Table 1. Patient characteristics

Characteristic	Oral ciprofloxacin and amoxicillin-clavulanate	Intravenous ceftazidime
Eligible episodes	22	19
Age (year)		
Median (range)	68 (54–76)	67 (51–75)
Gender		
Male/female	15/7	15/4
ECOG PS		
0/1	6/16	2/17
Smoking status		
Never	5	4
Past	4	5
Current	13	10
Smoking index		
Median (range)	910 (0–3480)	880 (0–2400)
Histologic type		
Adenocarcinoma	5	7
Squamous cell carcinoma	4	4
Large cell carcinoma	1	2
Small cell carcinoma	12	6
Absolute neutrophil count (at randomization)		
$\leq 100/mm^3$	3	0
$101–500/mm^3$	14	12
$501–1000/mm^3$	5	7
Duration of neutropenia after randomization (days)		
Median (range)	4 (2–7)	4 (2–12)
Treatment with G-CSF [no. (%)]	19 (86)	14 (74)

factor (G-CSF) support was allowed. The administration of NSAIDs was not allowed. The administration of aluminum- and magnesium-containing antacids and oral iron preparations was allowed if they were administered more than 3 h after the administration of ciplofloxacin. The use of other antibiotics was prohibited during the trial.

Diagnostic Criteria and Evaluation

Each febrile episode was classified as either a clinically or microbiologically documented infection or PUO. Microbiologically documented infection necessitated the isolation of a bacterial pathogen from blood, urine, pus or exudates, along with clinical, laboratory or radiographic evidence of infection at the same site. Clinical infection was diagnosed when clear evidence of an infection was present but an organism could not be isolated. PUO was defined as the requisite temperature elevation with no clinical or microbiologic evidence of infection within 72 h of enrolment in the study.

Clinical outcomes were evaluated at 48 h and 7 days after the start of antibiotic treatment. Each patient was physically examined every day. Patients who remained febrile (without a downward trend) after 48 h or who had a body temperature ≥37°C on day 7 were removed from the study and treated with appropriate therapy; antibiotic treatment in these patients was considered to have failed. Treatment outcome was classified into three categories (7). 'Success without modification' referred to episodes in which the patient successfully recovered from fever and neutropenia without the need of additional antimicrobial agents or the modification of the initial randomly assigned regimen. 'Success with modification' referred to episodes in which the patient successfully recovered from the fever and neutropenia but required a modification of the assigned regimen. 'Failure' referred to all other cases. The response rate was defined as the percentage of 'success without modification' cases among all eligible patients.

Statistical Analysis

Assuming a response rate to the intravenous regimen of 80%, the study was designed to enroll 63 patients per treatment arm to ensure that the oral regimen would not be 20% worse (i.e. 60%) at a level of significance alpha = 0.05 and 80% power using a two-sided chi-square test. An interim analysis was

Table 2. Response rate

	Oral regimen ($n = 22$)		Intravenous regimen ($n = 19$)	
	PUO	Documented infection	PUO	Documented infection
Success without modification	16	4	10	5
Success with modification	0	2	0	4
Response rate	91%		79% $P = 0.39$	

Response rate was defined as the percentage of success without modification cases among all eligible patients.

planned at an accrual level of 40 patients. If a significant difference in response rates ($P < 0.01$) was observed, or if septic shock appeared in more than 10% of the patients undergoing the oral regimen, the study was to be terminated. Comparisons between proportions were done using a Pearson chi-square test or a Fisher exact test, when appropriate.

RESULTS

Patient Population and Treatment

A total of 177 patients with lung cancer agreed to participate in this study prior to undergoing chemotherapy between May 1995 and February 2001. Among them, a total of 36 neutropenic patients with 42 febrile episodes were enrolled in the study. One episode was ineligible because of hyponatremia. Of the 41 episodes (in 35 patients) included in the analysis, four patients were enrolled more than once: three patients had two episodes each, and one patient had four episodes. The patient characteristics are listed in Table 1. Twenty-two episodes were assigned to the oral regimen and 19 episodes were assigned to the intravenous regimen (Fig. 1). No statistically significant difference was seen between the two groups with regard to age, gender, PS, smoking status, histologic subtype and absolute neutrophil count. During 33 episodes, G-CSF was administered in addition to the assigned treatment. The median duration of neutropenia was 4 days in both groups.

Evaluation before Antibiotic Therapy

PUO was observed in approximately two-thirds of all febrile episodes. Infection was documented in 15 episodes. Most documented infections consisted of bronchus or lung infections (10 episodes) or urinary tract infections (three episodes). Other infections included colitis and alveolar pyorrhea. Microbiological pathogens were detected in five episodes. *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Haemophilus influenzae* were isolated from sputum and *Pseudominas aeruginosa* and *Enterococcus faecalis* were isolated from urine.

Efficacy

The response rates were similar in the two groups (91% versus 79%, $P = 0.39$) (Table 2). PUO was successfully treated in all 26 episodes. On the other hand, documented infection was successfully treated in 60% of the patients (four out of six episodes in patients receiving the oral regimen and five out of nine episodes in patients receiving the intravenous regimen). A total of six patients received changes to their treatment regimen. Two patients in the oral regimen group were switched to piperacillin sodium or ceftazidime. Four patients in the intravenous regimen group were switched to carbapenem with or without the addition of clindamycin or amikacin.

In approximately half of the episodes in both groups, the fever disappeared by day 4 of the treatment. By day 8, the fever had resolved in 90% of all episodes.

Adverse Effects

Few adverse effects were encountered. One patient developed nausea while receiving the oral regimen. The oral regimen was therefore changed to an intravenous regimen (piperacillin sodium) in this patient.

DISCUSSION

Febrile neutropenia can be a life-threatening complication of cancer chemotherapy. Therefore, febrile neutropenic patients are usually hospitalized for the administration of empiric, broad-spectrum, intravenous antibiotic therapy. Several analyses have demonstrated that febrile neutropenic patients comprise heterogeneous subgroups among which are low-risk patients with a high response rate to antibiotic therapy and a low risk of serious complications (2–4). We conducted a randomized trial to compare the oral administration of ciplofloxacin and amoxicillin-clavulanate with the intravenous administration of ceftazidime in low-risk febrile neutropenic patients with lung cancer. However, this study was terminated in February 2001 because of slow enrolment and the publication of two large randomized trials comparing oral with intravenous antibiotic therapy for low-risk febrile patients who developed neutropenia during cancer chemotherapy (8,9). In one trial, oral ciplofloxacin plus amoxicillin-clavulanate was compared with intravenous ceftazidime (8). These regimens were almost identical to those in our trial. In the other trial, oral ciplofloxacin plus amoxicillin-clavulanate was compared with intravenous ceftriaxone plus amikacin (9). Both trials demonstrated that oral therapy with ciplofloxacin plus amoxicillin-clavulanate was as safe and effective as intravenous therapy. Our trial confirmed these results, in spite of the smaller sample size.

