] Baselga J, Rischin D, Ranson M, et al. Phase I safety, pharmacokinetic, and pharmacodynamic trial of ZD1839, a selective oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with five selected solid tumor types. J Clin Oncol 2002;20:4292–302.

[5] Fukuoka M, Yano S, Giaccone G, et al. A multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small cell lung cancer (The IDEAL 1 Trial). J Clin Oncol 2003;21:2237–46.

[6] Kris MG, Natale RB, Herbst RS, et al. Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial. JAMA 2003;290:2149–58.

[7] Inoue A, Saijo Y, Maemondo M, et al. Severe acute interstitial pneumonia and gefitinib. Lancet 2003;361:137–9.

[8] AstraZeneca Japan. Final report on interstitial lung disease (ILD) related to gefitinib (Iressa® Tablet 250) by Iressa Expert Committee; 26 March 2003.

[9] Shah NT, Miller VA, Kris MG, et al. Bronchioloalveolar histology and smoking history predict response to gefitinib [abstract 2524]. Proc Am Soc Clin Oncol 2003;22:628.

[10] Johnson DH, Arteaga C. Gefitinib in recurrent non-small-cell lung cancer: An IDEAL trial? J Clin Oncol 2003;21:2227–9.

[11] Bailey R, Kris MG, Wolf M, et al. Tumor epidermal growth factor receptor (EGFR) expression levels does not predict for response in patients receiving gefitinib ("Iressa", ZD1839) monotherapy for pretreated advanced non-small-cell lung cancer: IDEAL 1 and 2. Proc Am Assoc Cancer Res. 2003;1362.

[12] Arteaga C. The epidermal growth factor receptor: From mutant oncogene in nonhuman cancers to therapeutic target in human neoplasia. J Clin 2001;Oncol.19:32s–40s.

[13] Franklin WA, Veve R, Hirsch FR, et al. Epidermal growth factor receptor family in lung cancer and premalignancy. Semin Oncol 2002;29:3–14.

[14] Moasser MM, Basso A, Averbuch SD, et al. The tyrosine kinase inhibitor ZD1839 ("Iressa") inhibits HER2-driven signaling and suppresses the growth of HER2-overexpressing tumor cells. Cancer Res 2001;61:7184–8.

[15] Moulder SL, Yakes M, Muthuswamy SK, et al. Epidermal growth factor receptor (HER1) tyrosine kinase inhibitor ZD1839 (Iressa) inhibits HER2/Neu (erb-2)- overexpressing

breast cancer cells in vitro and in vivo. Cancer Res 2001;61: 8887–95.
[16] Anido J, Matar P, Albanell J, et al. ZD1839, a specific epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, induces the formation of inactive EGFR/HER2 and EGFR/HER3 heterodimers and prevents heregulin signaling in HER2-overexpression breast cancer cells. Clin Cancer Res 2003;9:1274–83.
[17] Hirsch FR, Varella-Garcia M, Franklin WA, et al. Evaluation of HER-2/neu gene amplification and protein expression in non-small cell lung carcinomas. Br J Cancer 2002;86:1449–56.
[18] Siegfried JM. Women and lung cancer: does oestrogen play a role? Lancet Oncol 2001;2:506–13.
[19] Hom YK, Young P, Wiesen JF, et al. Uterine and vaginal organ growth requires epidermal growth factor receptor signaling from stroma. Endocrinology 1998;139:913–21.
[20] Husgafvel-Pursiainen K, Kannio A. Cigarette smoking and p53 mutations in lung cancer and bladder cancer. Environ Health Perspect 1996;104(Suppl 3):553–6.
[21] Ahrendt SA, Decker PA, Alawi EA, et al. Cigarette smoking is strongly associated with mutation of the K-ras gene in patients with primary adenocarcinoma of the lung. Cancer 2001;92:1525–30.
[22] Cohen EEW, Rosen F, Stadler WM, et al. Phase II trial of ZD1839 in recurrent or metastatic squamous cell carcinoma of the head and neck. J Clin Oncol 2003;21:1980–7.
[23] Clark GM, Perez-Soler R, Siu L, et al. Rash severity is predictive of increased survival with erlotinib HCl [abstract 786]. Proc Am Soc Clin Oncol 2003;22:196.

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ORIGINAL REPORT

Comparison of Pharmacokinetics and Pharmacodynamics of Docetaxel and Cisplatin in Elderly and Non-Elderly Patients: Why Is Toxicity Increased in Elderly Patients?

Hironobu Minami, Yuichi Ohe, Seiji Niho, Koichi Goto, Hironobu Ohmatsu, Kaoru Kubota, Ryutaro Kakinuma, Yutaka Nishiwaki, Hiroshi Nokihara, Ikuo Sekine, Nagahiro Saijo, Kazuhiko Hanada, and Hiroyasu Ogata

From the Divisions of Oncology/Hematology and Thoracic Oncology, National Cancer Center Hospital East, Kashiwa; Division of Internal Medicine, National Cancer Center Hospital; Department of Biopharmaceutics, Meiji Pharmaceutical University, Tokyo, Japan.

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Address reprint requests to Hironobu Minami, MD, Division of Oncology/Hematology, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa 277-8577, Japan; e-mail: hminami@east.ncc.go.jp.

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ABSTRACT

Purpose
Following phase I studies of docetaxel and cisplatin in patients with non–small-cell lung cancer, the recommended doses of docetaxel were different for elderly (≥ 75 years) and non-elderly (< 75 years) patients. To elucidate the mechanism of the difference, the pharmacokinetics of docetaxel and cisplatin were investigated in two phase II studies separately conducted in elderly and non-elderly patients.

Patients and Methods
Twenty-seven elderly and 25 non-elderly patients were treated with three weekly administrations of docetaxel and cisplatin every 4 weeks. Doses of docetaxel were 20 and 35 mg/m^2 for elderly and non-elderly patients, respectively. All patients received 25 mg/m^2 of cisplatin. The pharmacokinetics and pharmacodynamics of docetaxel and cisplatin were compared in elderly and non-elderly patients.

Results
There were no differences in pharmacokinetics of docetaxel or cisplatin between elderly versus non-elderly patients with regard to clearance and volume of distribution. In the pharmacodynamic analysis, neutropenia was positively correlated with the area under the concentration-time curve for docetaxel but not for cisplatin. In evaluating the relationship between neutropenia and the area under the concentration-time curve of docetaxel, elderly patients experienced greater neutropenia than those predicted by a pharmacodynamic model developed in non-elderly patients; the residual for prediction of the percent change in neutrophil count was −11.2% (95% CI, −21.8 to −0.5%).

Conclusion
The pharmacokinetics of docetaxel and unchanged cisplatin were not different between elderly and non-elderly patients. The elderly patients were more sensitive to docetaxel exposure than the non-elderly patients, resulting in the different recommended doses for the phase II studies.

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INTRODUCTION

The elderly population has increased in recent years with the prolongation of the average life span, and the incidence of cancer in elderly people is also increasing. Accordingly, the number of elderly patients with cancer is expanding. Although most cancers occur in elderly individuals, elderly patients have been underrepresented in clinical trials of cancer chemotherapy.[1-5] Furthermore, many elderly patients have not been referred to medical oncologists and have been under-treated in oncologic practice because of concerns over toxicity.[5-9] Frequencies and severities of toxicity associated with cancer chemotherapy are higher in elderly patients than in younger patients.[10-14] Despite the increased susceptibility to toxicity in elderly patients, limited investigations have been conducted on changes in the pharmacokinetics of anticancer agents associated with aging.[15-18] In addition, few studies have focused on the alterations of

pharmacodynamics in elderly patients. Altered pharmacokinetics, increased pharmacodynamic sensitivity, or both can theoretically cause increased toxicity. It is important, therefore, to elucidate the pharmacokinetics and pharmacodynamics of anticancer agents in elderly patients in comparison to those of younger patients in terms of their increased toxicities.

Previous reports have stressed that in the elderly, physiologic age is more important than chronological age, and that age by itself is not a contraindication to cancer chemotherapy.[19,20] Some retrospective studies of chemotherapy failed to demonstrate an increased risk of toxicity among elderly patients; it has been claimed that elderly patients can tolerate chemotherapy as well as younger patients when they fulfill eligibility criteria for clinical studies of cancer chemotherapy, such as good performance status and normal organ functions.[21-24] However, in a feasibility study of chemotherapy for elderly patients with lung cancer, 71% of patients aged 75 years or older were excluded from the study because of comorbidity or poor performance status; furthermore, severe myelotoxicity was observed, even in patients who fulfilled the eligibility criteria.[25] Therefore, we believe that doses of anticancer agents for elderly patients should be determined by phase I studies, specifically conducted in such patients.

