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ORIGINAL REPORT

Phase III Randomized Trial of Docetaxel Plus Cisplatin Versus Vindesine Plus Cisplatin in Patients With Stage IV Non–Small-Cell Lung Cancer: The Japanese Taxotere Lung Cancer Study Group

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ABSTRACT

Purpose
Few randomized trials have demonstrated survival benefit of combination chemotherapy involving new agents plus cisplatin compared with classic combination chemotherapy in advanced non–small-cell lung cancer (NSCLC). The primary aim of this study was to test whether docetaxel plus cisplatin (DC) improves survival compared with vindesine plus cisplatin (VdsC) in patients with previously untreated stage IV NSCLC.

Patients and Methods
Eligible, stage IV, chemotherapy-naive patients (n = 311) were randomly assigned to receive docetaxel 60 mg/m^2 intravenously on day 1 plus cisplatin 80 mg/m^2 intravenously on day 1 of a 3- or 4-week cycle, or vindesine 3 mg/m^2 intravenously on days 1, 8, and 15 plus cisplatin 80 mg/m^2 intravenously on day 1 of a 4-week cycle. Cross-over administration of docetaxel and vindesine was prohibited for both treatment groups.

Results
Overall, 302 patients were eligible for evaluation. The DC arm demonstrated significant improvements compared with the VdsC arm in overall response rates (37% *v* 21%, respectively; $P < .01$) and median survival times (11.3 *v* 9.6 months, respectively; $P = .014$). Two-year survival rates were 24% for the DC arm compared with 12% for the VdsC arm. The physical domain of the Quality of Life for Cancer Patients Treated with Anticancer Drugs measure was significantly better in the DC arm than in the VdsC arm ($P = .020$). Toxicity was predominantly hematologic and was more severe in the VdsC arm.

Conclusion
As first-line treatment for stage IV NSCLC, DC resulted in greater clinical benefit in terms of response rate (with marked improvements in overall and 2-year survival rates) and quality of life than did treatment with VdsC.

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Lung cancer has been a leading cause of cancer death in industrialized countries in the 20th century [1]. Non–small-cell lung cancer (NSCLC) accounts for 75% to 80% of all lung cancer histology. Meta-analyses of randomized trials comparing chemotherapy with supportive care in patients with advanced NSCLC have demonstrated that cisplatin-based combination chemotherapy prolongs survival, whereas some studies showed palliative effects of cancer-related symptoms with chemotherapy [2,3]. Although significant long-term survivors have been observed in the treatment of stage III NSCLC with chemoradiotherapy [4-6], improvements in stage IV disease have been dismal, with only 10% to 15% of stage IV patients surviving 1 year after diagnosis with best supportive care (BSC) alone and 20% to 25% of stage IV patients surviving 1 year

after diagnosis with cisplatin-based chemotherapy [7]. In the 1990s, randomized trials using platinum in combination with new agents (vinorelbine and gemcitabine) have shown 1-year survival rates ranging between 36% and 39% [8,9]. However, many trials have failed to show a significant survival advantage of new compared with older combinations [10-12].

Docetaxel, a new agent, is a semisynthetic taxoid derived from the European yew *Taxus baccata* [13]. It is active against NSCLC and shows survival benefits not only in chemotherapy-naive patients, but also in those patients who have previously received platinum-based chemotherapy [14-21]. Phase II trials of docetaxel and platinum combinations have resulted in median survival rates ranging between 8.4 and 13.9 months, indicating that such combinations are active as first-line therapies [22-25]. Response rates of 30% to 67% for docetaxel with a platinum agent have also been demonstrated. Although docetaxel is usually administered as a 75 mg/m^2 dose, a phase II trial demonstrated that a response rate of 42% with an acceptable toxicity profile [26] could be achieved when 60 mg/m^2 of docetaxel and 80 mg/m^2 of cisplatin were administered to patients with stage IV NSCLC.

We conducted a randomized trial that compared docetaxel plus cisplatin (DC) with vindesine plus cisplatin (VdsC). The primary aim of this study was to compare the overall survival of stage IV NSCLC patients between the two regimens. Secondary end points included the response rate, duration of response, safety, and quality of life (QoL).

Eligibility Criteria

This multicenter, randomized trial was conducted at 58 institutions in Japan between March 1998 and March 2000. Eligible patients were between the ages of 20 and 75 years, with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2; life expectancy ≥ 3 months; and previously untreated, stage IV, histologically or cytologically proven NSCLC with measurable lesions. Patients with PS of 3 because of pain from bone metastases were admitted to the study. Other eligibility criteria included leukocyte count ≥ 4,000/μL and ≤ 12,000/μL, neutrophil count ≥ 2,000/μL, platelet count ≥ 10^5/μL, hemoglobin ≥ 9.5 g/dL, blood urea nitrogen less than or equal to the upper limit of the institutional normal range (ULN), serum creatinine less than or equal to the ULN, creatinine clearance ≥ 60 mL/min, serum bilirubin less than or equal to the ULN, serum ALT and AST ≤ 2 × ULN, and Pao_2 ≥ 70 mm Hg. Women who were pregnant or lactating were excluded from the study. Other exclusion criteria included patients with active infection, uncontrolled heart disease, interstitial pneumonia or active lung fibrosis, peripheral neuropathy, pleural or pericardial effusion that required drainage, past history of drug hypersensitivity, symptomatic brain metastasis, or active concomitant malignancy.

Patient eligibility was determined by the Patient Registration Center at the Tokyo Cooperative Oncology Group before patient registration. This study was approved by the institutional review boards at each participating center and all patients provided written informed consent.

Treatment Plan

Patients were randomly assigned to one of two treatment arms (Fig 1). In the experimental arm (DC), patients received docetaxel 60 mg/m^2 as a 1-hour intravenous infusion followed by cisplatin 80 mg/m^2 as a 2-hour infusion on day 1. Patients in the control arm (VdsC) received a bolus infusion of vindesine 3 mg/m^2 on days 1, 8, and 15, and cisplatin 80 mg/m^2 as a 2-hour infusion on day 1. Courses of treatment were repeated every 3 to 4 weeks in the DC arm, and once every 4 weeks in the VdsC arm.