The selection of low-risk patients with febrile neutropenia is very important. A multinational trial demonstrated that predictive factors for low risk complications included a burden of illness indicating the absence of symptoms or the presence of mild symptoms [weight, 5; odds ratio (OR), 8.21] or moderate symptoms (weight 3; OR, 3.70); the absence of hypotension (weight, 5; OR, 7.62); the absence of chromic obstructive pulmonary disease (COPD) (weight, 4; OR, 5.35); the presence of a solid tumor or the absence of previous fungal infection in patients with hematologic malignancies (weight, 4; OR, 5.07); an outpatient status (weight, 3; OR, 3.51); the absence of dehydration (weight, 3; OR, 3.81); and an age <60 years (weight, 2; OR, 2.45). A risk-index score ≥21 was considered to indicate a low-risk (10). In our trial, all of the enrolled patients had solid tumors (lung cancer) without hypotension or dehydration and no or mild symptoms. All but one patient had no COPD, producing a risk score of 21 or greater.

PUO was observed in 63% of the low-risk febrile neutropenic patients. The PUO percentage was identical to that reported in previous trials. All patients with PUO were successfully treated with oral or intravenous antibiotic therapy in our trial. Oral ciplofloxacin plus amoxicillin-clavulanate was effective for the treatment of PUO. Documented infections were successfully treated with an oral regimen in four out of six episodes and with an intravenous regimen in five out of nine episodes. Six patients needed to modify their regimen to an intravenous regimen containing cephalosporin or carbapenem. Oral ciplofloxacin plus amoxicillin-clavulanate was also effective in selected low-risk patients with documented infections.

Oral antibiotics produced a successful outcome in 91% of the patients, although 86% of the patients also received G-CSF support. Whether G-CSF support is needed in low-risk patients remains uncertain. The clinical practice guidelines of the American Society of Clinical Oncology recommend that G-CSF should not be routinely used as adjunct therapy for the treatment of uncomplicated fever and neutropenia (11). Uncomplicated fever and neutropenia are defined as follows: fever of ≤10 days in duration; no evidence of pneumonia, cellulites, abscess, sinusitis or hypotension; and no uncontrolled malignancies. Oral antibiotics with ciplofloxacin plus amoxicillin-clavulanate are probably effective even if G-CSF support is not performed and can be easily administered to febrile neutropenic outpatients. In a randomized trial, oral antibiotics (ciplofloxacin plus amoxicillin-clavulanate) with early hospital discharge was compared with inpatient intravenous antibiotics (gentamicin plus tazocin) for the treatment of low-risk febrile neutropenic patients with cancer (12). This study suggested that oral antibiotics with early discharge was feasible and an alternative to conventional intravenous antibiotic regimens.

In conclusion, our trial suggested that oral antibiotic therapy with ciplofloxacin plus amoxicillin-clavulanate is effective for the treatment of low-risk febrile neutropenic patients, although the trial was prematurely terminated because of slow enrolment.

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High Body Mass Index Correlates with Increased Risk of Venous Irritation by Vinorelbine Infusion

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Background: Vinorelbine is currently one of the most active chemotherapeutic agents. However, it is also a moderate vesicant that is well known to cause venous irritation and phlebitis. We conducted this study to identify clinical risk factors related to the incidence of venous irritation caused by peripheral vinorelbine infusion.

Methods: Medical records were used to investigate retrospectively a total of 201 cases of non-small cell lung cancer treated with a chemotherapeutic regimen containing vinorelbine. Venous irritation was evaluated in every course and graded according to the National Cancer Institute Common Toxicity Criteria version 2.0. Gender, age, body mass index (BMI), chemotherapeutic regimen, dose of vinorelbine and prior chemotherapy were used as clinical variables.

Results: A total of 928 vinorelbine infusions were administered to the 201 patients, among whom venous irritation occurred in 63 (31%). The incidence of venous irritation was 28% in the normal BMI (<25) group and 45% in the high BMI (25 or more) group and the difference between the two groups was statistically significant (P = 0.037). There were no significant correlations between the incidence of venous irritation and the clinical variables except BMI. In the multivariate analysis BMI was also a significant independent variable that correlated with increased risk of venous irritation (P = 0.017).

Conclusions: Care is required when using vinorelbine to treat patients with a high BMI, especially with regard to the development of venous irritation.

Key words: vinorelbine – venous irritation – phlebitis – body mass index – lung cancer

INTRODUCTION

Vinorelbine is a semi-synthetic *Vinca* alkaloid that differs chemically from vinblastine in a modification in the catharantine moiety of the molecule (1). Vinorelbine has been shown to have low neurotoxicity and clearly higher activity than other *Vinca* alkaloids. Vinorelbine is currently one of the most active agents for the treatment of a variety of solid tumors and it is especially used for the treatment of metastatic non-small-cell lung cancer (NSCLC) (2), breast cancer (3) and Hodgkin's disease (4). The highly selective affinity of vinorelbine for mitotic tubulin-associated protein may account for this pattern of toxicity. In clinical studies, toxic side-effects frequently reported for vinorelbine included myelosuppression, constipation and peripheral neuropathy, all at mild to moderate levels.

Vinorelbine is also a moderate vesicant that is known to cause venous irritation and the incidences of venous irritation of ~10–50% have been reported in patients who received vinorelbine as a 6–30 min peripheral infusion (3,5–10). Venous irritation is generally characterized by injection site reactions, local reactions or superficial phlebitis. Symptoms include erythema, pain at the injection site, vein discoloration and tenderness along the vein (7).

Several investigators have tried to reduce the incidence of venous irritation by various methods (11–13). However, the exact mechanism responsible for this phenomenon remains unknown and the risk factors related to incidence of venous irritation caused by peripheral infusion of vinorelbine have never been reported. Since cure of patients with metastatic solid tumors is rare, an important approach for them is to decrease toxicity and to increase the effectiveness of treatment. We conducted this study to identify clinical risk factors related to the incidence of venous irritation caused by peripheral infusion of vinorelbine.

