

course of tumor progression, genetic alterations that were not detectable in the metastases were present in the primary tumor. These findings indicate that the primary tumor progresses genetically even after the metastasis has occurred, that is, the predominant clone of some primary tumor components no longer represents the metastatic clones that we investigated.

Using multiple microdissected specimens within individual cases that included primary and metastatic tumors, we have shown highly frequent LOH at 5q and 17p even in the lowest-grade portions (ie, BA lesions) and found identical alleles to be deleted in all portions examined in each affected primary tumor and metastatic tumor, even though quite divergent histopathologically. These results suggest that LOH at 5q and 17p may be crucial steps in the early phase of the development to lymph node metastasis and that they are retained throughout successive clonal evolutions. A similar phenomenon was previously reported by Boland *et al*<sup>23</sup> based on an analysis of tumor progression schemes in colon cancers. They used multiple microdissected samples of colonic tumors showing cross-sections of the 'adenoma-carcinoma sequence' and detected a clear, abrupt occurrence of LOH at 5q at the transition phase from normal epithelium to adenoma. We observed LOH on at least one of the two loci on 5q and/or 17p uniformly in almost all cases examined (11/12; 92%). However, it is uncertain why such presumably early lesions are not present in all tumors. A number of cell types are thought to be potential precursors of lung cancers, and different initiation events may be involved depending on the differentiation pathway to which they are committed. Thus, certain cell types may not require inactivation of all putative tumor suppressor genes on 5q and 17p.

Previous studies have shown allelic loss at the 17p loci to be involved at a relatively early stage of NSCLC,<sup>8,24,25</sup> and its loss may be associated with the genesis of NSCLC. *p53* is believed to play a role as a 'guardian' that maintains the integrity of the genome by participating in the DNA damage checkpoints in the cell cycle. Inactivation of *p53* has been reported to lead to increased frequency of mutations, chromosomal rearrangements, and abnormal chromosomal segregations.<sup>26-29</sup> Recent studies have suggested that the LOH at specific chromosomal loci, 1p, 3p, 5q, 9p, 17q, and 22q, is associated with a worse prognosis of NSCLC, although studies of patients from different populations have yielded conflicting results.<sup>14,30-39</sup> LOH at the *APC/MCC* gene cluster at chromosome 5q has been reported to correlate with poorer survival of patients with NSCLC.<sup>38</sup> In the present study, the tumors were small but were associated with lymph node metastasis, and a worse prognosis was assumed. Seven of nine informative cases (78%) showed allelic losses at 5q in all foci, including BA lesions. Our previous study also concluded that this

deletion is a relatively early event in the progression of adenocarcinoma of the lung.<sup>6</sup> The high prevalence of 5q deletion in this study might indicate that 5q loss plays an important role in the progression of metastatic tumors and that it was determined in the early stage.

Although we showed frequent LOH at 18q in the tumors examined, approximately 40% of allelic losses were found in either metastatic lesions or invasive and metastatic lesions, not in all portions of each affected primary tumor and metastatic tumor examined. Therefore, LOH at 18q appears to have a role as late event in the metastatic progression of adenocarcinomas mixed BA and other subtypes of the lung. Shiseki *et al*<sup>8</sup> reported that loss at 18q plays an important role in the progression of NSCLC based on a comparison of stage I NSCLC and brain metastases. Lymph node metastases, most malignant portions, were shown to carry 18q deletions at even higher frequency than 5q or 17p deletions in the present study. However, it should be noted that accumulation of LOH at 18q occurred at various stages of tumor progression within individual tumors toward lymph node metastasis, that is, some LOH at 18q occurred in BA lesions, and some in metastatic lesions. This indicated a clear distinction from LOH at 5q and 17p, especially at 5q. Since approximately 60% of 18q deletions are present in all portions of individual tumors, it remains unclear whether LOH at 18q has a role both as an early event and a late event or acts at various steps in tumors that progress to lymph node metastasis.