When we determined recommended doses of cisplatin and docetaxel administered weekly for 3 consecutive weeks in patients with non–small-cell lung cancer, we conducted two individual phase I studies for elderly patients aged 75 years or older and for non-elderly patients younger than 75 years.[26] The only difference in eligibility criteria for these two phase I studies was age. The recommended dose of cisplatin was 25 mg/m^2 for both patient groups, but doses of docetaxel were different for elderly (20 mg/m^2) and non-elderly (35 mg/m^2) patients. Based on this information, two separate phase II studies against non–small-cell lung cancer were conducted in elderly patients and non-elderly patients, using the different recommended doses.[27,28] Eligibility criteria for the phase II studies were the same as those for phase I studies, except that a measurable disease for response evaluation was required for the phase II studies. To elucidate mechanisms of the difference in recommended doses of docetaxel for elderly and non-elderly patients, we investigated the pharmacokinetics and pharmacodynamics of docetaxel and cisplatin in the two phase II studies and compared them between elderly and non-elderly patients.

PATIENTS AND METHODS

Patient Selection

Eligibility criteria for the two phase II studies were identical except for age: 75 years or older for elderly patients and 20 to 74 years for non-elderly patients. Other eligibility criteria included histologically and/or cytologically confirmed non–small-cell lung cancer, stage IV or IIIB without an indication for curative radiotherapy, Eastern Cooperative Oncology Group performance status 0 or 1, no prior chemotherapy, the presence of measurable lesions, adequate hematologic function (WBC 4,000 to 12,000/μL; absolute neutrophil count $\geq$ 2,000/μL; platelet count $\geq$ 100,000/μL; hemoglobin $\geq$ 9.0 g/dL), adequate hepatic function (total bilirubin $<$ 1.1 mg/dL; AST and ALT $<$ 60 U/L), and adequate renal function (creatinine $<$ 1.2 mg/dL; creatinine clearance $>$ 60 mL/min). Exclusion criteria were active infection, severe heart disease, uncontrolled hypertension or diabetes mellitus, active concomitant malignancy, pleural and/or pericardial effusion requiring drainage, and pregnant/nursing women. In addition to written informed consent to the phase II studies with docetaxel and cisplatin, written informed consent to the pharmacologic study was required before patients were enrolled onto this study. These studies were approved by the institutional review board at the National Cancer Center (Tokyo, Japan).

Treatment and Follow-Up

After premedication with intravenous dexamethasone (16 mg) and granisetron (3 mg), docetaxel was infused over 30 minutes. Cisplatin was given as a 15-minute infusion 90 minutes after completion of the docetaxel infusion, and a total volume of 1,500 mL saline was infused on the day of chemotherapy for diuresis. The dose of docetaxel was 20 mg/m^2 for elderly patients and 35 mg/m^2 for non-elderly patients. All patients received cisplatin at a dose of 25 mg/m^2. These were the recommended doses determined by the phase I studies. Docetaxel and cisplatin was administered weekly for 3 consecutive weeks followed by 1 week of rest. This 4-week course was repeated until there was evidence of disease progression or unacceptable toxicity. Treatment with docetaxel and cisplatin was not given if WBC was less than 2,000/μL and/or platelet count was less than 50,000/μL on the day of chemotherapy.

Physical examination and toxicity assessment included complete blood cell counts with differential counts as well as platelet counts, blood chemistry, and urinalysis. These were performed before treatment and repeated at least weekly during the chemotherapy. Toxicity was graded according to the Japan Clinical Oncology Group criteria,[29] which are basically the same as the National Cancer Institute Common Toxicity Criteria.

Antitumor response was evaluated in lesions with a diameter $\geq$ 2 cm by carrying out a computed tomography scan according to WHO criteria.[30]

Pharmacokinetic Analysis

Blood sampling for pharmacokinetic analysis was performed after the first administration of the first course as follows: (1) blood samples for the measurement of docetaxel concentrations were obtained at the end of a docetaxel infusion, and 0.17, 1, 1.75, 3.25, 5.75, and 24 hours after the docetaxel infusion; (2) for analysis of the pharmacokinetics of cisplatin, blood was drawn at the end of a cisplatin infusion, and 0.25, 0.75, 1.5, 4, and 22.25 hours after the cisplatin infusion. Blood was immediately centrifuged and an aliquot of plasma was ultrafiltered using UFC3GC membranes (Japan Millipore, Tokyo, Japan). Plasma and ultrafiltrate samples were frozen at −80°C until analyzed.

The concentration of docetaxel in plasma was determined by using a previously reported high-performance liquid chromatography (HPLC) method,[31] and the concentration of unchanged cisplatin in the ultrafiltrate was measured according to

a HPLC method with on-line postcolumn derivatization, as reported previously.[32,33]

Because concentrations in plasma at the terminal phase could not be measured in some patients, pharmacokinetic parameters for individuals were calculated by Bayesian estimation after population pharmacokinetic parameters were estimated in the entire population. These calculations were performed using the NONMEM program (version V, level 1.1). A three-compartment open model with zero-order administration and first-order elimination (ADVAN 11 and TRANS 4) was used to describe the plasma concentration-time course for docetaxel in the entire population, and a one-compartment open model (ADVAN 1 and TRANS 2) was used for unchanged cisplatin in the ultrafiltrate. Assuming a log-normal distribution for inter-individual variability in pharmacokinetic parameters, the inter-individual variability was modeled as (eg, for clearance) $CL_j = \hat{CL} \exp(\eta_{jCL})$, where CL_j and $\hat{CL}$ are the estimated values in an individual j and the population mean for clearance, respectively, and η_{jCL} is the individual random perturbation from the population mean. Intrapatient residual variability was also described by a log-normal distribution model. Similarly inter- and intra-individual variability was modeled for the volume of the third compartment (docetaxel) or the central compartment (cisplatin). The area under the concentration-time curve (AUC) was calculated as dose divided by clearance in each patient.

Pharmacodynamic Analysis

Pharmacodynamic analysis was conducted using the AUC for docetaxel and unchanged cisplatin in individual patients. Neutrophil counts were monitored at least weekly and the nadir count during the first course was recorded. The percent change in neutrophil counts (dANC) was defined as:

$$dANC = \frac{\text{Pretreatment count} - \text{Nadir count}}{\text{Pretreatment count}} \times 100$$

and the relationship between dANC and the AUC of docetaxel or unchanged cisplatin was investigated using a sigmoid Emax model:

$$dANC = \frac{Emax \times AUC^r}{AUC^r + EC_{50}{}^r}$$

The Emax represents the maximal effect, and EC_{50} is the AUC value at which the effect is 50% of the maximum effect. The exponent r is a shape factor that determines the steepness of the response curve. These values were determined by using the computer program, WINNonlin (version 4.01, Scientific Consultant, Apex, NC).

Statistical Methods

Continuous variables, including pharmacokinetic parameters, were compared between elderly (75 years or older) and non-elderly patients (74 years or younger), using the Mann-Whitney U test. Differences in distribution of patient characteristics between the two groups were evaluated with the χ^2 test or Fisher's exact test, where appropriate. *P* values less than .05 were regarded as statistically significant, and all reported *P* values are two-tailed.

RESULTS

Of 33 elderly and 36 non-elderly patients who received docetaxel and cisplatin in the phase II studies, the pharmacokinetic study was performed in 25 and 27 patients, respectively (Table 1). There were no differences between the two groups in the distribution by sex, performance status, or the proportion of patients who had been treated with radiotherapy before entry into the study. Elderly patients had slightly lower levels of total protein, albumin and α_1-acid glycoprotein, and neutrophil counts than non-elderly patients, but the differences were small. Patients with hepatic or renal dysfunction were excluded from the phase II studies and there were no differences between groups in these functions except for ALT.

Because of technical problems with blood sampling or with HPLC systems, pharmacokinetic data for docetaxel and cisplatin could not be obtained in two non-elderly patients and one elderly patient, respectively. Therefore,

Table 1. Patient Characteristics

Characteristics	Non-Elderly Patients	Elderly Patients	*P*
No. of patients	27	25	
Age, years			< .001
Median	56	76	
Range	39-73	75-86	
Sex			.74
Female	5	6	
Male	22	19	
Performance status			.70
0	5	3	
1	22	22	
Prior radiotherapy			.50
No	20	21	
Yes	7	4	
Total protein, g/dL			.021
Mean	6.2	5.9	
SD	0.4	0.5	
Albumin, g/dL			.008
Mean	3.4	3.2	
SD	0.4	0.3	
α_1-acid glycoprotein, mg/dL			.018
Mean	121	97	
SD	33	34	
AST, U/L			.11
Mean	22.7	20.2	
SD	7.6	9.0	
ALT, U/L			.001
Mean	23.4	15.2	
SD	10.3	8.1	
Creatinine, mg/dL			.10
Mean	0.69	0.80	
SD	0.11	0.22	
Creatinine clearance, mL/min			.48
Mean	87.4	93.3	
SD	20.6	24.7	
Neutrophil counts, μL			.03
Mean	5,230	4,355	
SD	1,696	1,450	

Abbreviation: SD, standard deviation.