Patients received at least two cycles of treatment unless disease progression or unacceptable toxicity was documented. Thereafter, responders or patients without disease progression continued treatment until the appearance of progressive disease or

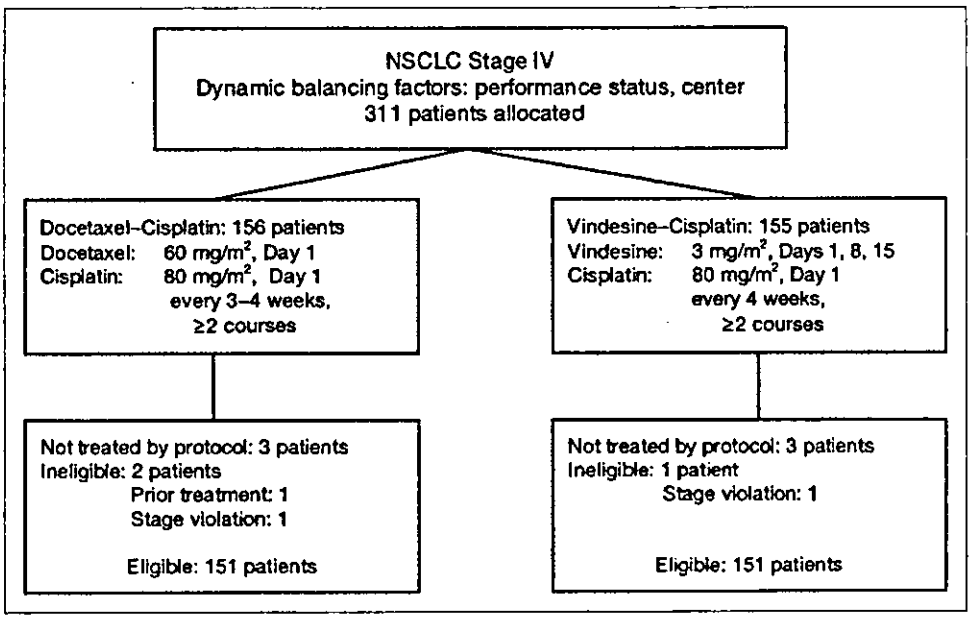

Fig 1. Study design and patient allocation. NSCLC, non-small-cell lung cancer.

a major toxicity. Because the efficacy of second-line docetaxel had not been established at the start of this study in 1998, cross-over administration of docetaxel and vindesine was prohibited in both treatment groups and the nature of second-line treatment was recorded.

No routine premedication was given for hypersensitivity reactions during the first cycle of treatment, although in subsequent cycles this was administered if a patient experienced a reaction. All hypersensitivity reactions were identified by the patient's physician and if deemed necessary, premedication drugs were administered by the investigator. However, recombinant human granulocyte colony-stimulating factor was administered when National Cancer Institute Common Toxicity Criteria grade 3 to 4 leukopenia or neutropenia occurred. If grade 4 neutropenia and/or leukopenia lasting for more than 3 days, grade 4 thrombocytopenia, grade 2 neuropathy, or grade 3 to 4 hepatotoxicity was observed, a 25% dose reduction of both drugs was implemented during the subsequent treatment cycle in both arms. If grade 3 stomatitis or renal toxicity occurred, the dose of cisplatin was reduced by 25%. Dose re-escalation was prohibited. Treatment was discontinued in the event of grade 3 neuropathy and again, dose re-escalation was prohibited. When leukocyte and platelet counts were less than 2,000/μL and 100,000/μL, respectively, or if infection developed at day 8 or 15, vindesine was withheld.

Patient Evaluation

Before chemotherapy, each patient underwent a complete medical history and physical examination, blood cell count determinations, biochemistry testing, chest x-ray, ECG, chest and whole-brain computed tomographic scan, abdominal ultrasound and/or computed tomographic scan, and isotope bone scan. Blood cell counts, differential WBC counts, and biochemistry testing were performed weekly during each course of chemotherapy.

Tumor responses were assessed radiographically and all responders were evaluated on extramural review. Treatment arms were blinded at the review. Standard WHO response criteria were used, and all responses were confirmed $\geq$ 28 days after initial documentation of the response.

QoL scores were measured using the validated instrument QoL Questionnaire for Cancer Patients Treated with Anticancer Drugs developed in Japan [27]. The instrument consists of five domains (functional, physical, mental, psychosocial, and global), and it was completed by the patient before treatment began, before the second and third therapy cycles, and 3 months after the last cycle of treatment. Evaluations were not only performed during the course of treatment but also 2 years after study treatment.

Statistical Considerations

Survival from the date of enrollment was the primary end point. The sample size was chosen on the basis of a log-rank test used to compare the two randomized groups. A sample size of 150 patients per group was estimated on the basis of a projected median survival of 42 weeks in the DC group and 30 weeks in the VdsC group, with an α level of 5% (two sided) and a power of 80% to compare both groups. Dynamic balancing factors (ie, prerandomization stratification factors) included ECOG PS and institutions, and these were used to minimize any imbalance in treatment assignment.

Secondary end points included objective tumor response, response duration, rate of adverse drug reactions, and changes in QoL. The survival time and response duration were estimated for each group using the Kaplan-Meier method [28]. Response duration was calculated from the first date of a 50% reduction in the tumor to the last date that tumor reduction was documented. The difference in response duration was evaluated using the generalized Wilcoxon test. Tumor responses in both groups were compared using Fisher's exact test. Other categoric data, such as treatment data and the incidence of adverse events, were compared between treatment groups using the χ^2 test. QoL analyses were performed using repeated-measures analysis of variance between treatment groups on data collected before the second and third treatment cycles, and 3 months after the last cycle of treatment, adjusting for baseline QoL values.

An interim analysis on the basis of overall survival was planned for 1 year after enrollment of the last patient. The predefined early-stopping rule was based on a two-sided significance level of 0.005. The DeMets and Lan method was applied for multiple comparisons [29]. The analysis was monitored by the Independent Data Monitoring Committee. The final analysis was conducted 2 years after enrollment of the last patient and the final significance level was maintained at 0.0491.

RESULTS

Patient Characteristics

From April 1998 to March 2000, 311 previously untreated patients from 58 institutions were randomly assigned to treatment in the trial (Fig 1). However, six patients did not receive any protocol treatment (three in the DC arm and three in the VdsC arm). In the DC arm, one patient withdrew informed consent, another experienced a rapid increase in serum bilirubin beyond levels acceptable for inclusion into the study, and the third patient had an accident causing a thoracic spine pressure fracture; all withdrawals occurred before the first cycle of treatment. Likewise, before the first cycle of treatment, one patient in the VdsC arm had superior vena cava syndrome, one patient contracted pneumonia and the investigator decided against this patient receiving protocol treatment, and one patient (who also had pneumonia) had brain metastases and was therefore excluded from the study. An additional three patients failed to fulfill the eligibility criteria for the following reasons: stage violations (two patients, one per treatment arm) and prior treatment (one patient, DC arm). Because nine patients were deemed ineligible, 302 patients were evaluated—151 in each arm. All 302 patients were evaluated for survival, response, and toxicity. The characteristics of eligible patients are listed in Table 1.