In summary, we examined the topographical distribution of LOH on 10 chromosome arms, and the results suggest that tumor cells accumulate genetic alterations as they evolve from the BA lesions to the invasive and metastatic lesions. Early occurrence of 5q and/or 17p deletions and successive clonal expansion during the progression of individual tumors was inferred. By contrast, LOH at 18q seemed to be acquired at various stages during tumor progression to metastasis. Similar studies analyzing more genetic loci in a larger number of cases are warranted. Furthermore, since the lung cancers resulted from various genetic and epigenetic alterations, it would also be interesting to examine the topographical differences in other genetic or epigenetic changes, such as DNA methylation.

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## Randomized Trial of Oral Versus Intravenous Antibiotics in Low-risk Febrile Neutropenic Patients with Lung Cancer

Seiji Niho, Yuichiro Ohe, Koichi Goto, Hironobu Ohmatsu, Taketoshi Matsumoto, Kaoru Kubota, Ryutaro Kakinuma and Yutaka Nishiwaki

Division of Thoracic Oncology, National Cancer Center Hospital East, Chiba, Japan

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**Background:** Neutropenic fever is one of the most serious adverse effects of cancer chemotherapy. Neutropenia may cause a life-threatening bacterial infection. Therefore, febrile neutropenic inpatients are empirically treated with intravenous broad-spectrum antibiotics. Recently, several studies have suggested the presence of low-risk groups among febrile neutropenic patients.

**Methods:** A prospective randomized trial was conducted to compare treatment with oral ciprofloxacin (200 mg) and amoxicillin-clavulanate (375 mg) administered every 8 h against that with intravenous ceftazidime (1 g) administered every 12 h in low-risk febrile neutropenic patients with lung cancer. All patients received chemotherapy and antibiotic therapy while being hospitalized.

**Results:** A total of 177 patients with lung cancer agreed to participate in this study prior to undergoing chemotherapy. Among them, a total of 36 neutropenic patients with 42 febrile episodes were enrolled in the study. Treatment was successful without the need for modification in 91% of the episodes in patients receiving the oral regimen and 79% of the episodes in patients receiving the intravenous regimen. No treatment-related deaths occurred. One patient developed nausea while receiving the oral regimen, so the oral regimen was changed to the intravenous regimen in this patient.

**Conclusions:** This prospective study suggested that treatment with oral antibiotics ciprofloxacin plus amoxicillin-clavulanate was effective for low-risk febrile neutropenic patients after chemotherapy.

*Key words: oral antibiotics – low-risk – febrile neutropenia*

### INTRODUCTION

Neutropenic fever is one of the most serious adverse effects in cancer chemotherapy. Neutropenia may cause a life-threatening bacterial infection. The risk of infection increases in patients with a neutrophil count of  $<1000/\text{mm}^3$  (1). As a result, most cancer patients remain in hospital after undergoing chemotherapy in Japan, and empirical broad-spectrum intravenous antibiotics are administered to febrile neutropenic patients. This approach is effective in reducing morbidity and mortality but is associated with toxicity related to intravenous antibiotics, as well as physical and psychological discomfort for the patient. In addition, parenteral antibiotic administration requires insertion of an intravenous catheter, which carries a risk of infection. Prolonged hospitalization may cause infec-

tion to drug-resistant organisms, is expensive, and has a detrimental effect on quality of life.

Recently, several studies have suggested the presence of low-risk groups among febrile neutropenic patients (2-4). Medical complications were less frequent overall for patients whose neutropenia ( $<500/\text{mm}^3$ ) resolved in 7 days or less, compared to other patients (4). A study demonstrated that neutropenia lasted for 1 week or less in 85% of the patients selected using the following exclusion criteria: hepatic insufficiency (alanine aminotransferase activity  $>$  four times normal), a history of recurrent pyrexia of undetermined origin (PUO), shock (systolic blood pressure  $<80$  mmHg or peripheral circulatory failure), any other comorbid conditions requiring hospitalization (except for anemia or thrombocytopenia) and the expectation of prolonged neutropenia ( $>7$  days) based on the presence of aplastic anemia, myelodysplasia, leukemia or other causes (5). Patients who did not meet any of these exclusion criteria were considered to belong to a low-risk group. A randomized trial comparing oral ciprofloxacin and amoxicillin-clavulanate with

For reprints and all correspondence: Seiji Niho, Division of Thoracic Oncology, National Cancer Center Hospital East, Kashiwanoha 6-5-1, Kashiwa, Chiba 277-8577, Japan. E-mail: siniho@east.ncc.go.jp