Table 2. Pharmacokinetic Parameters

	Non-Elderly Patients	Elderly Patients	*P*
Docetaxel			
No. of patients	25	25	
Clearance, L/hour			.86
Mean	45.9	45.6	
SD	17.1	16.5	
Volume of distribution, L			.11
Mean	350	273	
SD	216	215	
AUC, μg/mL × hour			< .001
Mean	1.40	0.79	
SD	0.64	0.34	
Cisplatin			
No. of patients	27	24	
Clearance, mL/min			.13
Mean	443	417	
SD	50	65	
Volume of distribution, L			.38
Mean	13.8	14.7	
SD	2.2	3.3	
AUC, μg/mL × min			.49
Mean	91.8	94.3	
SD	11.5	12.6	

Abbreviations: SD, standard deviation; AUC, area under the curve.

pharmacokinetic parameters for docetaxel in 25 elderly patients and 25 non-elderly patients and those for unchanged cisplatin in 24 elderly patients and 27 non-elderly patients were compared (Table 2). There was no difference in the clearance or volume of distribution of docetaxel between the elderly and non-elderly patients. Similarly, the clearance and volume of distribution of unchanged cisplatin were similar in both patient groups. The elderly and non-elderly patients were treated with different doses of docetaxel (20 and 35 mg/m^2, respectively), though the clearance of docetaxel was the same for both populations. Therefore, the AUC of docetaxel in the non-elderly patients was greater than that in the elderly patients.

Despite the fact that the AUC of docetaxel was higher in the non-elderly patients than in the elderly patients, the neutropenia observed was similar for the two groups of patients, with regard to toxicity grades and actual nadir counts (Table 3). Although administrations of docetaxel and cisplatin were omitted on day 8 or 15 of the first course in one elderly patient and in seven non-elderly patients, there was no difference in age between the eight patients who did not receive the treatment on day 8 or 15 and the other 44 patients who were administered chemotherapy three times (63.4 ± 9.9 years *v* 67.4 ± 12.8 years; $P = .41$). When the AUC of cisplatin and docetaxel was compared between patients who did or did not receive all administrations, the AUC of docetaxel was significantly higher for patients who missed a dose than patients who received all

Table 3. Neutropenia in the First Course

	Non-Elderly Patients	Elderly Patients	*P*
Neutropenia, No. of patients			.76
Grade			
0	19	17	
1	4	3	
2	2	4	
3	1	1	
4	1	0	
Nadir neutrophil counts, μL			.72
Mean	2,707	2,867	
SD	1,268	1,404	
Percent change in neutrophil counts, %			.12
Mean	46.0	34.5	
SD	23.3	25.6	
Frequency of measurements of neutrophil counts (per week)			.55
Mean	1.6	1.7	
SD	0.4	0.4	

Abbreviation: SD, standard deviation.

administrations (1.57 ± 0.88 *v* 1.03 ± 0.53 μg/mL × hour; $P = .03$), while the AUC of cisplatin was similar (90.6 ± 15.2 *v* 93.4 ± 11.5 μg/mL × min; $P = .54$).

The relationship between the AUC of docetaxel or cisplatin and percent changes in neutrophil counts was evaluated using a sigmoid Emax model in the elderly or non-elderly patients. The AUC of cisplatin was not correlated with the percent change in neutrophil counts in either elderly or non-elderly patients (Fig 1). On the other hand, the AUC of docetaxel was positively correlated with the percent change in neutrophil counts (dANC) in the non-elderly patients (Fig 2), and the relationship was described as:

$$dANC = \frac{59 \times AUC^{3.2}}{AUC^{3.2} + 0.86^{3.2}} \times 100$$

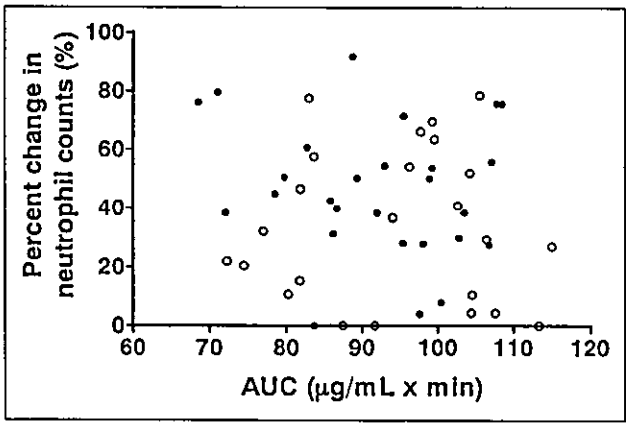

Fig 1. Relationship between the area under the curve (AUC) of cisplatin and percent changes in neutrophil counts in the elderly (○) and the non-elderly (●) patients.

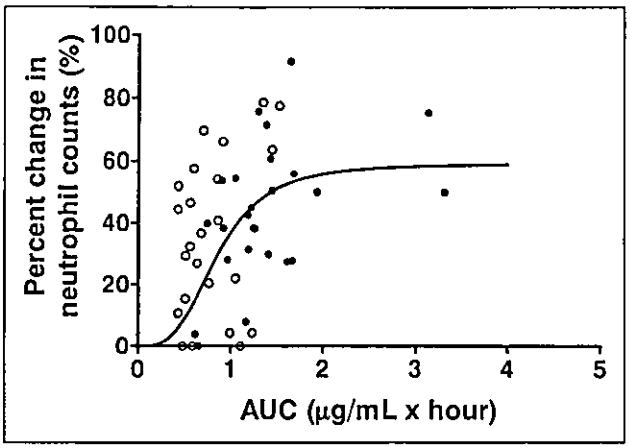

Fig 2. Relationship between the area under the curve (AUC) of docetaxel and percent changes in neutrophil counts in the elderly (○) and the non-elderly (●) patients. The solid line represents predictions by a sigmoid Emax model in the non-elderly patients.

Because the distribution range of the docetaxel AUC in the elderly patients was narrow, a sigmoid relationship between the AUC of docetaxel and the percent change in neutrophil counts was not apparent (Fig 2), and parameters in the sigmoid Emax model could not be calculated in the elderly group.

To investigate whether the pharmacodynamic relationship between the AUC of docetaxel and neutropenia for the elderly patients was different from that of the non-elderly patients, percent changes in neutrophil counts were predicted in the elderly patients. This was done using the sigmoid Emax model developed in the non-elderly patients, and residuals of the prediction (predicted value − observed value) were calculated. The neutropenia observed in the elderly patients was greater than that predicted by the model with a mean of residual of −11.2% (95% CI, −21.8% to −0.5%), while the model predicted neutropenia without bias in the non-elderly patients with a mean residual of 0.21% (95% CI, −7.4% to 7.8%), as expected. Elderly patients had a lower docetaxel AUC than non-elderly patients, and there were two non-elderly patients with a high docetaxel AUC who seemed to be outliers. Therefore, we analyzed the data after excluding non-elderly patients with AUC > 1.53 μg/mL × hour (the maximum value in elderly patients) or after excluding the two outliers. Both reanalyzed models also underestimated neutropenia in the elderly patients: −13.5% (range, −26.2% to −0.8%) and −12.5% (range, −23.7% to −1.3%), respectively.

Partial responses were observed in eight of 27 non-elderly patients, and among 25 elderly patients, a complete response and partial responses were documented in one and 12 patients, respectively. When the AUC of docetaxel and unchanged cisplatin was compared between responders and nonresponders, no differences were observed. The AUC values for docetaxel in responders and nonresponders were 1.02 ± 0.39 and 1.14 ± 0.70 μg/mL × hour, respectively, and the AUC values for unchanged cisplatin were 91.5 ± 12.8 and 94.0 ± 11.5 μg/mL × min, respectively.

DISCUSSION

The purpose of the pharmacologic study was to elucidate mechanisms of the difference in recommended doses of docetaxel in combination with cisplatin in elderly patients and non-elderly patients. We investigated the pharmacokinetics and pharmacodynamics of docetaxel and unchanged cisplatin in two subsequently conducted phase II studies.[27,28] For both docetaxel and cisplatin, the pharmacokinetics did not differ between elderly patients and non-elderly patients. While exposure to cisplatin was not correlated to the extent of neutropenia, there was a sigmoidal relationship between the AUC of docetaxel and neutropenia in the non-elderly patients. However, the relationship between the AUC of docetaxel and neutropenia in the elderly patients was different from that in the non-elderly patients. Although elderly patients had smaller AUC values than non-elderly patients, the same extent of neutropenia was observed in both patient groups (Table 3), and nonhematologic toxicities were mild and similar in both groups.[27,28] These observations suggest that elderly patients were more sensitive to the exposure of docetaxel than non-elderly patients.

There was no difference in docetaxel clearance between elderly and non-elderly patients (Table 2). This conclusion was not changed after the clearance of docetaxel was adjusted for body-surface area (29.6 and 28.2 L/h/m^2, for elderly and non-elderly patients, respectively). These values fall within the range of docetaxel clearance values previously published.[34-37] Furthermore, docetaxel clearance was not correlated to age as a continuous variable, and age was not a significant covariate in the population pharmacokinetic model. These observations seem to be inconsistent with those of a previous report, which found that age was inversely correlated to the clearance of docetaxel in a population pharmacokinetic model.[38] Although the exact reasons for this discrepancy are not clear, ethnic difference or coadministration of cisplatin might explain it. However, the estimated coefficient of age in the population model was small in the previous report. A difference of 20 years in age (the difference in the median ages of the elderly and the non-elderly groups in our study) would yield less than a 10% difference in the clearance of docetaxel. The previous population model was developed by using data from 547 patients, while in our study, data from 52 patients were used. It was possible that the smaller number of patients in our study precluded the detection of a small difference in docetaxel clearance between elderly and non-elderly patients. However, the difference in the dose of docetaxel between elderly patients (20 mg/m^2) and non-elderly pa-

tients (35 mg/m^2) did not seem to be explained by a less than 10% difference in docetaxel clearance values.