Treatment Delivery

The median number of cycles was three for the DC arm and two for the VdsC arm ($P < .01$; Table 2). One hundred thirty-two patients (87%) in the DC arm and 115 patients (76%) in the VdsC arm received at least two cycles of chemotherapy. The reasons for terminating chemotherapy before the second treatment cycle in the DC and VdsC arms, respectively, were disease progression (7% v 13%), adverse events (5% v 6%), patient refusal (0% v 2%), and adverse event with patient refusal (1% v 3%).

Table 1. Patient Characteristics

Characteristic	Treatment Group DC (n = 151)	VdsC (n = 151)
Age, years		
Median	63	64
Range	30–74	39–74
Sex, No. of Patients		
Male	97	103
Female	54	48
Histology, No. of patients		
Adenocarcinoma	120	103
Squamous cell	17	33
Large cell	9	11
Adenosquamous	0	2
Other	5	2
ECOG performance status, No. of patients		
0	46	41
1	99	105
2	5	4
3	1	1

Abbreviations: DC, docetaxel plus cisplatin; VdsC, vindesine plus cisplatin; ECOG, Eastern Cooperative Oncology Group.

Table 3. Treatment Outcomes

Outcome	Treatment Group DC (n = 151)	VdsC (n = 151)	P
Tumor response, No. of patients			
Complete	3	0	
Partial	53	32	
No change	63	76	
Progressive disease	27	38	
Not assessable	5	5	
Overall response rate, %	37.1	21.2	< .01
95% CI	29.4 to 45.3	15.0 to 28.6	
Median duration of response, weeks	10.0	8.4	.02
Survival			
Median, months	11.3	9.6	.014
95% CI	10.2 to 13.1	8.4 to 11.4	
1 year, %	47.7	41.4	
95% CI	39.7 to 55.6	33.5 to 49.3	
2 year, %	24.4	12.3	
95% CI	17.5 to 31.2	7.0 to 17.6	

Abbreviations: DC, docetaxel plus cisplatin; VdsC, vindesine plus cisplatin.

Response

Patients receiving DC had a significantly higher overall response rate than those receiving VdsC ($P = .0035$; Table 3). There were three complete responses and 53 partial responses, with an overall response rate of 37.1% (95% CI, 29.4% to 45.3%) in the DC arm. The VdsC arm resulted in 32 partial responses, with an overall response rate of 21.2% (95% CI, 15.0% to 28.6%). The median duration of response was 10.0 weeks in the DC arm versus 8.4 weeks in the VdsC arm ($P = .20$).

Survival

The median survival time, 11.3 months (95% CI, 10.2 to 13.1 months) for the DC arm, was significantly greater than the 9.6-month (95% CI, 8.4 to 11.4 months) median survival of the VdsC arm (log-rank test, $P = .014$; Fig 2). The 1- and 2-year survival rates were 47.7% (95% CI, 39.7% to 55.6%) and 24.4% (95% CI, 17.5% to 31.2%) for the DC group, and 41.4% (95% CI, 33.5% to 49.3%) and 12.3% (95% CI, 7.0% to 17.6%) for the VdsC group, respectively (Fig 2).

Table 2. Treatment Delivery

Cycle of Treatment	Received Cycle of Treatment: DC (n = 151) No. of Patients	%	VdsC (n = 151) No. of Patients	%
1	151	100	151	100
2	132	87	115	76
3	84	56	53	35
4	41	27	17	11
5	6	4	1	1
6	2	1	0	0
No. of cycles*				
Median	3		2	
Range	1–9		1–5	

Abbreviations: DC, docetaxel plus cisplatin; VdsC, vindesine plus cisplatin.
*$P = .01$.

Toxicity

National Cancer Institute Common Toxicity Criteria grade 3 and 4 hematologic toxicities, anemia, and leukopenia were significantly more severe among patients receiving VdsC compared with those receiving DC ($P < .01$; Table 4). Grade 4 neutropenia also occurred more frequently in the VdsC regimen (50.3%) than in the DC regimen (35.1%), but grade 3 or 4 thrombocytopenia was rare in both arms.

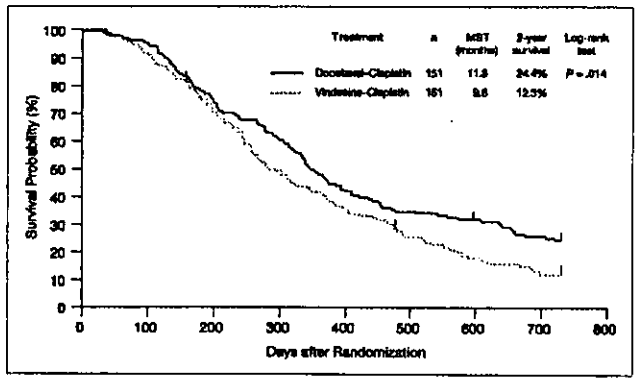

Fig 2. Kaplan-Meier survival estimates for patients treated with docetaxel plus cisplatin and patients treated with vindesine plus cisplatin. MST, median survival time.

Table 4. Grade 3 or 4 Hematologic Toxicities

Toxicity (grade)	Treatment Group: DC (n = 151) No. of Patients	%	VdsC (n = 151) No. of Patients	%	P
Anemia					< .01
3	15	10	34	23	
4	0		0		
Thrombocytopenia					
3	1	1	0	0	
4	0		0		
Leukopenia					< .01
3	66	46	92	68	
4	3		10		
Neutropenia					
3	59	74	41	77	
4	53		76		

Abbreviations: DC, docetaxel plus cisplatin; VdsC, vindesine plus cisplatin.

Table 6. Poststudy Treatment

Therapy	Treatment Group (% of patients): DC (n = 151)	VdsC (n = 151)
Chemotherapy	52	46
Platinum	29	23
Gemcitabine	26	19
Vinorelbine	15	15
Irinotecan	9	7
Paclitaxel	8	11
Gefitinib	3	1
Other	11	12
Docetaxel	23	5
Vindesine	0	7
Radiation	51	48
Surgery	2	2

Abbreviations: DC, docetaxel plus cisplatin; VdsC, vindesine plus cisplatin.