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Table 1. Patients' characteristics

Variable	No. of patients
Total No. of patients	201
Gender	
Male	155
Female	46
Age (years)	
Median	64
Range	31–81
BMI	
Normal: <25	161
High: ≥25	40
Chemotherapeutic regimen	
VNR + CDDP	123
VNR + GEM	58
VNR + CDDP + MMC	8
VNR + CDDP + GEM	5
VNR alone	7
VNR (dose, mg/m^2)	
25	198
20	3
Prior chemotherapy	
Negative	175
Positive	26

VNR, vinorelbine; CDDP, cisplatin; GEM, gemcitabine; MMC, mitomycin-C.

SUBJECTS AND METHODS

PATIENTS

We retrospectively reviewed the medical records of 201 NSCLC patients treated with a chemotherapeutic regimen containing vinorelbine between July 1999 and August 2002 at the National Cancer Center Hospital East. The chemotherapeutic regimens consisted of vinorelbine (VNR) 20–25 mg/m^2 weekly, alone or in combination with cisplatin (CDDP), gemcitabine (GEM) or mitomycin-C (MMC). VNR was diluted in 50 ml of normal saline and all infusions were administered through a peripheral vein over a period between 6 and 10 min, followed by flushing the vein with 200 ml of fluid to minimize the risk of venous irritation. All patients who received at least one dose of VNR were considered assessable for this study. The characteristics of all patients are listed in Table 1. Body mass index (BMI) (body weight in kilograms divided by the square of body height in meters) was used as the criterion for obesity. In accordance with the standard of the Japan Society for the Study of Obesity, a BMI of below 25 was defined as normal and 25 or more as high (14).

EVALUATION OF VENOUS IRRITATION

The medical records were used to evaluate venous irritation for every course and it was graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0 for injection site reaction: grade 0, none; grade 1, pain, itching or erythema; grade 2, pain or swelling, with inflammation or phlebitis; and grade 3, ulceration or necrosis that is severe or prolonged or requires surgery. Venous irritation was categorized as positive or negative, with positive being defined as experience of grade 1 or more venous irritation at least once during treatment.

STATISTICAL ANALYSIS

The correlations between the incidence of venous irritation and the clinical variables were evaluated by the chi-squared test or Fisher's exact test, as appropriate. We used gender (male, female), age (lower, <70 years; higher, ≥70 years), BMI (normal, <25, high, ≥25), chemotherapeutic regimen (VNR alone, VNR in combination: VNR + CDDP, VNR + GEM, VNR + CDDP + MMC or VNR + CDDP + GEM), dose of VNR per body (<40, ≥40 mg/body) and prior chemotherapy (positive, negative) as clinical variables. Multivariate analysis was performed by the logistic regression procedure to determine the relationship between the incidence of venous irritation and the clinical variables. P values <0.05 were considered significant. A two-sided statistical test was used in all analyses. Statistical analysis software (StatView-J Version 5.0, Macintosh) was used for the analyses.

RESULTS

INCIDENCE OF VENOUS IRRITATION

A total of 928 infusions of VNR were administered to the 201 patients. The median number of infusions per patient was four (range, 1–14). Venous irritation occurred in 63 of the 201 patients (31%) infused with VNR and after 74 of the 928 infusions (8%), with 17% of the venous irritation events (11/63) occurring after the first VNR infusion. Five of 18 high BMI patients who developed venous irritation experienced two or more episodes of venous irritation (27%). In contrast, three of 45 normal BMI patients who developed venous irritation experienced two or more episodes of venous irritation (7%). A significant difference was observed between the two groups (P = 0.036). Grade 1 venous irritation was observed in 15% (n = 11), grade 2 in 81% (n = 60) and grade 3 in 4% (n = 3). The relationship between venous irritation and the clinical variables is summarized in Table 2. The incidence of venous irritation was 28% in the normal BMI (<25) group and 45% in the high BMI (≥25) group and the difference between the two groups was statistically significant (P = 0.037). On the other hand, there were no significant correlations between the incidence of venous irritation and the clinical variables except BMI.

Table 2. Relationship between clinical variables and venous irritation

Variable	No. of patients ($n = 201$)	Incidence of venous irritation (%)	*P*-value
Gender			
Male	155	33 (51/155)	0.38
Female	46	26 (12/46)	
Age (years)			
Lower age: <70	150	34 (51/150)	0.16
Higher age: ≥70	51	24 (12/51)	
BMI			
Normal: <25	161	28 (45/161)	0.037
High: ≥25	40	45 (18/40)	
Chemotherapeutic regimen			
VNR alone	7	29 (2/7)	>0.99
VNR in combination	194	31 (61/194)	
VNR dose per body (mg)			
<40	83	31 (26/83)	0.99
≥40	118	31 (37/118)	
Prior chemotherapy			
Negative	175	32 (56/175)	0.6
Positive	26	27 (7/26)	

VNR, vinorelbine.

Multivariate Analysis

The results of the multivariate analysis of six variables (gender, age, BMI, chemotherapeutic regimen, dose of VNR and prior chemotherapy) are shown in Table 3. BMI (normal versus high) turned out to be a significant independent variable correlated with increased risk of venous irritation ($P = 0.017$).

Table 3. Multivariate analysis: relationship between clinical variables and venous irritation

Variable	Odds ratio	95% CI	*P*-value
Gender			
(male, female)	0.563	0.246–1.292	0.17
Age (years)			
(lower <70, higher ≥70)	0.518	0.242–1.108	0.09
BMI			
(normal <25, high ≥25)	2.522	1.176–5.411	0.017
Chemotherapeutic regimen			
(VNR alone, VNR in combination)	0.976	0.177–5.383	0.97
VNR dose per body (mg)			
(<40, ≥40)	0.645	0.317–1.315	0.22
Prior chemotherapy			
(negative, positive)	0.763	0.295–1.971	0.57

VNR, vinorelbine; CI, confidence interval.

DISCUSSION

We examined the clinical risk factors related to the incidence of venous irritation caused by peripheral infusion of vinorelbine. The results showed that high BMI was associated with a significantly increased risk of venous irritation over normal BMI ($P = 0.017$). The reasons for this are considered to be as follows. One is the relationship between obesity and venous thrombotic disease. Obesity, as indicated by an elevated BMI, is clearly associated with cardiovascular disease and diabetes worldwide and is also a detectable risk marker of venous thrombotic disease including superficial vein thrombosis and phlebitis (15). In our study, the incidences of history of cardiovascular diseases and venous thrombosis were 55% (22/40) in the high BMI group and 20% (32/161) in low BMI group, the difference being statistically highly significant ($P < 0.0001$). Patients with high BMI would therefore be expected to have impaired venous valve functions and be prone to superficial vein thrombosis and thus tend to have stagnant venous return as a result. Because of this, vinorelbine may adhere to the peripheral vein in the injection site and cause venous irritation and phlebitis. Another is that for patients with high BMI there may be technical difficulties with injection. The peripheral vein of patients with high BMI is often difficult to locate compared with that of patients with normal BMI and therefore there may be practically no reasonable venous access for peripheral infusion. Consequently, patients with high BMI may tend to develop minor leakage that might be a cause of venous irritation owing to failure of peripheral infusion. Moreover, as another possible risk factor related to the incidence of venous irritation, the infusion site of VNR such as the difference in the diameter of the vein may also be considered to be a risk factor. However, unfortunately, we could not clarify the relationship between infusion site of VNR and venous irritation, because this study was a retrospective analysis.