Although the concentration of ultrafiltrable platinum was measured in most of the pharmacokinetic studies with cisplatin, measuring the concentration of unchanged cisplatin is clinically more relevant because ultrafiltrable platinum contains inactive low molecular-weight metabolites.[39] The pharmacokinetics of unchanged cisplatin were not different between elderly and non-elderly patients, and there was no correlation between age and the clearance of cisplatin. The clearances of unchanged cisplatin for elderly and non-elderly patients in our study were similar to those reported previously.[40-44]

In the pharmacodynamic analysis in the present study, exposure to docetaxel was correlated to the extent of neutropenia in the non-elderly patients, but the relationship between docetaxel exposure and neutropenia was unclear in the elderly patients. Therefore, for comparison of pharmacodynamics between the elderly and non-elderly patients, we applied the pharmacodynamic model developed in the non-elderly patients to the data from the elderly patients. The residuals of prediction by the model were less than zero in the elderly patients, indicating that the model underestimated the extent of neutropenia in the elderly patients. Although this analysis might be exploratory because uncertainty in the estimates of model parameters was not considered, the results suggest that elderly patients are more sensitive to neutropenia induced by docetaxel than non-elderly patients. This is further supported by observations that the elderly patients and non-elderly patients experienced neutropenia to the same extent, despite the fact that the AUC of docetaxel was greater in the non-elderly patients than the elderly patients.

We used a sigmoid Emax model for pharmacodynamic analysis. Since it is a nonlinear model, parameter estimation may depend on the distribution of variables. Because elderly patients had lower docetaxel AUC than non-elderly patients, and because there were two outliers in the non-elderly patients, we reanalyzed the data after excluding data of non-elderly patients with AUC greater than the maximum for elderly patients, or excluding the two outliers. The results of these reanalyses were the same and confirmed that elderly patients are more sensitive to neutropenia induced by docetaxel. Another approach would be modeling the all data simultaneously and investigating interaction between age and parameters in the model. However, incorporation of age into a sensitivity parameter (EC_{50}) or a shape parameter (r) did not improve model performance (data not shown).

These findings are in agreement with clinical observations in many previous reports; elderly patients experienced more profound myelotoxicity and had greater risk of chemotherapy-related death than younger patients in various cancers.[10,13,14,45-48] We showed that the greater risk of hematologic toxicity in the elderly patients was related to the greater sensitivity of bone marrow function to combination chemotherapy of docetaxel and cisplatin using a weekly schedule without altered pharmacokinetics. The greater sensitivity of myeloid cells to chemotherapeutic agents in the elderly was also in agreement with our previous pharmacodynamic analysis of leukopenia.[49] In that study, we developed a novel pharmacodynamic model relating the entire time course of leukopenia to the time course of drug concentration. A parameter corresponding to the sensitivity of myeloid cells to chemotherapeutic agents showed a significant correlation with age, and myeloid cells of elderly patients showed greater sensitivity than those of younger patients without altered pharmacokinetics of anticancer agents.[49,50] Furthermore, in a pharmacologic analysis of etoposide, elderly patients had greater sensitivity with regard to neutropenia than younger patients at the same level of drug exposure.[18] These observations were in accordance with those made in the current study.

The exact reason why bone marrow function of elderly patients showed greater sensitivity to chemotherapeutic agents than that of younger patients is not clear. Factors stimulating neutrophil production, such as granulocytopoietic cytokines, should be increased during the neutropenic period after chemotherapy. However, the production of these cytokines is reduced in the elderly,[51] and a decreased response to granulocytopoietic stimuli in infection has been reported in aged mice and humans.[52-54] These factors may explain the greater sensitivity of elderly patients to chemotherapeutic agents, although kinetics of cytokines after chemotherapy would also need to be investigated.

Potential drawbacks of this study may be the small number of patients and low incidence of significant neutropenic events, which might be explained by divided doses of docetaxel and restriction of eligibility to patients with a good performance status. It is unclear whether difference in the sensitivity to neutropenia could fully explain the difference in the dose of docetaxel between the elderly patients and the non-elderly patients, considering that the observed neutropenia was moderate. However, nonhematologic toxicities were mild and similar in both groups[26] despite the fact that the AUC of docetaxel was greater in the non-elderly patients than in the elderly patients. These observations suggest that elderly patients are more sensitive to toxicities than non-elderly patients.

It is notable that a high response rate was observed in elderly patients, though a reduced dose of docetaxel was used, compared to non-elderly patients. Further studies of chemotherapy in elderly patients with non–small-cell lung cancer are warranted.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