Grade 3 and 4 nonhematologic toxicities are listed in Table 5. The incidences of the majority of grade 3 or 4 nonhematologic toxicities were similar in both arms, with no significant differences between treatments. However, the incidences of grade 3 or 4 nausea and vomiting, anorexia, and diarrhea were significantly more frequent in the DC arm compared with the VdsC arm ($P < .05$, $P < .01$, and $P < .01$, respectively). There were two deaths in the DC arm that probably were related to treatment. One patient had acute myocardial infarction and died on day 2 of the first cycle of treatment; the second patient had obstructive pneumonia in the same lobe as the primary tumor and died on day 25 of the first course of therapy.

Table 5. Grade 3 or 4 Nonhematologic Toxicities*

Toxicity (grade)	Treatment Group: DC (n = 151) No. of Patients	%	VdsC (n = 151) No. of Patients	%	P
Nausea and vomiting					< .05
3	13	9	7	5	
4	0		0		
Anorexia					< .01
3	30	21	14	9	
4	1		0		
Diarrhea					< .01
3	6	9	2	1	
4	8		0		
Malaise					
3	6	4	3	3	
4	0		1		
Dysrhythmia					
3	3	2	2	1	
4	0		0		
AST elevation					
3	0		3	2	
4	0		0		
ALT elevation					
3	2	1	4	3	
4	0		0		
Bilirubin					
3	3	2	3	2	
4	0		0		

Abbreviations: DC, docetaxel plus cisplatin; VdsC, vindesine plus cisplatin.
*Occurring in ≥ 2% patients in at least one arm.

Poststudy Treatment

A total of 52% of patients receiving DC and 46% of patients receiving VdsC also received second-line chemotherapy. The agents used as second-line therapy in both arms were similar without usage of docetaxel and vindesine. Although cross-over treatments were considered to be protocol deviations, 5% of patients receiving first-line vindesine received second-line docetaxel, and these patients were included in survival analyses. Palliative radiotherapy was used in 51% of patients in the DC arm and 48% of patients in the VdsC arm (Table 6).

QoL

QoL questionnaires were completed at baseline, before the second and third treatment cycles, and 3 months after the last cycle of treatment by 82.1%, 83.1%, 76.6%, and 54.9% of patients in the DC arm (n = 151) and 82.8%, 89.6%, 61.6%, and 55.4% of patients in the VdsC arm (n = 151), respectively. Least squares mean scale values for the functional, physical, and mental domains tended to improve among patients receiving DC, but the difference only achieved statistical significance for the functional (nonphysical) domain ($P = .02$; Fig 3). A separate, more detailed analysis of QoL data currently is ongoing.

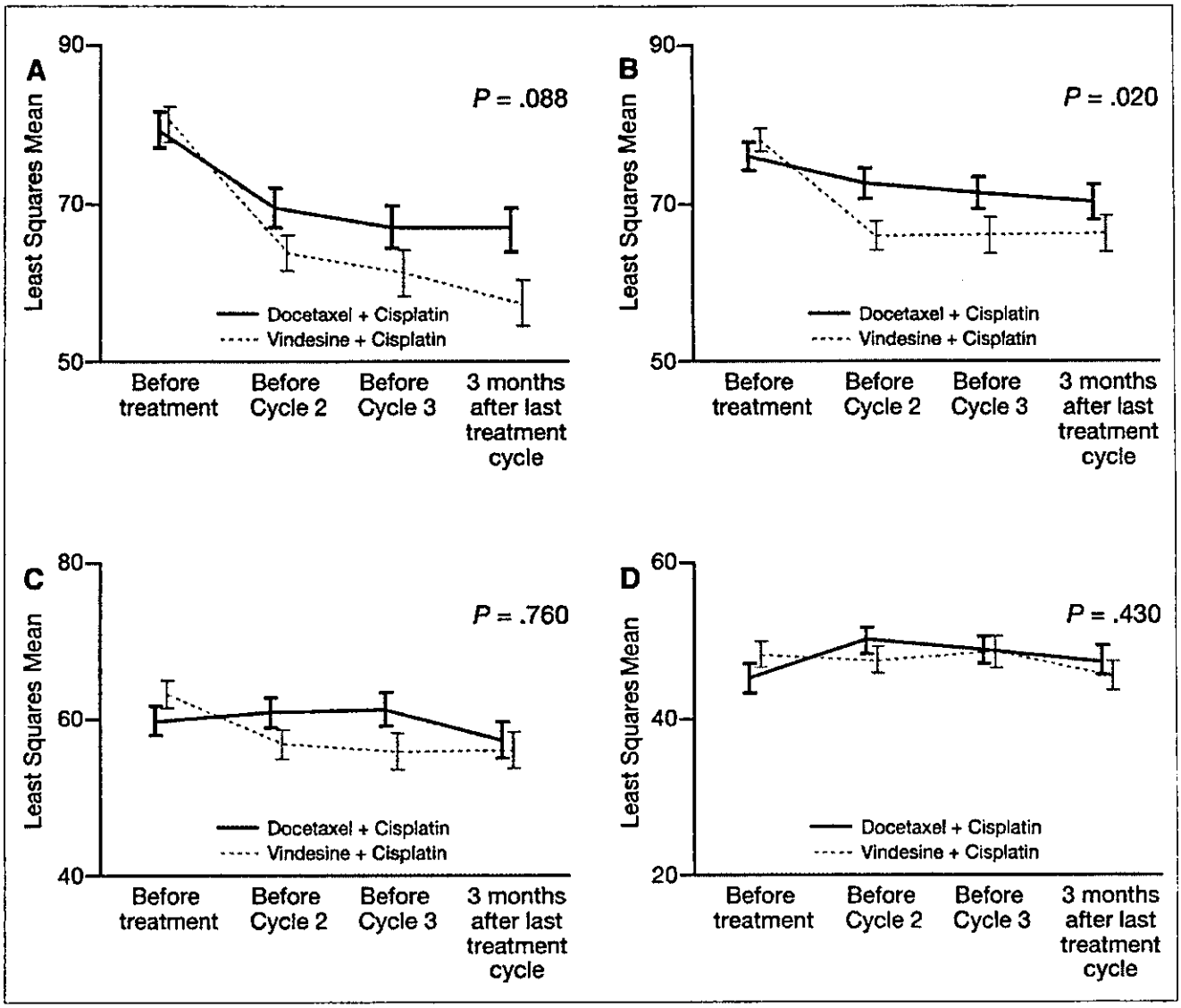

Fig 3. Quality-of-life assessments across four domains of the Quality of Life Questionnaire for Cancer Patients Treated with Anticancer Drugs instrument, among patients treated with docetaxel plus cisplatin and vindesine plus cisplatin. (A) Functional; (B) physical; (C) mental; and (D) psychosocial. Vertical bars represent least square means ± SE. Higher score indicates better quality of life.