Vinorelbine is generally well tolerated and can be administered safely in outpatient settings. However, it is a moderate vesicant with the potential to cause venous irritation and phlebitis (16). Our results suggest that care is required, especially with regard to the development of venous irritation, if vinorelbine is administered through a peripheral vein to patients with a high BMI.

The use of drugs with anti-thrombotic and protective endothelial cell activity, such as heparin and defibrotide, has been investigated in an attempt to reduce the incidence of venous irritation by vinorelbine. Lozano et al. (13) administered heparin with vinorelbine. In their study, a population of 23 patients was randomized to arm A, in which vinorelbine plus 5000 U of heparin was diluted in 500 ml of normal saline and infused over 2 h, or arm B, in which vinorelbine was diluted in 50 ml of normal saline and infused over 10 min. However, arm A, with heparin, was found to be inferior to arm B in terms of pain control at the injection site (13). In another study, defibrotide was used to prevent venous irritation. A total

of 360 infusions were delivered and the incidence of venous irritation was 5%. Maisano et al. reported that defibrotide could be used to prevent venous irritation by vinorelbine (12). Incidentally, vinorelbine has been shown to be a mast cell activator and to induce histamine release in rats (17,18). On the basis of these findings, cimetidine, which inhibits histamine actions in endothelial cells, was administered prior to vinorelbine infusion and an incidence of phlebitis of only 6% among a total of 127 vinorelbine infusions was reported (11). Recently, a retrospective study reported the incidence of phlebitis with administration of vinorelbine by intravenous bolus injection (19). The results indicated that the incidence of phlebitis by bolus injection was lower than that with drip infusion but other toxicities were equivalent. Although these methods of preventing venous irritation may show promise, there have been no randomized controlled trials to verify the benefit of these methods, hence a randomized controlled study is needed to draw definite conclusions about their efficacy.

In conclusion, our study is the first to statistically investigate clinical risk factors related to the incidence of venous irritation caused by peripheral infusion of vinorelbine. Our findings indicated that high BMI is associated with a significantly increased risk of venous irritation by vinorelbine. Care is required especially in regard to the development of venous irritation when vinorelbine is administered through a peripheral vein to patients with a high BMI. We suggest that BMI (high or normal) should be considered as a stratification factor in randomized controlled trials to compare the incidence of venous irritation caused by peripheral infusion of vinorelbine. Currently in our department, a randomized controlled study of 1 min bolus injection versus 6 min drip infusion is being conducted in order to investigate the best intravenous administration of vinorelbine.

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Prognosis and histologic features of small pulmonary adenocarcinoma based on serum carcinoembryonic antigen level and computed tomographic findings

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Abstract

Objectives: In 2001, we proposed the criteria for combined evaluation of the serum carcinoembryonic antigen (CEA) level and the tumor shadow disappearance rate (TDR) to predict pathologic N0 (pN0) disease in pulmonary adenocarcinomas. The objective of the present study was to determine the prognosis and histologic features in small-sized pulmonary adenocarcinomas according to serum CEA level and TDR. **Methods**: We reviewed clinical records of 189 consecutive patients with peripheral pulmonary adenocarcinoma 3.0 cm or smaller who underwent major lung resection and systematic lymph node dissection: 50 patients with TDR 0.8 or more and normal CEA level (group I) and 139 patients with TDR <0.8 and/or elevated CEA level (group II). Among them, we investigated histologic features of 177 adenocarcinomas according to serum CEA level and TDR. **Results**: The 5-year survival rates were 95% for group I and 75% for group II ($P = 0.002$), and for pN0 patients, 97% in group I and 87% in group II ($P = 0.04$). In univariate analyses, TDR, preoperative serum CEA level, and the maximum tumor dimension on computed tomographic (CT) scan were significantly associated with prognosis. Multivariate analysis showed that only preoperative serum CEA level and TDR were significant independent prognostic factors, and the maximum tumor dimension was not significant. Group I patients developed no local recurrence, including lymph node metastases. In 25 group I adenocarcinomas 2.0 cm or smaller, no lymph node involvement, two lymphatic permeation, two vascular invasion, and one pleural involvement tumors were observed. These signs of local invasiveness were less frequent than the remaining adenocarcinomas. CT findings correlated well with histologic findings in small-sized adenocarcinomas. **Conclusions**: Combined evaluation of preoperative serum CEA level and TDR may enable us to identify minimally invasive adenocarcinomas with good prognosis. Candidates for limited lung resection without systematic lymph node dissection could be selected based on these findings.

Keywords: Lung cancer; Limited surgery; Carcinoembryonic antigen; Computerized tomography scan; Adenocarcinoma

1. Introduction

Many small-sized lung cancers, especially peripheral adenocarcinomas, have been found as a result of the introduction of computed tomographic (CT) screening for lung cancer [1]. Among them, bronchioloalveolar carcinoma (BAC) with small invasive foci has been found increasingly. Several investigators reported that these BAC type adenocarcinomas are likely to appear as localized ground glass attenuation (GGA) [2–5]. In the latest edition of World Health Organization (WHO) classification of lung tumors [6], BAC is classified as non-invasive carcinoma. If the relationship between GGA and BAC is conclusive, candidates for limited lung resection could be selected based on CT findings.

We previously reported that pathologic N0 (pN0) status in peripheral pulmonary adenocarcinoma was predictable by the combined evaluation of serum carcinoembryonic antigen (CEA) level and a radiological parameter, tumor shadow disappearance rate (TDR) [7]. TDR is the ratio of a maximum tumor area in mediastinal window setting images to that in

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pulmonary window setting images on conventional CT scans. We speculated that TDR could be interpreted as the extent of both GGA and BAC. However, we did not show in the previous study the data on the correlation between TDR and histologic features and prognostic implication of TDR.

The objective of the present study was to determine the prognosis and histologic features in small-sized pulmonary adenocarcinomas according to serum CEA level and TDR.