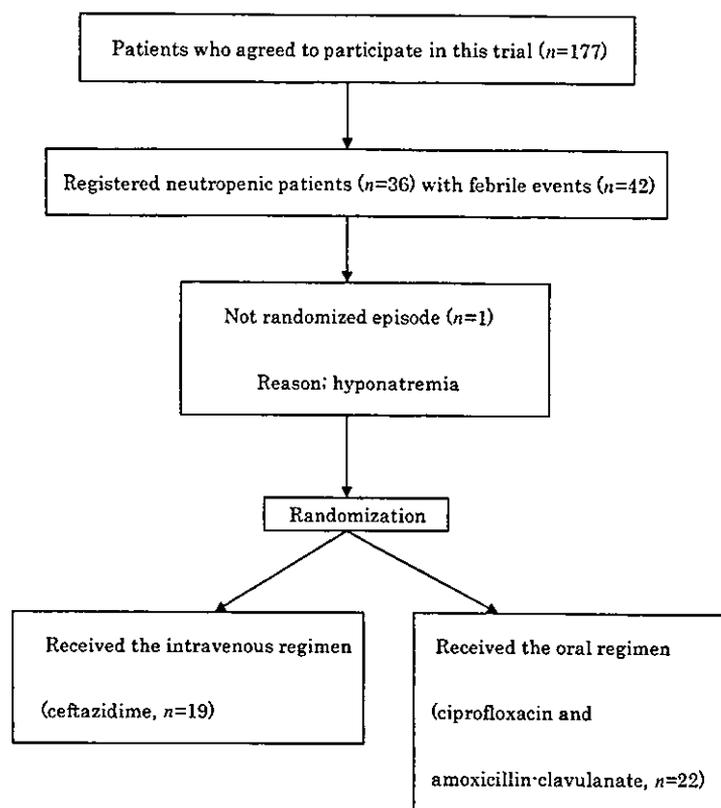


Figure 1. Study flow diagram.

intravenous aztreonam and clindamycin was conducted in these low-risk febrile neutropenic patients (6). This trial demonstrated that oral antibiotics were as effective as intravenous ones.

We conducted a randomized trial to compare oral ciprofloxacin and amoxicillin-clavulanate with intravenous ceftazidime, which was empirically used, in low-risk febrile neutropenic patients with lung cancer. The combination of ciprofloxacin and amoxicillin-clavulanate provides sufficient coverage against gram-negative enteric bacilli and gram-positive cocci. The aim of our trial was to determine whether an oral regimen was an acceptable alternative to an intravenous regimen in low-risk patients.

## PATIENTS AND METHODS

### CRITERIA FOR ELIGIBILITY

Eligible patients included those with lung cancer and neutropenia after having undergone platinum-based chemotherapy. Patients were required to have a single axillary temperature of  $37.5^{\circ}\text{C}$  or higher after platinum-based chemotherapy, an absolute leukocyte count  $\leq 1000/\text{mm}^3$  or a neutrophil count  $\leq 500/\text{mm}^3$ . Other criteria included an age of 20 years or more and an ECOG performance status (PS) of between 0 and 2 (inclusive). The exclusion criteria included the following conditions: previous anaphylactic reactions or hypersensitivity to

any of the antibiotics used or related products; antibiotic treatment within the preceding 96 h; prior administration of non-steroidal anti-inflammatory drugs (NSAIDs); recurrent PUO; renal insufficiency (serum creatinine  $\geq 2.5$  mg/dl or need for dialysis); hepatic insufficiency (aspartate aminotransferase/alanine aminotransferase levels  $>$  four times the normal value); systolic blood pressure  $\leq 90$  mmHg or peripheral circulatory failure; uncontrolled hypercalcemia; altered sensorium; respiratory rate  $\geq 30$  breaths/min; serum sodium  $\leq 128$  mg/dl; and the inability to take oral medications because of painful mouth ulcers, intestinal malabsorption or severe nausea and vomiting. All patients were required to provide their written informed consent prior to undergoing chemotherapy, and the institutional review board at the National Cancer Center approved the study's protocol.