Platinum-based combination chemotherapy is the treatment of choice for stage IV NSCLC patients with good performance status. The Big Lung Trial recently conducted in England confirmed the survival advantage of platinum-based combination chemotherapy in this setting [30]. The results of the present multicenter randomized trial reveal a significant survival advantage for DC when compared with VdsC in the treatment of patients with stage IV NSCLC. It is noteworthy that the 2-year survival rate in the DC arm was 24.3%—double that observed in the control arm. This is comparable to results for patients with stage III NSCLC who were treated with sequential chemoradiotherapy [4].

VdsC was chosen as the control arm because this regimen showed significant survival advantage over BSC in a Canadian trial [31]. In addition, this combination has long been the standard regimen for advanced NSCLC [22,31,32]. For instance, two randomized trials conducted in Japan, which compared the more recently developed agent irinotecan plus cisplatin with VdsC, failed to show an overall survival advantage for the irinotecan-containing regimen in advanced NSCLC [33,34]. In the European study, 612 patients were randomly assigned to receive vinorelbine plus cisplatin, vindesine plus cisplatin, or vinorelbine alone. In this study, the unadjusted log-rank test comparing the survival of patients who received vinorelbine plus cisplatin versus VdsC yielded a *P* value of .085 in favor of vinorelbine

plus cisplatin. Patients with both stage III and local recurrence (41%), or metastatic NSCLC (59%) were included, and nearly half of the patients received thoracic irradiation after chemotherapy [22]. The treatment strategy of locally advanced NSCLC is different from that of metastatic disease. Thus, the advantage of vinorelbine plus cisplatin over VdsC in patients with stage IV NSCLC has not been clearly defined.

Despite undergoing more treatment cycles, fewer patients on the DC arm experienced severe hematologic toxicities (including anemia and leukopenia) than patients treated with VdsC. Although diarrhea, nausea and vomiting, and anorexia were more frequently observed in the DC arm, such toxicities were easily managed with standard care.

DC has been evaluated in other phase III trials. In the ECOG trial, 1,207 patients were randomly assigned to paclitaxel plus cisplatin, gemcitabine plus cisplatin, docetaxel plus cisplatin, or paclitaxel plus carboplatin [35]. The response rate and median survival were similar among the four regimens for eligible patients at 19% and 7.9 months, respectively. In a large international trial (TAX-326), 1,218 chemotherapy-naive patients were randomly assigned to docetaxel plus cisplatin, docetaxel plus carboplatin, or vinorelbine plus cisplatin [36]. The DC arm favored a longer median survival time compared with the vinorelbine plus cisplatin arm (11.3 *v* 10.1 months) and response (31.6% *v* 24.5%). Although we must be careful when making retrospective comparisons, both survival figures and response data of the present study and TAX-326 were virtually identical and were better than those of the ECOG trial [35]. It is suggested that patients with more favorable prognostic factors entered in TAX-326 and the current study.

More recently, attention has focused on improving QoL as a goal of therapy for patients with advanced NSCLC [37]. One trial of docetaxel as second-line therapy versus BSC showed that chemotherapy resulted in significantly better control of pain and fatigue than did BSC [20]. In a similar comparative phase III trial, docetaxel, administered as first-line in chemotherapy-naive patients, was significantly better than BSC in controlling not only pain but also dyspnea and emotional functioning [19]. In the present study, QoL measures demonstrated that the physical domain was significantly better in the DC arm over the VdsC arm ($P = .020$). This finding of a QoL benefit with a docetaxel plus platinum combination is also supported by the results of TAX-326 [38]. This investigation indicated that patients in receipt of a docetaxel plus platinum combination reported greater global QoL benefit in terms of patient pain or less Karnofsky performance status deterioration than patients receiving vinorelbine plus cisplatin when the EuroQol and Lung Cancer Symptom Scale instruments were used [39,40].

In this study, we used 60 mg/m^2 of docetaxel on the basis of the phase II study conducted in Japan [26]. The dose of docetaxel is lower than the doses used in ECOG1594 and TAX-326 (docetaxel and cisplatin 75 mg/m^2) [35,36]. In a randomized trial comparing docetaxel alone with BSC in patients previously treated with platinum-based chemotherapy, docetaxel 100 mg/m^2 was not tolerated but docetaxel 75 mg/m^2 demonstrated significant survival benefit [20]. Therapeutic index was also better for the lower dose of docetaxel in another randomized trial of second-line chemotherapy, which compared 100 or 75 mg/m^2 of docetaxel against a control regimen of vinorelbine or ifosfamide [21]. The docetaxel dose of 60 mg/m^2 might be optimal when it is combined with a standard dose of cisplatin. Additional study is warranted regarding this dose issue.

In summary, this randomized phase III trial demonstrates that DC is superior, in terms of response rate and survival, to VdsC in the treatment of previously untreated patients with stage IV NSCLC. A doubling in the 2-year survival rate is reported for DC compared with the classic standard regimen. Given the results of this trial, DC should be considered as a standard regimen for the first-line treatment of stage IV NSCLC, and it is suggested that the classic combination regimen should no longer be regarded as a suitable control arm in future randomized studies of patients with stage IV NSCLC.

Appendix

The appendix is included in the full-text version of this article, available on-line at www.jco.org. It is not included in the PDF (via Adobe® Acrobat Reader®) version.

Authors' Disclosures of Potential Conflicts of Interest

The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Performed contract work within the last 2 years: Kaoru Kubota, Aventis Pharma Ltd; Koshiro Watanabe, Aventis Pharma Ltd; Hideo Kunitoh, Aventis Pharma Ltd; Kazumasa Noda, Aventis Pharma Ltd; Yukito Ichinose, Aventis Pharma Ltd; Nobuyuki Katakami, Aventis Pharma Ltd; Takahiko Sugiura, Aventis Pharma Ltd; Masaaki Kawahara, Aventis Pharma Ltd; Akira Yokoyama, Aventis Pharma Ltd; Soichiro Yokota, Aventis Pharma Ltd; Shuichi Yoneda, Aventis Pharma Ltd; Kaoru Matsui, Aventis Pharma Ltd; Shinzo Kudo, Aventis Pharma Ltd; Masahiko Shibuya, Aventis Pharma Ltd; Takeshi Isobe, Aventis Pharma Ltd; Yoshihiko Segawa, Aventis Pharma Ltd; Yutaka Nishiwaki, Aventis Pharma Ltd; Yasuo Ohashi, Aventis Pharma Ltd; Hisanobu Niitani, Aventis Pharma Ltd.