2. Patients and methods

2.1. Patients

From August 1992 to April 1997, 189 consecutive patients with peripheral adenocarcinoma 3.0 cm or smaller who underwent major lung resection and systematic lymph node dissection at the National Cancer Center Hospital East were reviewed. One hundred and eighty-five lobectomies, three lobectomies with bronchoplastic procedures, and one pneumonectomy were carried out. There were 89 men and 100 women. The mean age was 63 years, ranging from 33 to 84 years.

2.2. Outcome and patterns of failure

All clinical records were carefully reviewed to examine patterns of failure and outcome. The median follow-up period for the 189 patients was 57 months. The length of survival was defined as the interval in months between the day of surgical intervention and the date of death due to any cause or the last follow-up. The survival rates were calculated by the Kaplan–Meier method, and the curve differences were tested using the log-rank test. Because the median follow-up time was less than 5 years, we calculated 3- and 5-year survival rates separately.

As in our previous report [7], the following tumor dimensions on conventional CT scan was defined: pDmax, the maximum dimension of a tumor on pulmonary window setting images; pDperp, the largest dimension perpendicular

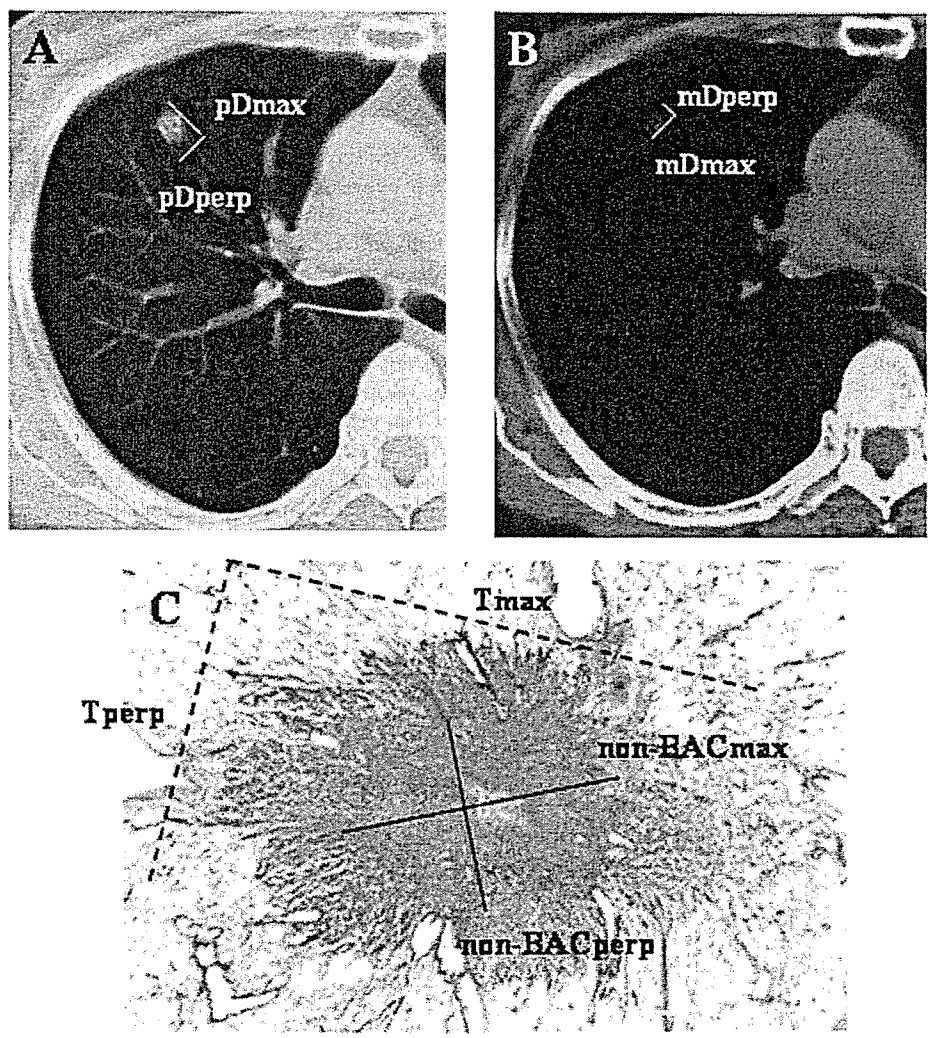

Fig. 1. We measured pDmax and pDperp on pulmonary window setting images (A), and mDmax and mDperp on mediastinal window setting images (B). We also measured Tmax, Tperp, non-BACmax, and non-BACperp at the maximum tumor dimension on low power views (hematoxylin and eosin stain, original magnification 5 ×) as illustrated (C).

to the maximum axis on pulmonary window setting images; mDmax, the maximum dimension of a tumor on mediastinal window setting images; and mDperp, the largest dimension perpendicular to the maximum axis on mediastinal window setting images (Fig. 1A and B). TDR was calculated by the following formula as previously described [7]:

$$\mathrm{TDR} = 1 - \frac{(\mathrm{mDmax}) \times (\mathrm{mDperp})}{(\mathrm{pDmax}) \times (\mathrm{pDperp})}$$

Univariate and multivariate analyses were performed by means of Cox's proportional hazards model on Stat View 5.0 (Abecus Concepts, Inc., Berkeley, CA). In multivariate analysis, forward and backward stepwise procedures were used to determine the combination of preoperatively available factors that were essential in predicting prognosis. The present multivariate analysis included five variables: gender, age, TDR, preoperative serum CEA level, and pDmax. In the statistical analyses, we used continuous variables for age, pDmax, and TDR. Because the distribution of serum CEA values was positively skewed, we used the log-transformed values to normalize the distribution.

2.3. Histologic features

Two authors (K.T. and T.Y.) reviewed 177 of 189 pathologic materials of tumors to investigate histologic features. The resected specimens were fixed with 10% formalin or 99.8% methanol injected directly through the bronchial tree or pleura to be fully expanded. Because material fixation was inappropriate for histologic review, 12 cases were excluded. We studied lymphatic permeation, vascular invasion, pleural involvement, and scar grade [8]. Additionally, we measured the following tumor parameters at the maximum tumor dimension on low power view: Tmax, the maximum tumor dimension; Tperp, the largest tumor dimension perpendicular to the maximum axis; non-BACmax, the maximum dimension of a tumor component other than BAC; and non-BACperp, the largest dimension perpendicular to the maximum axis of the non-BAC component (Fig. 1C). The BAC component was defined as a component of lepidic growth patterns of tumor cells. The non-BAC component was composed of papillary, tubular, and/or solid growth pattern components, with or without fibrotic focus, collapse, necrosis, and/or mucus in a tumor. The size of the non-BAC component was evaluated microscopically on elastica van Gieson as well as standard hematoxylin and eosin staining preparations.