### TREATMENT PLAN

All patients received chemotherapy and antibiotic therapy on an inpatient basis. The baseline evaluation included a physical examination (blood pressure, pulse and respiratory rate, temperature). Cultures were obtained of blood, sputum, throat, urine and feces (anal swabs). Patients were randomly assigned to one of two regimens using consecutive sealed envelopes. The oral regimen consisted of ciprofloxacin (200 mg) plus amoxicillin-clavulanate (375 mg) administered every 8 h, while the intravenous regimen consisted of ceftazidime (1 g) administered every 12 h. Granulocyte colony-stimulating

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)		
$\leq 100/\text{mm}^3$	3	0
101-500/ $\text{mm}^3$	14	12
501-1000/ $\text{mm}^3$	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 ciprofloxacin. 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  $\geq 37^\circ\text{C}$  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% <i>P</i> = 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 *Pseudomonas 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 epi-

sodes 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 ciprofloxacin 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 ciprofloxacin plus amoxicillin-clavulanate was compared with intravenous ceftazidime (8). These regimens were almost identical to those in our trial. In the other trial, oral ciprofloxacin plus amoxicillin-clavulanate was compared with intravenous ceftriaxone plus amikacin (9). Both trials demonstrated that oral therapy with ciprofloxacin 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 chronic 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  $\geq 21$  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 ciprofloxacin 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 ciprofloxacin 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  $\leq 10$  days in duration; no evidence of pneumonia, cellulites, abscess, sinusitis or hypotension; and no uncontrolled malignancies. Oral antibiotics with ciprofloxacin 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 (ciprofloxacin 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 ciprofloxacin 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

Kiyotaka Yoh, Seiji Niho, Koichi Goto, Hironobu Ohmatsu, Kaoru Kubota, Ryutaro Kakinuma and Yutaka Nishiwaki

Division of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan

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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 catharanthine 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.

For reprints and all correspondence: Kiyotaka Yoh, Division of Thoracic Oncology, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577, Japan. E-mail: kyoh@east.ncc.go.jp

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 <sup>2</sup> )	
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<sup>2</sup> 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 ( $P = 0.017$ ).

#### 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

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.

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

Kazuya Takamochi<sup>a,\*</sup>, Junji Yoshida<sup>b</sup>, Mitsuyo Nishimura<sup>b</sup>, Tomoyuki Yokose<sup>c</sup>, Satoshi Sasaki<sup>d</sup>, Yutaka Nishiwaki<sup>b</sup>, Kazuya Suzuki<sup>a</sup>, Kanji Nagai<sup>b</sup>

<sup>a</sup>First Department of Surgery, Hamamatsu University School of Medicine, 1-20-1 Handayama, Shizuoka, Hamamatsu 431-3192, Japan

<sup>b</sup>Division of Thoracic Oncology, National Cancer Center Hospital East, Chiba, Japan

<sup>c</sup>Pathology Division, National Cancer Center Research Institute East, Chiba, Japan

<sup>d</sup>National Institute of Health and Nutrition, Tokyo, Japan

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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.

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**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

\* Corresponding author. Tel.: +81-53-435-2276; fax: +81-53-435-2272.  
E-mail address: ktakamoc@hama-med.ac.jp (K. Takamochi).