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Objective definition and measurement method of ground-glass opacity for planning limited resection in patients with clinical stage IA adenocarcinoma of the lung☆

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Abstract

Objective: The standard operation for patients with stage IA lung adenocarcinoma is considered to be a lobectomy. Recently, some researchers have reported that patients with tumors showing greater proportions of ground-glass opacity (GGO) at computed tomography (CT) could be candidates for limited resection, because of its less aggressive nature. However, the lack of a precise definition or standard measuring method of GGO prevents its general use as an index for planning limited resection. Therefore, we attempted to define GGO based on CT number and measured it more objectively. **Methods**: Between 1998 and 2001, 90 patients with clinical stage IA adenocarcinoma, who underwent standard or intentional limited resection and whose images of chest high-resolution CT were preserved in Digital Imaging and Communications in Medicine (DICOM) format, constituted the study population. The tumor shadow seen on the solid window (WL, −160 HU; WW, 2 HU) was regarded as the central solid area of the tumor seen on the lung window, and GGO was defined as the whole tumor area with the exception of the central solid area. Each area was measured using Scion Image (Scion Corp., Frederick, MD). We analyzed the relationship between the proportion of GGO and both of pathologic findings and recurrence. **Results**: Among the 90 tumors, 31 (34.4%) were calculated to have a GGO area greater than or equal to 50%. Of these, 27 (87%) tumors were bronchioloalveolar carcinoma. Lymphatic and vascular invasions, or nodal involvement were found only in patients with a smaller proportion of GGO (<50%) ($P < 0.05$). During the follow-up period (median 36 months), recurrences occurred in eight patients who were diagnosed as having tumors showing smaller proportion of GGO (<50%). **Conclusions**: Tumors with a greater proportion of GGO measured by our method are thought to have a less invasive nature. Our objective measuring method of GGO could be useful for future multicenter trials to elucidate the value of limited resection for clinical stage IA adenocarcinoma based on the proportion of GGO.

Keywords: Lung neoplasms; High-resolution computed tomography; Lung neoplasms; Adenocarcinoma; Bronchioloalveolar carcinoma; Limited operation; Ground-glass opacity

1. Introduction

The standard operation for patients with T1N0M0 stage IA non-small cell lung cancer is still lobectomy with systematic nodal dissection, because limited resection for such patients was reported to increase local recurrence and decrease the survival rate compared to lobectomy in a randomized control trial conducted by the Lung Cancer Study Group [1]. Candidates for limited resection, therefore, are thought to be rather a group of patients that have less invasive tumors and a better prognosis than the whole group of stage IA non-small cell lung cancer patients [2]. Much research has been conducted to identify the group of patients with less invasive tumors preoperatively based on the tumor size. However, the tumor size turned out to be less useful, because the incidence of lymph node metastasis in patients with tumors smaller than 2 cm in diameter were reported to be 10–20% [3,4].

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Jang et al. reported that the focal area of ground-glass opacity (GGO) on high-resolution computed tomography (HRCT) could be an early sign of localized bronchioloalveolar carcinoma (BAC) [5]. We demonstrated that in patients with clinical T1N0M0 adenocarcinoma the patients with a higher proportion of GGO area (≥50%) on HRCT by visual estimation had neither lymph node metastasis nor lymphatic invasion and were alive without recurrence [6]. From these results, it is considered that such patients may be candidates for limited resection.

However, the lack of a precise definition or standard measuring method of GGO prevents its general use as an index for planning limited resection. To resolve the problems, we characterized the GGO using CT number, and developed more objective measurement methods using Scion Image to quantitate the proportion of GGO area. Then, we tested whether or not this method was useful in predicting less invasive tumors in clinical stage IA adenocarcinoma patients.

2. Materials and methods

Between January 1998 and December 2001, 284 patients with primary lung cancer underwent surgical resection of the lung at our hospital. Of these, 103 patients were given a diagnosis of clinical stage IA lung adenocarcinoma. Among the patients, 90 underwent standard surgical resection or intentional limited resection and their lung images of HRCT were preserved in Digital Imaging and Communications in Medicine (DICOM) format. These patients constituted the study population. For four patients with multiple lung cancer, we investigated the most advanced tumor. Fifty-one patients were men, and the average age was 60.3 years (range 36–78 years). CT scanning was performed on X-Vigor or Aquilion (Toshiba Medical Systems, Tokyo, Japan). HRCT scans were performed over a range of 50 mm, covering the entire lesion. The scanning parameters were a tube voltage of 120 kV, a tube current of 250 mAs for X-Vigor and 150 mAs for Aquilion, 1 or 2 mm collimation, and a reconstruction interval of 1 or 2 mm by using a bone algorithm. The field of view was focused at about 20 cm. GGO was defined as a hazy increase in lung attenuation without obscuring the underlying vascular marking. We tried to define the GGO based on CT number (Hounsfield unit (HU)). When we fixed the window width of CT at 2 HU, the tumor shadow represented the area where the CT value was greater than that of the window level. We changed the window level from 40 to −320 HU to select the best window level at which the tumor shadow was visually almost identical to the central solid area on the lung window. As a result, we decided the best window level was −160 HU, and referred to the window setting as 'solid window' (window level −160 HU; window width 2 HU). The tumor shadow seen on the solid window was thought to represent the central solid area seen on the lung window. Therefore, the GGO area was defined as the tumor shadow on solid window subtracted from tumor shadow on lung window. The areas of the tumor shadows were measured with Scion Image (Scion Corp., Frederic, MD, USA) on one level of each tumor shadow equator on each window settings. Scion Image is an image processing and analysis program for windows computer that is based on the popular NIH Image (NIH, Bethesda, MD, USA) for Macintosh computer. These are freely available for download from their respective website. We used the 'Density slice' command to segment the target area. The details of how to use the Scion Image are also referable to the manual in the website.