In order to examine the correlation between tumor measurements on CT scans and those on pathologic specimens, we calculated Pearson's correlation coefficient (r). The χ^2-test was used to compare several variables between subgroups according to serum CEA level and TDR. In all statistical analyses, differences were considered statistically significant when $P < 0.05$.

Table 1
Clinicoradiologic characteristics of patients according to TDR and serum CEA level

	TDR ≥ 0.8 and normal CEA level (group I)	TDR < 0.8 and/or elevated CEA level (group II)
No. of patients	50	139
No. of pN0 patients (%)	49 (98)	93 (67)
Age (years, mean ± SD)	64 ± 10	62 ± 10
Gender (male/female)	14/36	75/64
CEA (ng/ml) median	2.3	3.8
(25th, 75th percentile)	(1.8, 3.3)	(2.4, 7.1)
pDmax , mm (mean ± SD)	19 ± 6	23 ± 5
pDperp, mm (mean ± SD)	15 ± 5	18 ± 5
mDmax, mm (mean ± SD)	3 ± 4	16 ± 7
mDperp, mm (mean ± SD)	2 ± 2	12 ± 6
TDR (mean ± SD)	0.96 ± 0.05	0.55 ± 0.22

3. Results

3.1. Patients

The clinical characteristics of the patients are presented in Table 1. There were 49 (98%) pN0 cases and one pathologic N1 (pN1) case in the 50 peripheral adenocarcinoma patients with TDR 0.8 or more and normal preoperative serum CEA level (group I). There were 93 (67%) pN0 cases in the 139 peripheral adenocarcinoma patients with TDR < 0.8 and/or elevated preoperative serum CEA level (group II).

3.2. Outcome and patterns of failure

The overall 3- and 5-year survival rates were 88 and 80%, respectively. The 3- and 5-year survival rates of group I patients were 98 and 95%, and those of group II patients were 84 and 75%, respectively. The survival curves showed a statistically significant difference between the two groups ($P = 0.002$; Fig. 2). In pN0 patients, the overall 3- and 5-year

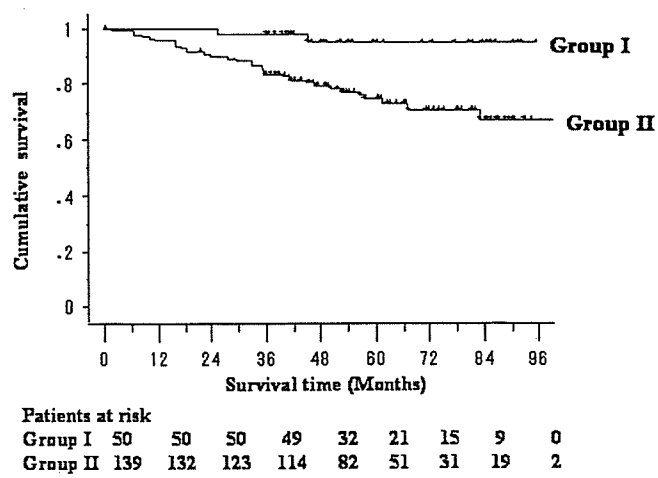

Fig. 2. Survival curves for group I and II patients. A statistically significant difference was observed between the outcomes of group I and II patients (log-rank test, $P = 0.002$).

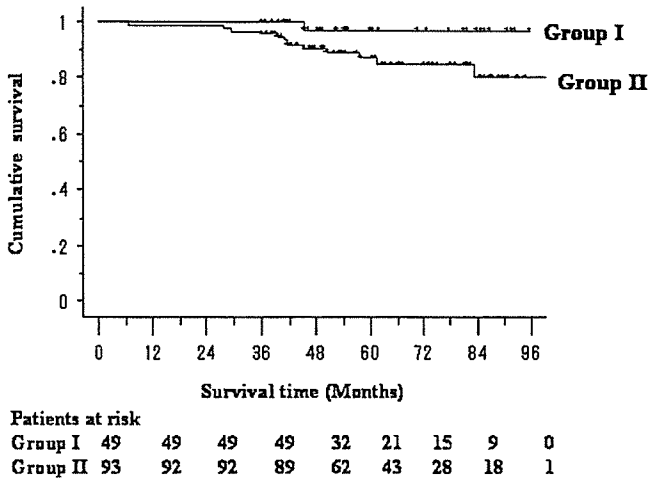

Fig. 3. Survival curves for group I and II pathologic N0 patients. A statistically significant difference was observed between the outcomes of pathologic N0 patients in groups I and II (log-rank test, $P = 0.04$).

survival rates were 97 and 91%, respectively. The 3- and 5-year survival rates of pN0 patients in group I were 100 and 97%, and those in group II were 96 and 87%, respectively. The survival curves also showed a statistically significant difference between the two groups ($P = 0.04$; Fig. 3).

Two patients in group I died during follow-up period. One developed brain and bone metastases 44 months after initial surgical resection, and died of primary lung cancer. The other was the only patient with pN1 disease and died of lower gingival cancer without any signs of primary lung cancer recurrence. No group I patients developed local recurrence including mediastinal lymph node metastases. The other 48 group I patients were alive with no signs of recurrence. Of 139 group II patients, 36 (26%) developed local and/or distant recurrences: 7 (5%) patients showed mediastinal lymph node metastases, 5 (4%) supraclavicular lymph node metastases, and 31 (22%) distant metastases (Table 2).

In univariate analyses (Table 3), TDR ($P = 0.004$), preoperative serum CEA level ($P = 0.002$), and pDmax ($P = 0.008$) were significantly associated with prognosis. In multivariate analysis, TDR ($P = 0.02$) and preoperative serum CEA level ($P = 0.03$) were shown to be independently significant prognostic factors.

Table 2
Patterns of failure in peripheral pulmonary adenocarcinoma according to TDR and serum CEA level

	TDR ≥ 0.8 and normal CEA level (group I, $n = 50$)	TDR < 0.8 and/or elevated CEA level (group II, $n = 139$)
No. of recurrence (%)	1 (2)	36 (26)
Site of recurrence (%)		
Mediastinal lymph node	0 (0)	7 (5)
Supraclavicular lymph node	0 (0)	5 (4)
Distant metastases	1 (2)	31 (22)

Table 3
Univariate analyses of prognostic factors in peripheral pulmonary adenocarcinoma

Variable	Hazard ratio	95% CI	*P*-value
Age	0.996	0.964–1.028	0.8
Gender	0.732	0.379–1.413	0.4
CEA[a]	2.231	1.346–3.696	0.002
pDmax	1.093	1.023–1.168	0.008
TDR	0.158	0.045–0.554	0.004

CI, confidence interval.
[a] Log-transformed serum CEA levels were used.