REFERENCES

1. Trimble EL, Carter CL, Cain D, et al: Representation of older patients in cancer treatment trials. Cancer 74:2208-2214, 1994
2. Hutchins LF, Unger JM, Crowley JJ, et al: Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med 341:2061-2067, 1999
3. Sateren WB, Trimble EL, Abrams J, et al: How sociodemographics, presence of oncology specialists, and hospital cancer programs affect accrual to cancer treatment trials. J Clin Oncol 20:2109-2117, 2002
4. Lewis JH, Kilgore ML, Goldman DP, et al: Participation of patients 65 years of age or older in cancer clinical trials. J Clin Oncol 21:1383-1389, 2003
5. Yee KW, Pater JL, Pho L, et al: Enrollment of older patients in cancer treatment trials in Canada: Why is age a barrier? J Clin Oncol 21:1618-1623, 2003
6. Benson AB 3rd, Pregler JP, Bean JA, et al: Oncologists' reluctance to accrue patients onto clinical trials: An Illinois Cancer Center study. J Clin Oncol 9:2067-2075, 1991
7. Earle CC, Neumann PJ, Gelber RD, et al: Impact of referral pattern on the use of chemotherapy for lung cancer. J Clin Oncol 20:1786-1792, 2002
8. de Rijke JM, Schouten LJ, Schouten HC, et al: Age-specific differences in the diagnostics and treatment of cancer patients aged 50 years and older in the province of Limburg, the Netherlands. Ann Oncol 7:677-685, 1996
9. Newcomb PA, Carbone PP: Cancer treatment and age, patient perspectives. J Natl Cancer Inst 85:1580-1584, 1993
10. Armitage JO, Potter JF: Aggressive chemotherapy for diffuse histiocytic lymphoma in the elderly, increased complications with advanced age. J Am Geriatr Soc 32:269-273, 1984
11. Mayer RJ, Davis RB, Schiffer CA, et al: Intensive postremission chemotherapy in adults with acute myeloid leukemia. N Engl J Med 331:896-903, 1994
12. Gomez H, Mas L, Casanova L, et al: Elderly patients with aggressive non-Hodgkin's lymphoma treated with CHOP chemotherapy plus granulocyte-macrophage colony-stimulating factor: Identification of two age subgroups with differing hematologic toxicity. J Clin Oncol 16: 2352-2358, 1998
13. Langer CJ, Manola J, Bernardo P, et al: Cisplatin-based therapy for elderly patients with advanced non-small-cell lung cancer: Implications of Eastern Cooperative Oncology Group 5592, a randomized trial. J Natl Cancer Inst 94:173-181, 2002
14. Kubota K, Furuse K, Kawahara M, et al: Cisplatin-based combination chemotherapy for elderly patients with non-small-cell lung cancer. Cancer Chemother Pharmacol 40:469-474, 1997
15. Yamamoto N, Tamura T, Maeda M, et al: The influence of ageing on cisplatin pharmacokinetics in lung cancer patients with normal organ function. Cancer Chemother Pharmacol 36:102-106, 1995
16. Gauvin A, Pinguet F, Culine S, et al: Bayesian estimate of vinorelbine pharmacokinetic parameters in elderly patients with advanced metastatic cancer. Clin Cancer Res 6:2690-2695, 2000
17. Kokenberg E, Sonneveld P, Sizoo W, et al: Cellular pharmacokinetics of daunorubicin: Relationships with the response to treatment in patients with acute myeloid leukemia. J Clin Oncol 6:802-812, 1988
18. Ando M, Minami H, Ando Y, et al: Pharmacological analysis of etoposide in elderly patients with lung cancer. Clin Cancer Res 5:1690-1695, 1999
19. Monfardini S, Chabner B: Joint NCI-EORTC consensus meeting on neoplasia in the elderly. Eur J Cancer 27:653-654, 1991
20. Conti JA, Christman K: Cancer chemotherapy in the elderly. J Clin Gastroenterol 21:65-71, 1995
21. Popescu RA, Norman A, Ross PJ, et al: Adjuvant or palliative chemotherapy for colorectal cancer in patients 70 years or older. J Clin Oncol 17:2412-2418, 1999
22. Carbone PP: Advances in the systemic treatment of cancers in the elderly. Crit Rev Oncol Hematol 35:201-218, 2000
23. Borkowski JM, Duerr M, Donehower RC, et al: Relation between age and clearance rate of nine investigational anticancer drugs from phase I pharmacokinetic data. Cancer Chemother Pharmacol 33:493-496, 1994
24. Chiara S, Nobile MT, Vincenti M, et al: Advanced colorectal cancer in the elderly: Results of consecutive trials with 5-fluorouracil-based chemotherapy. Cancer Chemother Pharmacol 42:336-340, 1998
25. Ohsita F, Kurata T, Kasai T, et al: Prospective evaluation of the feasibility of cisplatin-based chemotherapy for elderly lung cancer patients with normal organ functions. Jpn J Cancer Res 86:1198-1202, 1995
26. Ohe Y, Niho S, Kakinuma R, et al: Phase I studies of cisplatin and docetaxel administered by three consecutive weekly infusions for advanced non-small cell lung cancer in elderly and non-elderly patients. Jpn J Clin Oncol 31:100-106, 2001
27. Niho S, Ohe Y, Kakinuma R, et al: Phase II study of docetaxel and cisplatin administered as three consecutive weekly infusions for advanced non-small lung cancer. Lung Cancer 35:209-214, 2002
28. Ohe Y, Niho S, Kakinuma R, et al: A phase II study of cisplatin and docetaxel administered as three consecutive weekly infusions for advanced non-small-cell lung cancer in elderly patients. Ann Oncol 15:45-50, 2003
29. Tobinai K, Kohno A, Shimada Y, et al: Toxicity grading criteria of the Japan Clinical Oncology Group. The Clinical Trial Review Committee of the Japan Clinical Oncology Group. Jpn J Clin Oncol 23:250-257, 1993
30. Miller AB, Hoogstraten B, Staquet M, et al: Reporting results of cancer treatment. Cancer 47:207-214, 1981
31. Vergniol J, Bruno R, Montay G, et al: Determination of Taxotere in human plasma by a semi-automated high-performance liquid chromatographic method. J Chromatogr 582:273-278, 1992
32. Kinoshita M, Yoshimura N, Ogata H: High-performance liquid chromatographic analysis of unchanged cis-diamminedichloroplatinum (cisplatin) in plasma and urine with post-column derivatization. J Chromatogr 529:462-467, 1990
33. Hanada K, Nagai N, Ogata H: Quantitative determination of unchanged cisplatin in rat kidney and liver by high-performance liquid chromatography. J Chromatogr B Biomed Appl 663:181-186, 1995
34. Extra J-M, Rousseau F, Bruno R, et al: Phase I and pharmacokinetic study of taxotere (RP 56976; NSC 628503) given as a short intravenous infusion. Cancer Res 53:1037-1042, 1993
35. Burris H, Irvin R, Kuhn J, et al: Phase I clinical trial of taxotere administered as either a 2-hour or 6-hour intravenous infusion. J Clin Oncol 11:950-958, 1993
36. Rosing H, Lustig V, van Warmerdam LJ, et al: Pharmacokinetics and metabolism of docetaxel administered as a 1-h intravenous infusion. Cancer Chemother Pharmacol 45:213-218, 2000
37. Yamamoto N, Tamura T, Kamiya Y, et al: Correlation between docetaxel clearance and estimated cytochrome P450 activity by urinary metabolite of exogenous cortisol. J Clin Oncol 18:2301-2308, 2000
38. Bruno R, Hille D, Riva A, et al: Population pharmacokinetics/pharmacodynamics of docetaxel in phase II studies in patients with cancer. J Clin Oncol 16:187-196, 1998
39. Andrews PA, Wung WE, Howell SB: A high-performance liquid chromatographic assay with improved selectivity for cisplatin and active platinum (II) complexes in plasma ultrafiltrate. Anal Biochem 143:46-56, 1984
40. Reece PA, Stafford I, Davy M, et al: Disposition of unchanged cisplatin in patients with ovarian cancer. Clin Pharmacol Ther 42:320-325, 1987
41. Reece PA, Stafford I, Abbott RL, et al: Two- versus 24-hour infusion of cisplatin, pharmacokinetic considerations. J Clin Oncol 7:270-275, 1989
42. Andersson A, Fagerberg J, Lewensohn R, et al: Pharmacokinetics of cisplatin and its monohydrated complex in humans. J Pharm Sci 85:824-827, 1996
43. Nagai N, Ogata H, Wada Y, et al: Population pharmacokinetics and pharmacodynamics of cisplatin in patients with cancer: Analysis with the NONMEM program. J Clin Pharmacol 38: 1025-1034, 1998
44. Hanada K, Nishijima K, Ogata H, et al: Population pharmacokinetic analysis of cisplatin and its metabolites in cancer patients, possible misinterpretation of covariates for pharmacokinetic parameters calculated from the concentrations of unchanged cisplatin, ultrafiltrered platinum and total platinum. Jpn J Clin Oncol 31:179-184, 2001
45. Stein BN, Petrelli NJ, Douglass HO, et al: Age and sex are independent predictors of 5-fluorouracil toxicity. Cancer 75:11-17, 1995
46. Begg CB, Carbone PP: Clinical trials and drug toxicity in the elderly: The experience of the Eastern Cooperative Oncology Group. Cancer 52:1986-1992, 1983
47. Poplin E, Thompson B, Whitacre M, et al: Small cell carcinoma of the lung: influence of age on treatment outcome. Cancer Treat Rep 71: 291-296, 1987

48. Tirelli U, Zagonel V, Serraino D, et al: Non-Hodgkin's lymphomas in 137 patients aged 70 years or older: A retrospective European Organization for Research and Treatment of Cancer Lymphoma Group Study. J Clin Oncol 6:1708-1713, 1988

49. Minami H, Sasaki Y, Saijo N, et al: Indirect-response model for the time course of leukopenia with anticancer drugs. Clin Pharmacol Ther 64:511-521, 1998

50. Minami H, Sasaki Y, Watanabe T, et al: Pharmacodynamic modeling of the entire time course of leukopenia after a 3-hour infusion of paclitaxel. Jpn J Cancer Res 92:231-238, 2001

51. Fliedner TM, Cronkite EP, Killmann SA, et al: Granulocytopoiesis II. Emergence and pattern of labeling of neutrophilic granulocytes in humans. Blood 24:683-700, 1964

52. Rothstein G, Christensen RD, Nielsen BR: Kinetic evaluation of the pool sizes and proliferative response of neutrophils in bacterially challenged aging mice. Blood 70:1836-1841, 1987

53. Timaffy M: A comparative study of bone marrow function in young and old individuals. Gerontol Clin (Basel) 4:13-18, 1962

54. Selig C, Nothdurft W: Cytokines and progenitor cells of granulocytopoiesis in peripheral blood of patients with bacterial infections. Infect Immun 63:104-109, 1995

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

Ikuo Sekine,[1] Kazumasa Noda,[3] Fumihiro Oshita,[3] Kouzou Yamada,[3] Manabu Tanaka,[3] Kosuke Yamashita,[4] Hiroshi Nokihara,[1] Noboru Yamamoto,[1] Hideo Kunitoh,[1] Yuichiro Ohe,[1] Tomohide Tamura,[1] Tetsuro Kodama,[1] Minako Sumi[2] and Nagahiro Saijo[1]

Divisions of [1]Thoracic Oncology and Internal Medicine and [2]Radiotherapy, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045; and Divisions of [3]Thoracic Oncology and [4]Radiation Oncology, Kanagawa Cancer Center, 1-1-2 Nakao, Asahi-ku, Yokohama 241-0815

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

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

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

Patients and Methods

Patient selection. The eligibility criteria were: histologically or cytologically proven NSCLC; unresectable stage IIIA or IIIB disease; no previous treatment; measurable disease; tumor within an estimated irradiation field no larger than half the hemithorax; age between 20 years and 74 years; Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1[14]; adequate bone marrow function (12.0×10^9/liter ≥white blood cell [WBC] count ≥4.0×10^9/liter, neutrophil count ≥2.0×10^9/liter, hemoglobin ≥10.0 g/dl, and platelet count ≥100×10^9/liter), liver function (total bilirubin ≤1.5 mg/dl and transaminase ≤twice the upper limit of the normal value), and renal function (serum creatinine ≤1.5 mg/dl and creatinine clearance ≥60 ml/min); and a PaO_2 of 70 Torr or more. Patients were excluded if they had malignant pleural or pericardial effusion, active double cancer, a concomitant serious illness, such as uncontrolled angina pectoris, myocardial infarction in the previous 3 months, heart failure, uncontrolled diabetes mellitus, uncontrolled hypertension, interstitial pneumonia or lung fibrosis identified by a chest X-ray, chronic obstructive lung disease, infection or other diseases contraindicating chemotherapy or radiotherapy, pregnancy, or breast-feeding. All patients gave their written informed consent.