Vessels or bronchi in the tumor shadow were erased if the areas were larger than 5% of the tumor shadow. The proportion of GGO was calculated as follows: [(Area on lung window − Area on solid window)/Area on lung window] × 100. A representative case is shown in Fig. 1.

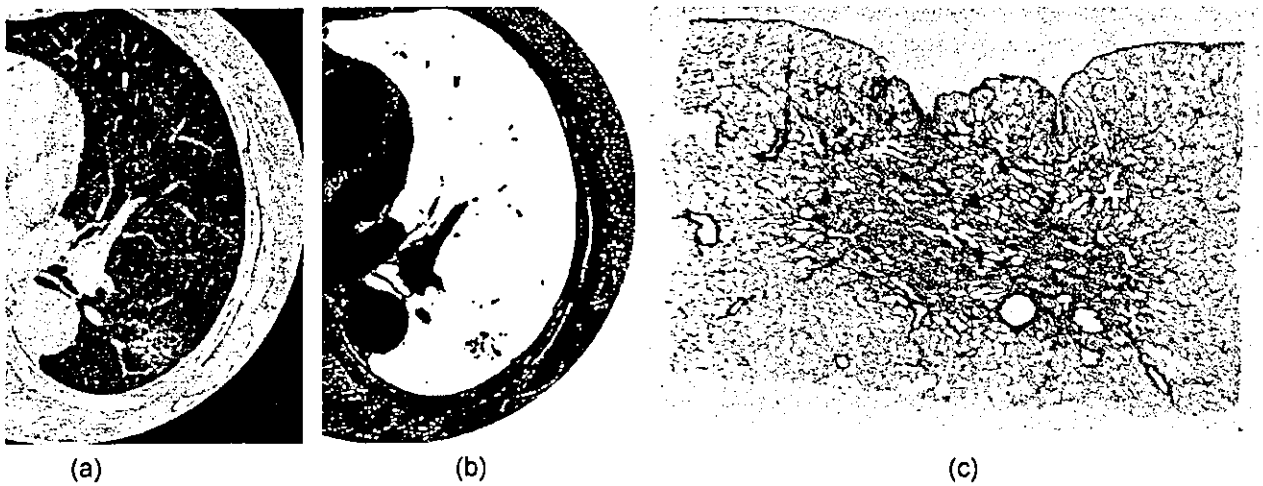

Fig. 1. Seventy-seven-year-old woman with a pulmonary nodule detected by annual screening using chest X-ray examination. Her HRCT images showed a GGO nodule dotted with small solid areas (a). The proportion of GGO was calculated at 86% (b). Pathologic examination revealed that the tumor was BAC. She was alive without any sign of recurrence at 42 months after operation (c).

Table 1
Relationship between proportion of GGO and both pathological findings and recurrence

% GGO	Number of patients	Number of BAC patients	Lymphatic invasion	Vascular invasion	Pleural invasion	Nodal involvement	Recurrence
90–100	14	14	0	0	0	0	0
80–89	8	7	0	0	0	0	0
70–79	4	4	0	0	0	0	0
60–69	3	2	0	0	0	0	0
50–59	2	0	0	0	0	0	0
40–49	10	5	1	0	1	0	0
30–39	7	2	0	1	2	0	1
20–29	8	0	1	1	1	1	0
0–19	34	1	12	9	5	11	7

Four-micrometer sections, including the largest piece cut from the surface of the tumor in each case, were stained with hematoxilin and eosin and elastica van Gieson and examined by means of light microscopy. Intra-tumoral vascular invasion was determined by means of the identification of tumor cells in blood vessels. Lymphatic invasion was also morphologically distinguished from vascular invasion. Pleural invasion was judged as positive if tumor cells invaded across the visceral pleural elastic layer. The tumors were classified into two histologic subtypes according to the classification determined by the World Health Organization (WHO), BAC and other subtypes including acinar, papillary, solid carcinoma with mucin, and adenocarcinoma with mixed subtype [7]. Pathologic stages were classified according to the International System for Staging Lung Cancer criteria [8].

All patients were followed up until death, or the last date of the follow-up (December 31, 2002). The average length of follow-up was 36 months. We investigated the relationship between the proportion of GGO area calculated using our method compared with the pathologic findings and recurrence. The χ^2-test or Fisher's exact test was used to compare several clinical or pathological factors.

3. Results

The distribution of pathologic BAC, nodal status, lymphatic, vascular and pleural invasions, and recurrence by proportion of GGO were shown in Table 1. Among the 90 tumors, 31 (34.4%) were calculated to have a GGO area greater than or equal to 50%. Among the 31 tumors showing a greater GGO proportion ($\geq$ 50%), 27 (87%) tumors were BACs, and no tumors accompanied vessel invasion, pleural invasion, or lymph node metastasis. On the other hand, among the 34 tumors with a GGO area smaller than 20%, 12 (35%) had lymphatic invasion and 11 (32%) accompanied lymph node metastasis. Lymphatic and vascular invasions, or nodal involvement was found more frequently in patients with a smaller proportion of GGO ($<$50%) than patients with a greater proportion of GGO ($\geq$50%) ($P < 0.05$). During the follow-up period, eight patients had tumor recurrences. Of the patients, six were diagnosed as having mediastinal nodal involvement after surgery. There were three local recurrence cases, three distant recurrence cases, and two both local and distant recurrence cases. Seven patients had tumors showing less than 20% of GGO, and one patient had a tumor showing 33% of GGO.

4. Discussion

Detections of nodules showing greater proportion of GGO had increased strikingly since lung cancer screening with low dose CT began [9]. Higashiyama and colleagues investigated the relation between the proportion of BAC component and prognosis. They documented that the greater degree of BAC involvement might reflect the less frequent nodal involvement and good prognosis [10]. We reported the relation between the proportion of GGO and both clinicopathologic characteristics and recurrence in patients with clinical T1N0M0 adenocarcinoma [6]. In this study,

Table 2
Measurement methods of GGO in article

Source	Year	Slice	Method	Parameter	Window setting
Kuriyama et al.	1999	One	Visual	Area	Lung window
Kim et al.	2001	One	Visual	Area	Lung window
Kodama et al.	2001	One	Visual	Area	Lung window
Aoki et al.	2001	One	Measure	Diameter	Lung window
Kondo et al.	2002	One	Visual	Area	Lung /mediastinal window
Matsuguma et al.	2002	All	Visual	Area	Lung window
Takashima et al.	2002	One	Measure	Area	Lung window

the GGO was estimated using visual estimation on all slices in which the tumor appeared. The patients with a higher proportion of GGO area (≥50%) on HRCT had neither lymph node metastasis nor lymphatic invasion and were alive without recurrence. Besides our study, several studies focusing on GGO have been reported to date (Table 2) [11–16]. In many studies including ours, proportions of GGO were semiquantitated by visual estimation. In one study, diameters of nodules and central solid portions were measured instead of area [14]. And in only one study, GGO area was measured using transparent overlay with crossing points of vertical and transverse lines [16]. We think that calculating the area is better than focusing on dimensions because the shape of the central solid portions are often irregular, and sometimes separate as can be seen in our case in Fig. 1.