3.3. Histologic features

The relationship between tumor histologic characteristics and TDR and serum CEA level combined according to tumor size (2.0 cm or smaller versus 2.1–3.0 cm) is shown in Table 4. No lymph node involvement was found in group I tumors 2.0 cm or smaller. Although there was one pN1, no pathologic N2 cases were found in group I tumors 2.1–3.0 cm in size. There were significantly more pN0 tumors in group I than in group II. Group I tumors were more frequently negative for lymphatic permeation and vascular invasion, and there were more lower scar grade tumors (grade 1/2 versus grade 3/4) than group II tumors. Pleural involvement tended to be negative in group I tumors 2.0 cm or smaller ($P = 0.06$) and was significantly more frequently negative in group I tumors 2.1–3.0 cm in size ($P = 0.005$) compared with group II.

Statistical correlation was shown between pDmax and Tmax ($r = 0.63$, $P < 0.0001$), pDperp and Tperp ($r = 0.61$, $P < 0.0001$), mDmax and non-BACmax ($r = 0.56$, $P < 0.0001$), mDperp and non-BACperp ($r = 0.60$, $P < 0.0001$), pDmax × pDperp and Tmax × Tperp ($r = 0.62$, $P < 0.0001$), mDmax × mDperp and non-BACmax × non-BACperp ($r = 0.58$, $P < 0.0001$; Fig. 4). These findings suggested that the measurements of non-BAC component in pathologic specimens correlated well with those of tumor opacity on mediastinal window setting images.

4. Discussion

Adenocarcinoma is the most common histologic type of lung cancer, and its incidence has been increasing [9]. Many small peripheral adenocarcinomas with BAC component have, in particular, been found since helical CT scanning was introduced for lung cancer screening [1]. In the latest edition of WHO classification [6], BAC is clearly defined as an adenocarcinoma with a pure bronchioloalveolar growth pattern and no evidence of stromal, vascular or pleural invasion. Noguchi et al. [10] classified small peripheral adenocarcinomas into six subtypes (types A–F). Type A

Table 4
The relationship between tumor histologic characteristics and TDR and serum CEA level combined according to tumor size

	pDmax 0–20 mm ($n = 69$)			pDmax 21–30 mm ($n = 108$)		
	TDR ≥ 0.8 and normal CEA level (group I) (%)	TDR < 0.8 and/or elevated CEA level (group II) (%)	P^a	TDR ≥ 0.8 and normal CEA level (group I) (%)	TDR < 0.8 and/or elevated CEA level (group II) (%)	P^a
No. of tumors	25	44		21	87	
Lymph node status						
N0	25 (100)	32 (73)		20 (95)	57 (66)	
N1	0 (0)	4 (9)		1 (5)	10 (11)	
N2	0 (0)	8 (18)	0.004	0 (0)	20 (23)	0.007
Lymphatic permeation						
Negative	23 (92)	26 (59)		18 (86)	46 (53)	
Positive	2 (8)	18 (41)	0.004	3 (14)	41 (47)	0.006
Vascular invasion						
Negative	23 (92)	27 (61)		18 (86)	45 (52)	
Positive	2 (8)	17 (39)	0.006	3 (14)	42 (48)	0.005
Pleural involvement						
Negative	24 (96)	35 (80)		21 (100)	62 (71)	
Positive	1 (4)	9 (20)	0.06	0 (0)	25 (29)	0.005
Scar grade						
1 or 2	16 (64)	8 (18)		14 (67)	18 (21)	
3 or 4	9 (36)	36 (82)	0.0001	7 (33)	69 (79)	<.0001

[a] P-value in χ^2-test.

(localized BAC) and type B (localized BAC with a focus of collapsed alveolar structure) showed no lymph node metastasis, rare vascular invasion and excellent prognosis of 100% 5-year survival rate. BAC and Noguchi's types A/B could be regarded as minimally invasive, possibly in situ, adenocarcinomas.

Recently, several investigators reported that GGA on high-resolution computed tomography (HRCT) corresponded to lepidic tumor growth in the BAC component [2–5]. A greater extent of GGA in a tumor opacity on HRCT scans correlated with histopathologic lower invasiveness and better outcomes [2,11–13]. Others reported better outcomes in adenocarcinoma with a greater extent of BAC components in pathologic specimens [14,15]. Suzuki et al. [16] reported that in peripheral pulmonary adenocarcinomas 3.0 cm or smaller, a good correlation was demonstrated between the size of central fibrosis in pathologic specimens and outcome. The central fibrosis or non-BAC component in a tumor would appear as consolidation on HRCT scans [3,5].

Based on these previous findings, we can assume that histopathologically minimally invasive adenocarcinomas, possible candidates for limited surgical resection, are predictable based on CT findings: greater extent of GGA or minimal consolidation in a tumor opacity. However, no quantitative analyses comparing the size of GGA or consolidation in tumor opacities on CT scans, with the sizes of BAC or non-BAC components in pathologic specimens have been reported previously. In this study, we showed that the size of non-BAC component

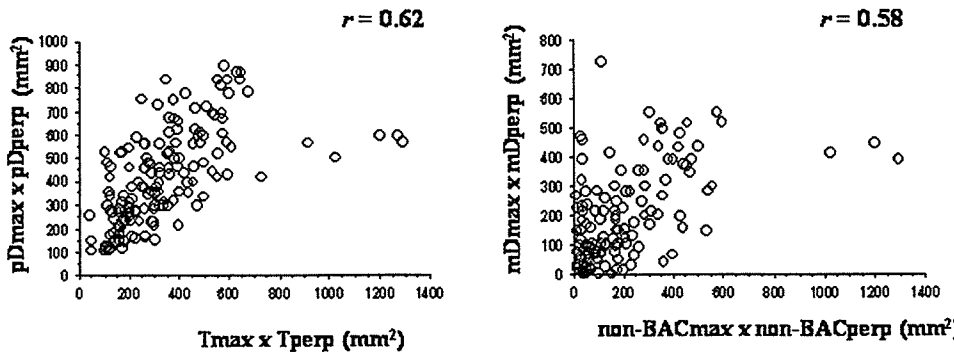

Fig. 4. Statistical correlation was shown between pDmax × pDperp and Tmax × Tperp ($r = 0.62$, $P < 0.0001$), mDmax × mDperp and non-BACmax × non-BACperp ($r = 0.58$, $P < 0.0001$).

correlated well with that of tumor opacity in mediastinal window setting images on conventional CT scans.