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

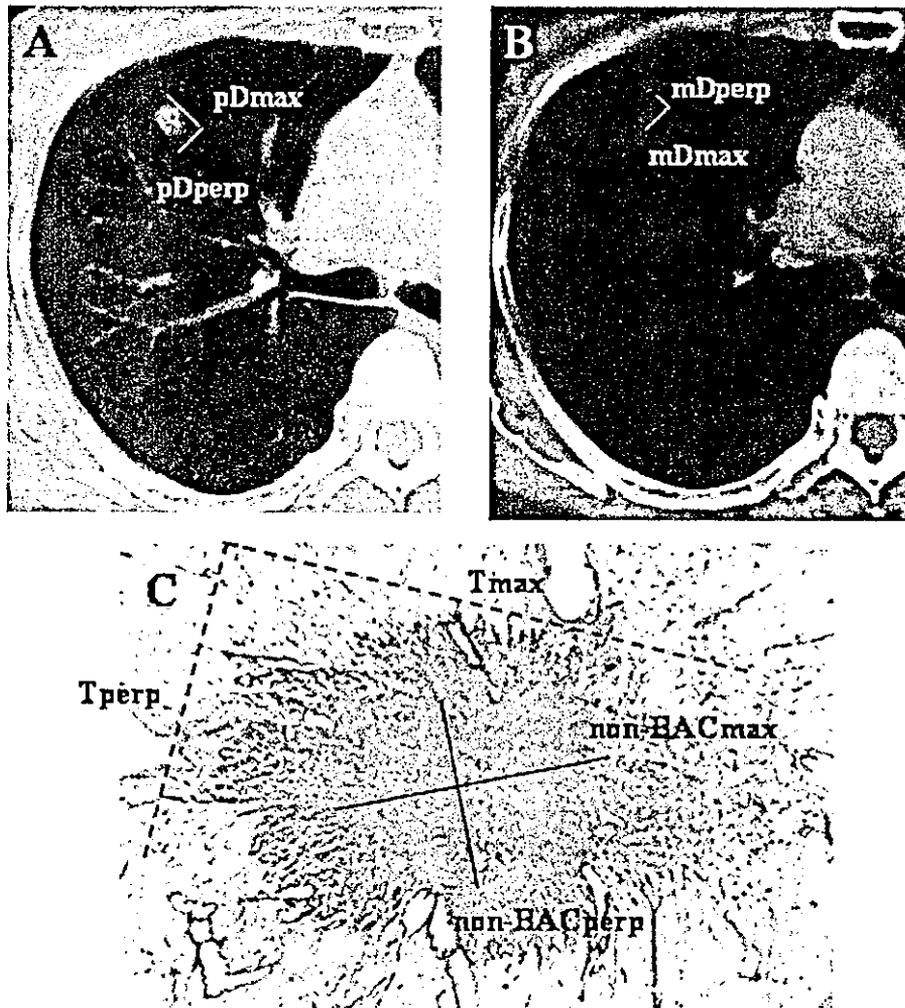


Fig. 1. We measured pDmax and pDperp on pulmonary window setting images (A), and mDmax and mDperp on mediastinal window setting images (B). We also measured Tmax, Tperp, non-BACmax, and non-BACperp at the maximum tumor dimension on low power views (hematoxylin and eosin stain, original magnification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

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

Univariate and multivariate analyses were performed by means of Cox's proportional hazards model on Stat View 5.0 (Abacus 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  $\chi^2$ -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 $\geq$ 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 $\pm$ SD)	64 $\pm$ 10	62 $\pm$ 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 $\pm$ SD)	19 $\pm$ 6	23 $\pm$ 5
pDperp, mm (mean $\pm$ SD)	15 $\pm$ 5	18 $\pm$ 5
mDmax, mm (mean $\pm$ SD)	3 $\pm$ 4	16 $\pm$ 7
mDperp, mm (mean $\pm$ SD)	2 $\pm$ 2	12 $\pm$ 6
TDR (mean $\pm$ SD)	0.96 $\pm$ 0.05	0.55 $\pm$ 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

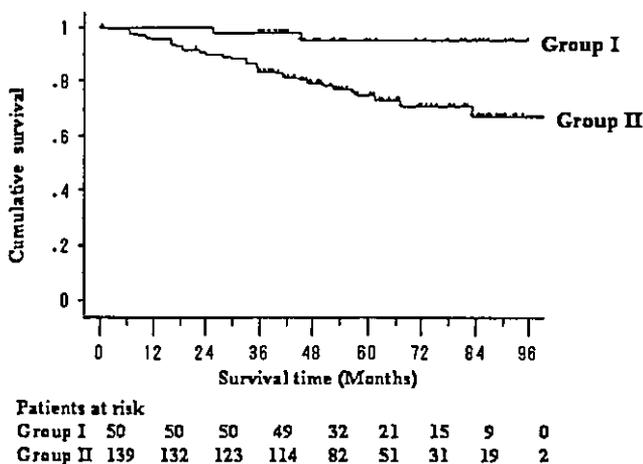
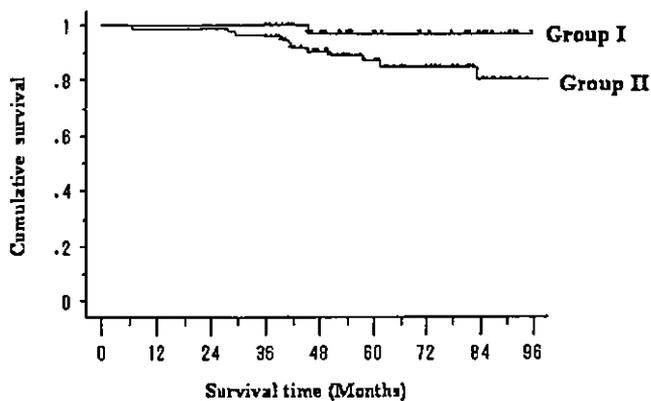