Standardization for dealing with GGO in selecting candidates for limited resection is urgently needed so that the data from many studies can be compared. Below, we have listed some problems regarding our former published method of measuring GGO. First, visual estimation is somewhat vague and less reproducible. Second, the definition of GGO itself is determined by visual judgment and can result in inter-observer difference. Third, there is a question as to whether the cut-off value of 50% of GGO is or is not the most valuable point in identifying a candidate for limited resection. This is because the cut-off value of 50% was fixed in order to simplify visual judgment. To resolve these problems, we characterized GGO with a CT number, and the proportion of GGO is quantitated more objectively using software. As a result, we obtained almost the same results as our previous study. Furthermore, it has become much clearer that the tumor shows more invasiveness as its proportion of GGO decreases. From our results, the most useful cut-off value for area of GGO may be around 50%, even when using our method. However, future prospective studies are needed to evaluate the effectiveness of limited resection for patients in the early stages of lung cancer based on the objective measurement of GGO. As mentioned above, NIH Image and Scion Image are now freely available. If the images are saved only on the hard-copy film, not as digital data as we have done, you only have to save a few additional images on solid window on hard copy film in addition to the standard lung and mediastinal window images, and transform them into digital data using a scanner. We believe that our methods could be useful and easily available throughout the world.

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Appendix A. Conference discussion

Dr Hyun-Sung Lee (South Korea): Regarding the proportion of GGO, you measured only the area of tumor and GGO, in other words, a two-dimensional evaluation, but I think the proportions of GGO should be

evaluated by the volume, not the area. With the hypothesis that the shape of tumor and GGO is a sphere, the area is proportional to the square of the diameter, but volume is proportional to the squared 3 of the diameter. By its volume or three-dimensional evaluation, the proportion of GGO will lead the different results. I think this is more reliable. What do you think?

Dr Matsuguma: In our previous study we measured the GGO on all slices and in this study we measured on one slice. One slice is two-dimensional and all slices is three-dimensional, so I cannot directly compare these results. We measured the GGO proportion using the software, so we precisely measured GGO. GGO is not equally distributed around the central solid portion, but we measured on both slices of the maximum shadow of the nodule and maximum shadow of the central solid portion. I thought it might almost represent the nature of the GGO tumor.

Dr P. De Leyn (Leuven, Belgium): This entity will gain importance also in West Europe when we will have screening programs. We will see more of these patients than we see now.

When you talk about limited resection, do you mean for nodal dissection, or would you also perform wedge resections for these types of lesions?

Dr Matsuguma: In this study?

Dr De Leyn: Not only in this study, but in your country you see more of these patients and you have a lot of experience. Would you perform wedge resections for these kinds of lesions instead of lobectomy?

Dr Matsuguma: Our limited resection included segmentectomy and wedge resection. In this study there were 10 patients who underwent wedge resection and 7 patients who underwent segmentectomy, that were based on the GGO proportion. Usually we carried out the standard operation for a solid nodule.

Dr F. Rea (Padova, Italy): I don't understand. Do you know the histology before planning your operation? Do you do frozen section? Do you decide, using a frozen section?

Dr Matsuguma: Preoperatively?

Dr Rea: Yes, preoperatively. Do you know preoperatively the diagnosis?

Dr Matsuguma: In many cases we diagnosed preoperatively, but in some cases, such as pure GGO or small nodule, were not diagnosed preoperatively.

Dr Rea: And then you decide with the frozen section!

Dr Matsuguma: Yes.

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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?

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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.

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:

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

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

$$\text{dANC} = \frac{\text{Emax} \times \text{AUC}^r}{\text{AUC}^r + \text{EC}_{50}^r}$$

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:

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

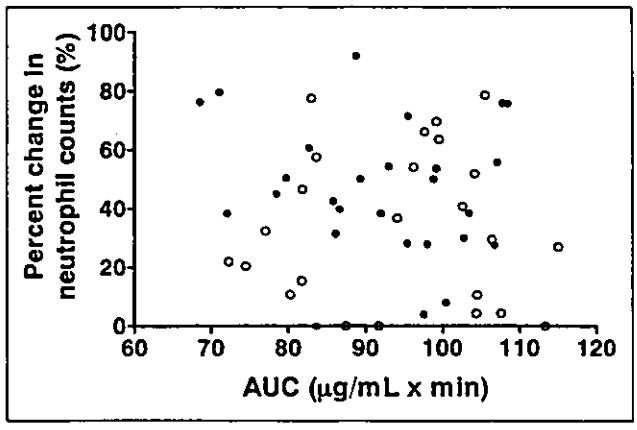

Fig 1. Relationship between the area under the curve (AUC) of cisplatin and percent changes in neutrophil counts in the elderly (○) and the non-elderly (●) patients.

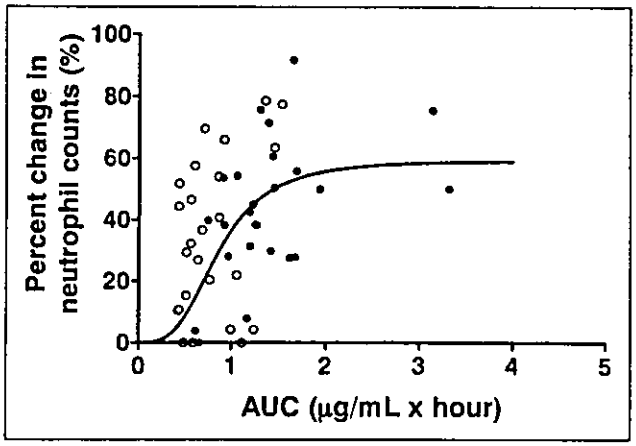

Fig 2. Relationship between the area under the curve (AUC) of docetaxel and percent changes in neutrophil counts in the elderly (○) and the non-elderly (●) patients. The solid line represents predictions by a sigmoid Emax model in the non-elderly patients

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.

[redacted]

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.

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