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

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

E-mail: isekine@ncc.go.jp

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

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

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

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

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

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

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

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

Results

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

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

Table 2. Patients' characteristics

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

Table 3. Treatment delivery

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

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

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

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

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

Table 4. Acute toxicity

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

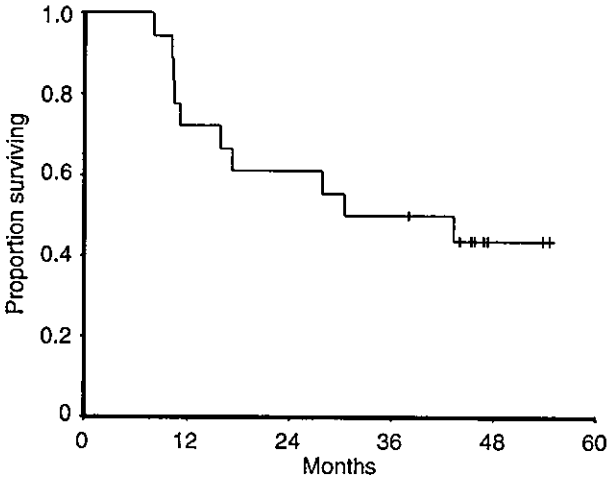

Fig. 1. Overall survival in 18 patients. The median (range) follow-up period of censored cases has been 35.4 (32.0–43.4) months, and the median overall survival time has not yet been reached.

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

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

Discussion

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

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

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

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

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

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

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1. Mountain CF. Revisions in the International System for Staging Lung Cancer. *Chest* 1997; **111**: 1710–7.
2. Jett JR, Scott WJ, Rivera MP, Sause WT and American College of Chest Physicians. Guidelines on treatment of stage IIIB non-small cell lung cancer. *Chest* 2003; **123**: 221S–5S.
3. Pierre F, Maurice P, Gilles R, Pascal T, Pierre-Jean S, Hervé L, Alain V, Jean-Yves D, Francoise M, Fancoise M. A randomized phase III trial of sequential chemoradiotherapy in locally advanced non-small-cell lung cancer. *Proc Am Soc Clin Oncol* 2001; **20**: 312a (abstr 1246).
4. Curren W Jr, Scott C, Langer C, Komaki R, Lee J, Hauser S, Movsas B, Wasserman TH, Rosenthal S, Byhardt R, Sause W, Cox J. Phase III comparison of sequential vs concurrent chemoradiation for patients with unresectable stage III non-small-cell lung cancer (NSCLC): initial report of the Radiation Therapy Oncology Group (RTOG) 9410. *Proc Am Soc Clin Oncol* 2000; **19**: 484a (abstr 1891).
5. Furuse K, Fukuoka M, Kawahara M, Nishikawa H, Takada Y, Kudoh S, Katagami N, Ariyoshi Y. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. *J Clin Oncol* 1999; **17**: 2692–9.
6. Kubota K, Tamura T, Fukuoka M, Furuse K, Ikegami H, Ariyoshi Y, Kurita Y, Saijo N. Phase II study of concurrent chemotherapy and radiotherapy for unresectable stage III non-small-cell lung cancer: long-term follow-up results. Japan Clinical Oncology Group Protocol 8902. *Ann Oncol* 2000; **11**: 445–50.
7. Furuse K, Kubota K, Kawahara M, Kodama N, Ogawara M, Akira M, Nakajima S, Takada M, Kusunoki Y, Negoro S, Matsui K, Masuda N, Takifuji N, Kudoh S, Nishioka M, Fukuoka M. Phase II study of concurrent radiotherapy and chemotherapy for unresectable stage III non-small-cell lung cancer. Southern Osaka Lung Cancer Study Group. *J Clin Oncol* 1995; **3**: 869–75.
8. Atagi S, Kawahara M, Hosoe S, Ogawara M, Kawaguchi T, Okishio K, Naka N, Sunami T, Mitsuoka S, Akira M. A phase II study of continuous concurrent thoracic radiotherapy in combination with mitomycin, vindesine and cisplatin in unresectable stage III non-small cell lung cancer. *Lung Cancer* 2002; **36**: 105–11.
9. Sekine I, Saijo N. Novel combination chemotherapy in the treatment of non-small cell lung cancer. *Exp Opin Pharmacother* 2000; **1**: 1131–61.
10. Furuse K, Fukuoka M, Kuba M, Yamori S, Nakai Y, Negoro S, Katagami N, Takada Y, Kinuwaki E, Kawahara M, Kubota K, Sakuma A, Niitani H. Randomized study of vinorelbine (VRB) versus vindesine (VDS) in previously untreated stage IIIB or IV non-small-cell lung cancer (NSCLC). The Japan Vinorelbine Lung Cancer Cooperative Study Group. *Ann Oncol* 1996; **7**: 815–20.
11. Le Chevalier T, Brisgand D, Douillard JY, Pujol JL, Alberola V, Monnier A, Riviere A, Lianes P, Chomy P, Cigolari S, Gottfried M, Ruffie P, Panizo A, Gaspard MH, Ravaioli A, Besenval M, Besson F, Martinez A, Berthaud P, Tursz T. Randomized study of vinorelbine and cisplatin versus vindesine and cisplatin versus vinorelbine alone in advanced non-small-cell lung cancer: results of a European multicenter trial including 612 patients. *J Clin Oncol* 1994; **12**: 360–7.
12. Perol M, Guerin JC, Thomas P, Poirier R, Carles P, Robinet G, Kleisbauer JP, Paillotin D, Vergnenegre A, Balmes P, Touron D, Grivaux M, Pham E. Multicenter randomized trial comparing cisplatin-mitomycin-vinorelbine versus cisplatin-mitomycin-vindesine in advanced non-small cell lung cancer. 'Groupe Francais de Pneumo-Cancerologie.' *Lung Cancer* 1996; **14**: 119–34.
13. Kawahara M, Furuse K, Nishiwaki Y, Horai T, Saijo N, Hasegawa K, Ohashi Y, Niitani H. Randomized study of vinorelbine (VRB) or vindesine (VDS) with cisplatin (C) and mitomycin (M) as induction chemotherapy in stage IIIB or IV non-small cell lung cancer (NSCLC)-final results. *Proc Am Soc Clin Oncol* 2000; **19**: 489a (abstr 1914).
14. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbonne PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; **5**: 649–55.
15. JCOG Administrational Committee: National Cancer Institute-Common Toxicity Criteria (NCI-CTC Version 2.0, Jan 30, 1998). Japanese edition by JCOG. Available at http://www.med.gunma-u.ac.jp/event/CTCJ_v20.pdf
16. WHO. Handbook for reporting results of cancer treatment. WHO Offset Publication no. 48. Geneva: World Health Organization; 1979.
17. Armitage P, Berry G. Survival analysis. In: Statistical methods in medical research. 3rd ed. Oxford: Blackwell Sci Publ; 1994. p. 469–92.
18. Sekine I, Matsuda T, Saisho T, Watanabe H, Yamamoto N, Kunitoh H, Ohe Y, Tamura T, Kodama T, Saijo N. Bacterial meningitis observed in a phase I trial of vinorelbine, cisplatin and thoracic radiotherapy for non-small cell lung cancer: report of a case and discussion on dose-limiting toxicity. *Jpn J Clin Oncol* 2000; **30**: 401–5.
19. Masters GA, Haraf DJ, Hoffman PC, Drinkard LC, Krauss SA, Ferguson MK, Olak J, Samuels BL, Golomb HM, Vokes EE. Phase I study of vinorelbine, cisplatin, and concomitant thoracic radiation in the treatment of advanced chest malignancies. *J Clin Oncol* 1998; **16**: 2157–63.
20. Vokes EE, Herndon JE 2nd, Crawford J, Leopold KA, Perry MC, Mikker AA, Green MR. Randomized phase II study of cisplatin with gemcitabine or paclitaxel or vinorelbine as induction chemotherapy followed by concomitant chemoradiotherapy for stage IIIB non-small-cell lung cancer: cancer and leukemia group B study 9431. *J Clin Oncol* 2002; **20**: 4191–8.
21. Zatloukal P, Petruzelka L, Zemanova M, Krejbich F, Havel L. Vinorelbine (VRL) plus cisplatin (CDDP) and concurrent radiotherapy in advanced non-small cell lung cancer. *Proc Am Soc Clin Oncol* 1998; **17**: 505a (abstr 1947).
22. Alcedo J, Gallardo D, Lopez-Mariscal A, Calderillo G, Green L, Correa E, Zamora J, Mohar A. Cisplatin/vinorelbine (CDDP/VNR) and radiotherapy (XRT) in advanced non-small cell lung cancer (ANSCLC): an effective and feasible option with no need for dose reduction. *Proc Am Soc Clin Oncol* 1999; **18**: 494a (abstr 1905).
23. Hotta K, Sekine I, Tamura T, Sawada M, Watanabe H, Kusaba H, Akiyama Y, Inoue A, Shimoyama T, Nokihara H, Ueda Y, Yamamoto N, Kunitoh H, Ohe Y, Kodama T, Saijo N. A phase I/II study of cisplatin and vinorelbine chemotherapy in patients with advanced non-small cell lung cancer. *Jpn J Clin Oncol* 2001; **31**: 596–600.