The most common definition of GGA is "a hazy increased attenuation of lung, but with preservation of bronchial and vascular structure" [17]. However, it is sometimes difficult to accurately define the edges of GGA when measuring its size. GGA area usually disappears in mediastinal window setting images. Measuring the size of tumor opacity in a mediastinal window-setting image is an easy and reproducible way to evaluate the size of a non-GGA area. Calculating TDR is more objective than quantifying GGA by visual estimation in a pulmonary window setting image as in previous studies [3,11,12]. However, the reproducibility and inter-observer variations in calculating TDR need to be verified in a larger prospective study. Since HRCT should yield more accurate measurements than conventional CT scans, especially in small-sized tumors, we are planning a similar study using HRCT data.

Kondo et al. [13] classified surgically resected pulmonary adenocarcinomas 2.0 cm or smaller into two types: 'air-containing type' and 'solid density type'. The air-containing type was defined as a tumor in which the tumor opacity area on a mediastinal window setting image was half or less of that on a pulmonary window setting image by visual estimation on HRCT. The solid density type, on the other hand, was defined as a tumor in which the tumor opacity area on mediastinal window setting images was more than half of that on a pulmonary window-setting image. Among 66 air-containing type adenocarcinomas, no lymph node involvement, one lymphatic permeation, one vascular invasion, and one pleural involvement tumors were observed histopathologically. The air-containing type adenocarcinoma could be considered minimally invasive. All patients with air-containing type adenocarcinomas were alive and relapse-free after a mean observation period of 851 days following resection. These results were consistent with ours. In our study, no lymph node involvement, two lymphatic permeation, two vascular invasion, and one pleural involvement tumors were observed in 25 adenocarcinomas 2.0 cm or smaller in patients with TDR 0.8 or more and normal preoperative serum CEA level. Shimosato et al. [8] initially reported prognostic impact of fibrotic focus (scar) in patients with adenocarcinomas 3.0 cm or smaller. They proposed scar grade, which correlated well with tumor invasiveness such as lymph node involvement, vascular invasion, and pleural involvement. They suggested that a small peripheral adenocarcinoma <3.0 cm with no or little collagenization (grade 1 or 2) could be considered to be in an 'early stage' of development and could be surgically curable. There were more grade 1/2 tumors in group I patients than in group II in our series. If limited lung resection is curative enough for small-sized adenocarcinomas with no or minimal invasiveness, preoperative combined evaluation of serum CEA level and TDR is useful in selecting candidates for limited lung resection.

Although a number of prognostic factors have been reported for patients with surgically resected non-small cell lung cancer, tumor size and lymph node status are considered to be the most significant prognostic factors. We showed that the outcome of group I patients was excellent (5-year survival rate: 95%) and significantly better than group II patients with completely resected adenocarcinomas 3.0 cm or smaller. Even when the prognostic impact of pathologic lymph node status was excluded, the same result was demonstrated. Multivariate analysis showed that both preoperative serum CEA level and TDR were significant independent prognostic factors. Maximum tumor dimension on CT scan was significant in univariate analysis, but not significant in multivariate analysis. These results indicate that tumor size does not have independently significant impact on prognosis in adenocarcinomas 3.0 cm or smaller.

Patients with an adenocarcinoma 2.0 cm or smaller, if preoperative serum CEA level was normal and TDR was 0.8 or more, showed no lymph node involvement (pN0) and developed no local recurrence including lymph nodes. The results suggest that limited lung resection without systematic mediastinal lymph node dissection might be acceptable for these patients. Because these factors are available preoperatively, they are useful not only to predict outcome but also to determine the extent of resection.

In summary, peripheral small-sized pulmonary adenocarcinomas predicted as pN0 by combining serum CEA level and TDR showed no mediastinal lymph node involvement and resulted in excellent outcomes without local recurrence. CT findings correlated well with histologic findings in small-sized adenocarcinomas. Signs of local invasiveness such as lymphatic permeation, vascular invasion, and pleural involvement, were rare in small-sized adenocarcinomas with normal preoperative serum CEA level and a TDR of 0.8 or more. Combined evaluation of preoperative serum CEA level and TDR may enable us to identify minimally invasive adenocarcinomas with good prognosis.

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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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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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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:

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

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:

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

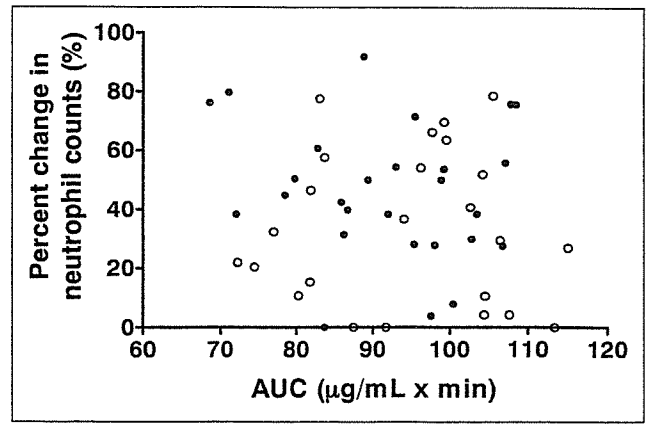

Fig 1. Relationship between the area under the curve (AUC) of cisplatin and percent changes in neutrophil counts in the elderly (○) and the non-elderly (●) patients.

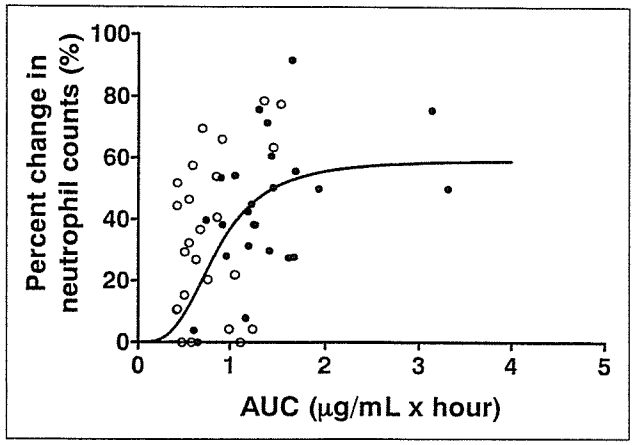

Fig 2. Relationship between the area under the curve (AUC) of docetaxel and percent changes in neutrophil counts in the elderly (○) and the non-elderly (●) patients. The solid line represents predictions by a sigmoid Emax model in the non-elderly patients.

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.

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.