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REVIEW ARTICLE

Yuichiro Ohe

Chemoradiotherapy for lung cancer: current status and perspectives

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Abstract For many years, thoracic radiotherapy had been regarded as the standard treatment for patients with unresectable locally advanced non-small cell lung cancer. However, meta-analyses show that cisplatin-containing chemoradiotherapy is significantly superior to radiotherapy alone in terms of survival. Moreover, concurrent chemoradiotherapy yields a significantly increased response rate and enhanced survival duration when compared with the sequential approach. Cisplatin-based chemotherapy with concurrent thoracic radiotherapy yields a 5-year survival rate of approximately 15% for patients with unresectable locally advanced non-small cell lung cancer. The state-of-the-art treatment for limited-stage small cell lung cancer is considered to be four cycles of combination chemotherapy with cisplatin plus etoposide combined with early concurrent twice-daily thoracic irradiation (45 Gy). If patients achieve complete remission, prophylactic cranial irradiation should be administered. A 5-year survival rate of approximately 25% is expected with the state-of-the-art treatment for limited-stage small cell lung cancer. Chemoradiotherapy is considered to be a standard treatment for both unresectable locally advanced non-small cell lung cancer and limited-stage small cell lung cancer. Several new strategies are currently being investigated to improve the survival of these patients. The incorporation of target-based drugs such as gefitinib is considered to be the most promising strategy for unresectable locally advanced non-small cell lung cancer. The incorporation of irinotecan is also a promising strategy to improve the survival of patients with limited-stage small cell lung cancer. The Japan Clinical Oncology Group is conducting clinical trials to develop new treatment strategies for both unresectable locally advanced non-small cell lung cancer and limited-stage small cell lung cancer.

Y. Ohe (✉)
Department of Internal Medicine, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
Tel. +81-3-3542-2511; Fax +81-3-3542-7006
e-mail: yohe@ncc.go.jp

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Introduction

Lung cancer is one of the most common carcinomas not only in Japan but also in the United States and Europe. Approximately 15%–20% of lung cancer patients have small cell lung cancer (SCLC) and the other patients have non-small cell lung cancer (NSCLC), such as adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. In Japan, more than 55 000 patients died of lung cancer in 2001, and mortality continues to rise.[1,2] In particular, the number of elderly lung cancer patients in Japan is increasing.[2] Lung cancer is the leading cause of cancer death in males in Japan and is anticipated to become the leading cause of cancer death in females.[1] However, the cure rate for lung cancer is still very low.

Surgery is the most effective curative treatment for early-stage NSCLC; however, only 30% of patients with NSCLC receive a curative resection.[3] Platinum-based chemotherapy offers a survival benefit and symptom relief for patients with metastatic NSCLC, and the combination of cisplatin-containing chemotherapy with thoracic radiotherapy has been considered as the standard treatment for patients with unresectable locally advanced NSCLC.[4] Approximately 15% of patients with unresectable locally advanced NSCLC can be cured by concurrent chemoradiotherapy.[5] Most patients with SCLC are not considered to be candidates for surgery. SCLC is one of the most chemosensitive solid tumors, and the outcome of SCLC patients is slowly but surely improving. Combination chemotherapy achieves a high response rate and survival prolongation for extensive-stage (ED) SCLC.[6–8] Combination chemotherapy consisting of cisplatin plus etoposide and concurrent twice-daily thoracic radiotherapy has yielded a 5-year survival rate of approximately 25% in limited-stage (LD) SCLC patients.[9,10] Chemoradiotherapy plays a very

important role in the treatment of both patients with unresectable locally advanced NSCLC and patients with LD-SCLC.

Chemoradiotherapy for non-small cell lung cancer

Patient selection

Most patients with stage I or II NSCLC are candidates for primary surgery with or without adjuvant chemotherapy. However, patients with superior sulcus tumor are candidates for induction chemoradiotherapy or radiotherapy followed by surgery.[11] Patients with stage IIIA and stage IIIB disease without pleural effusion, pericardiac effusion, and pleural dissemination are candidates for chemoradiotherapy. Only selected patients with stage IIIA NSCLC are considered to be candidates for surgery.[12] Chemoradiotherapy for unresectable locally advanced NSCLC achieves a long-term survival rate comparable to that of resectable N2 NSCLC after surgery.[5,13–15] Patients who are to receive chemoradiotherapy should have a good performance status and adequate organ function. If a patient is to receive radiotherapy with a radiation field including the contralateral hilum and more than half of the lung, such a patient should be excluded from concurrent chemoradiotherapy. Preexistent pulmonary fibrosis identified on plain chest X-ray film is reported to be a very strong risk factor for treatment-related death in thoracic radiotherapy, due to pneumonitis.[16,17] Thus, patients with pulmonary fibrosis identified on plain chest X-ray film should be excluded from chemoradiotherapy.

Chemoradiotherapy versus radiotherapy alone or chemotherapy alone

For many years, thoracic radiotherapy had been regarded as the standard treatment for patients with unresectable locally advanced NSCLC.[18,19] However, a meta-analysis of 1780 cases in 11 randomized trials showed that cisplatin-containing chemoradiotherapy was significantly superior to radiotherapy alone in terms of survival.[4] Other meta-analyses have also demonstrated the survival superiority of chemoradiotherapy compared with radiotherapy alone for patients with unresectable locally advanced NSCLC.[20,21] On the other hand, Kubota et al.[22] reported that the addition of radiotherapy to chemotherapy for locally advanced NSCLC significantly improved the 2- and 3-year survival rates compared to chemotherapy alone. Sculier et al.[23] reported the results of a randomized phase III trial that compared further chemotherapy and chest irradiation as a consolidation treatment after the achievement of a response to induction chemotherapy in patients with non-metastatic unresectable NSCLC. There was no significant difference in survival or response duration, but chest irradiation was associated with a significantly greater duration of local control than chemotherapy. Thus, the combination of cisplatin-containing chemotherapy with thoracic radiotherapy has been considered as the standard treatment for patients with unresectable locally advanced NSCLC.

Timing of chemotherapy and radiotherapy

Randomized phase III trials to compare the sequence schedule of chemoradiotherapy with concurrent chemoradiotherapy have been conducted by the Japan Clinical Oncology Group (JCOG)[14] and by the Radiation Therapy Oncology Group (RTOG[15]; Table 1). In the JCOG trial, 320 patients with unresectable locally advanced NSCLC were randomized to chemotherapy with cisplatin, vindesine, and mitomycin followed by radiotherapy (sequential arm) or concurrent chemoradiotherapy (concurrent arm). The response rate for the concurrent arm was significantly higher (84.0%) than that of the sequential arm (66%; $P = 0.0002$). The median survival time was significantly longer in patients receiving concurrent therapy (16.6 months), as compared with those receiving sequential therapy (13.3 months; $P = 0.03998$). The 2-, 3-, 4-, and 5-year survival rates in the concurrent group (34.6%, 22.3%, 16.9%, and 15.8%, respectively) were better than those in the sequential group (27.4%, 14.7%, 10.1%, and 8.9%, respectively). The concurrent approach yielded a significantly increased response rate and enhanced median survival time when compared with the sequential approach.[14] Similar results were reported from the RTOG trial.[15] The survival was significantly superior in the concurrent arm (with a median survival time of 17.0 months and a 4-year survival rate of 21%) than in the sequential arm (14.6 months and 12%, respectively; $P = 0.046$). This report also demonstrated the long-term survival benefit of the concurrent delivery of cisplatin-based chemotherapy with thoracic radiotherapy as compared with the sequential delivery of these therapies.[15] In these trials, acute toxicities, such as myelosuppression and esophagitis, were greater among patients on the concurrent arm than on the sequential arm. Based on these phase III trials, concurrent chemoradiotherapy appears to result in better survival than sequential therapy.

There are some limitations to the generalization of the results of these trials, because old-generation cisplatin-based combination chemotherapies were used in these trials: cisplatin and vindesine plus mitomycin, or cisplatin plus vinblastine.[14,15] These old-generation cisplatin-based chemotherapies could be combined with concurrent radiotherapy using a full dose. Several new anticancer agents were developed in the 1990s, such as irinotecan, paclitaxel, docetaxel, gemcitabine, and vinorelbine.[24–31] The combination of platinum and these new agents is more effective than the old-generation combination chemotherapy for metastatic NSCLC.[30,31] However, these new agents could not be combined with concurrent radiotherapy at the full dose.[32–35] A French cooperative group conducted a phase III trial to compare sequential versus concurrent chemoradiotherapy for unresectable NSCLC.[36] The sequential arm consisted of three cycles of cisplatin plus vinorelbine followed by thoracic radiotherapy. The concurrent arm consisted of two cycles of cisplatin plus etoposide with concurrent thoracic

Table 1. Randomized trials of sequential versus concurrent chemoradiotherapy

Author	Treatment	*n*	MST	2-Year Survival	5-Year Survival	*P* Value
Furuse[14]	CDDP + VDS + MMC; sequential TRT	158	13.3 Months	27.4%	8.9%	
	CDDP + VDS + MMC; concurrent TRT	156	16.6 Months	34.6%	15.8%	$P = 0.03998$
Curran[15]	CDDP + VBL; sequential TRT		14.6 Months	32%	12% (4-Year)	–
	CDDP + VBL; concurrent TRT	610 (Total)	17.0 Months	35%	21% (4-Year)	$P = 0.046$
	CDDP + ETOP; concurrent TRT (twice daily)		15.2 Months	34%	17% (4-Year)	$P = 0.296$
Pierre[36]	CDDP + VNR; sequential TRT	103	13.8 Months	23%		
	CDDP + ETOP; concurrent TRT f/b CDDP + VNR	104	15.0 Months	35%		$P = 0.41$
Zatloukal[37]	CDDP + VNR; sequential TRT	102 (Total)	396 Days			
	CDDP + VNR; concurrent TRT		619 Days			$P = 0.0216$

CDDP, cisplatin; VDS, vindesine; MMC, mitomycin; VBL, vinblastine; ETOP, etoposide; VNR, vinorelbine; TRT, thoracic radiotherapy; f/b, followed by

radiotherapy followed by two cycles of cisplatin plus vinorelbine. More than 200 patients were enrolled in this trial. The median survival time was 13.8 months in the sequential arm and 15.0 months in the concurrent arm. The 2-year survival rates were 23% and 35%, respectively.[36] While there was a trend in favor of concurrent therapy, it was not statistically significant ($P = 0.41$). There are no data from large phase III trials comparing sequential chemoradiotherapy using full-dose new-generation chemotherapy with concurrent chemoradiotherapy using reduced-dose new-generation chemotherapy. Only a small randomized phase II study has been reported[37] (Table 1).

Fractionation

Radical radiotherapy for NSCLC is most commonly given in daily fractions, Monday to Friday, for a total dose of 60–70 Gy over 6–8 weeks.[38,39] Novel fractionation schedules have been explored with the aim of improving local tumor control and survival without increasing late morbidity (Table 2).[40–51] In hyperfractionated radiotherapy, the dose per fraction is reduced and the total dose is increased to give improved tumor control without increased late morbidity. The RTOG clinical trials used hyperfractionated radiotherapy, 1.2 Gy/fraction, twice a day, for a total dose of 69.6 Gy.[40–42] However, this hyperfractionation schedule has not been shown to have significant benefit when compared to conventional radiotherapy plus chemotherapy.[15,41,42] Schild et al.[43] reported the results of a phase III study which compared split-course accelerated hyperfractionated radiotherapy (AHFRT), 1.5 Gy/fraction, twice a day (60 Gy) with standard radiotherapy (STDRT), 2 Gy/fraction, once a day (60 Gy) combined with concurrent chemotherapy. The toxicity, tumor control, and survival rates were similar with AHFRT and STDRT. The JCOG retrospectively compared STDRT and AHFRT from the data of six JCOG clinical trials.[5] In this study also, AHFRT did not show a clear tendency to improve the survival of the patients with locally advanced NSCLC. Twice-daily fractionation, both 1.2 Gy/fraction and 1.5 Gy/fraction twice a day, have not demonstrated any superiority compared with standard once-daily fractionation for patients with locally advanced NSCLC.[5,15,41–43]

More recently, continuous hyperfractionated accelerated radiotherapy (CHART) and hyperfractionated accelerated radiation therapy (HART) have been investigated.[45–51] CHART consisted of 36 small fractions of 1.5 Gy given three times per day, to give 54 Gy in only 12 consecutive days, including the weekend. CHART, compared with conventional radiotherapy, gave a significant improvement in the survival of patients with NSCLC.[45,46] However, this result was obtained from randomized phase III trials of radiotherapy alone. No randomized trials of chemoradiotherapy using CHART have been reported. HART consisted of a total dose of 57.6 Gy in 36 fractions, delivered over 15 days, with the use of three daily fractions with a 4-h interval between fractions and an 8-h interval between on-cord fields.[48,49] Patients are not treated on weekends. The results of a phase III study which compared standard thoracic radiotherapy with HART after induction chemotherapy for patients with unresectable NSCLC were reported from the Eastern Cooperative Oncology Group (ECOG).[50] The study was closed prematurely due to poor accrual. However, induction chemotherapy of carboplatin plus paclitaxel followed by HART resulted in an acceptable

Table 2. Once-daily versus multiple-daily radiotherapy for unresectable NSCLC

Author	Chemotherapy	Radiotherapy	*n*	MST (Months)	2-Year Survival	5-Year Survival	*P* Value
Sause[41,42]	Non	2 Gy/Day, 60 Gy, 5 days/week; continuous	163	11.4	21%	5%	–
	CDDP + VBL × 2; induction	2 Gy/Day, 60 Gy, 5 days/week; continuous	164	13.2	32%	8%	$P = 0.04$
	Non	1.2 Gy × 2/Day, 69.6 Gy, 5 days/week; continuous (HFRT)	163	12.0	24%	6%	NR
Schild[43]	CDDP + ETOP × 2; concurrent	2 Gy/Day, 60 Gy 5 days/week; continuous	117	14	37%	13%	
	CDDP + ETOP × 2; concurrent	1.5 Gy × 2/Day, 60 Gy, 5 days/week; split (AHFRT)	117	15	40%	20%	$P = 0.4$
Saunders[45,46]	Non	2 Gy/Day, 60 Gy, 5 days/week; continuous	225	NR	20%	NR	
	Nor	1.5 Gy × 3/Day, 54 Gy, 7 days/week; continuous (CHART)	338	NR	29%	NR	$P = 0.004$
Belani[50]	CBDCA + PTX × 2; induction	2 Gy/Day, 64 Gy, 5 days/week; continuous	56	13.7	30%	NR	
	CBDCA + PTX × 2; induction	1.5-1.8-1.5 Gy/Day, 57.6 Gy, 5 days/week; continuous (HART)	55	20.3	44%	NR	$P = 0.20$

NR, not reported; CDDP, cisplatin; VBL, vinblastine; ETOP, etoposide; CBDCA, carboplatin; PTX, paclitaxel; HFRT, hyperfractionated radiotherapy; AHFRT, accelerated hyperfractionated radiotherapy; CHART, continuous hyperfractionated accelerated radiotherapy; HART, hyperfractionated accelerated radiation therapy

toxicity profile and provocative efficacy, with a median survival of 20.3 months, in contrast to a median survival of 13.7 months in the standard thoracic radiotherapy arm.[50] Ishikura et al.[51] reported the results of a pilot study of HART following induction cisplatin and vinorelbine for stage III NSCLC. Thirty patients were enrolled in this study. The overall objective response rate was 83% and the median survival time was not reached. The 1- and 2-year overall survivals were 68% and 58%, respectively.[51] Further investigations of CHART or HART with chemotherapy are warranted.

Selection of anticancer agents

In the 1980s to the early 1990s, old-generation cisplatin-based chemotherapies, such as cisplatin plus etoposide, cisplatin plus vindesine, cisplatin plus vinblastine or cisplatin, and vindesine plus mitomycin, were commonly used in chemoradiotherapy with both sequential and a concurrent schedules for locally advanced NSCLC.[14,15] In the 1990s, several new anticancer agents were developed, such as irinotecan, paclitaxel, docetaxel, gemcitabine, and vinorelbine.[24–31] These new agents have different mechanisms of action from those of the old-generation agents. A full dose of the old-generation combination chemotherapy could be combined with concurrent radiotherapy.[14,15] However, if we wish to use the new-generation chemotherapy with thoracic radiotherapy, we have to use reduced-dose chemotherapy with concurrent thoracic radiotherapy, or full-dose chemotherapy followed by sequential radiotherapy.[32–34] No results of comparisons between the full-dose old-generation combination chemotherapy together with concurrent radiotherapy and the reduced-dose new-generation chemotherapy together with concurrent thoracic radiotherapy have been reported. Only very few reports have compared chemotherapy regimens used with concurrent thoracic radiotherapy. To evaluate the new drugs, gemcitabine, paclitaxel, and vinorelbine, in combination with cisplatin in unresectable locally advanced NSCLC, the Cancer and Leukemia Group B (CALGB) conducted a randomized phase II study of two cycles of induction chemotherapy followed by two additional cycles of the same drugs with concomitant radiotherapy.[33] One hundred and seventy-five patients received four cycles of cisplatin at 80 mg/m^2 on days 1, 22, 43, and 64, with gemcitabine 1250 mg/m^2 on days 1, 8, 22, and 29 and 600 mg/m^2 on days 43, 50, 64, and 71; or paclitaxel 225 mg/m^2 for 3 h on days 1 and 22 and 135 mg/m^2 on days 43 and 64; or vinorelbine 25 mg/m^2 on days 1, 8, 15, 22, and 29 and 15 mg/m^2 on days 43, 50, 64, and 71. Radiotherapy was initiated on day 43, at 2 Gy/day, for a total dose of 66 Gy. Response rates after the completion of radiotherapy were 74%, 67%, and 73% for the gemcitabine, paclitaxel, and vinorelbine arms, respectively. The median survival times were 18.3 months (95% confidence interval [CI], 13.8 to 23.6), 14.8 months (95% CI, 12 to 19.5), and 17.7 months (95% CI, 12.4 to 24.7) for the gemcitabine, paclitaxel, and vinorelbine arms, respectively.[33] No consistent standard chemotherapy regimens for chemoradiotherapy have been established.

Concomitant low-dose daily or weekly chemotherapies also use radiotherapy as a radiosensitizer. Cisplatin or