Fig. 2. Survival curves for group I and II patients. A statistically significant difference was observed between the outcomes of group I and II patients (log-rank test,  $P = 0.002$ ).



Patients at risk									
Group I	49	49	49	49	32	21	15	9	0
Group II	93	92	92	89	62	43	28	18	1

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 $\geq 0.8$ 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)
<i>Site of recurrence (%)</i>		
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 <sup>a</sup>	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.

<sup>a</sup> 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  $\times$  pDperp and Tmax  $\times$  Tperp ( $r = 0.62$ ,  $P < 0.0001$ ), mDmax  $\times$  mDperp and non-BACmax  $\times$  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)		P <sup>a</sup>	pDmax 21–30 mm (n = 108)		P <sup>a</sup>
	TDR ≥ 0.8 and normal CEA level (group I) (%)	TDR < 0.8 and/or elevated CEA level (group II) (%)		TDR ≥ 0.8 and normal CEA level (group I) (%)	TDR < 0.8 and/or elevated CEA level (group II) (%)	
No. of tumors	25	44		21	87	
<i>Lymph node status</i>						
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
<i>Lymphatic permeation</i>						
Negative	23 (92)	26 (59)		18 (86)	46 (53)	
Positive	2 (8)	18 (41)	0.004	3 (14)	41 (47)	0.006
<i>Vascular invasion</i>						
Negative	23 (92)	27 (61)		18 (86)	45 (52)	
Positive	2 (8)	17 (39)	0.006	3 (14)	42 (48)	0.005
<i>Pleural involvement</i>						
Negative	24 (96)	35 (80)		21 (100)	62 (71)	
Positive	1 (4)	9 (20)	0.06	0 (0)	25 (29)	0.005
<i>Scar grade</i>						
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

<sup>a</sup> P-value in  $\chi^2$ -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

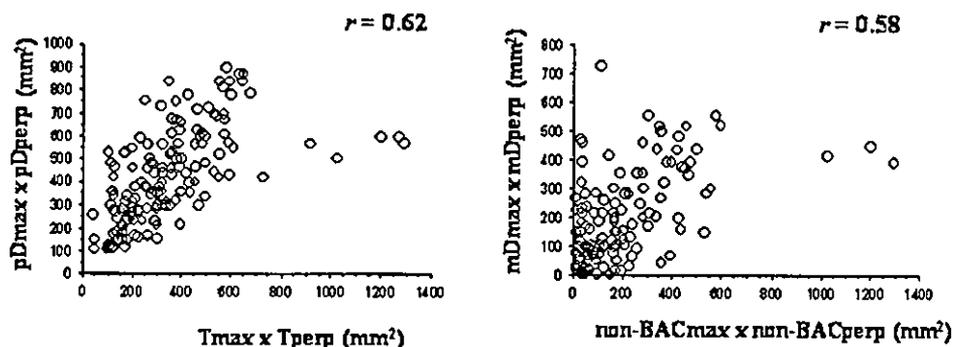


Fig. 4. Statistical correlation was shown between pDmax × pDperp and Tmax × Tperp ( $r = 0.62$ ,  $P < 0.0001$ ), mDmax × mDperp and non-BACmax × non-BACperp ( $r = 0.58$ ,  $P < 0.0001$ ).

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

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

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

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

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### ABSTRACT

#### Purpose

Following phase I studies of docetaxel and cisplatin in patients with non-small-cell lung cancer, the recommended doses of docetaxel were different for elderly ( $\geq 75$  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<sup>2</sup> for elderly and non-elderly patients, respectively. All patients received 25 mg/m<sup>2</sup> 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.<sup>1-5</sup> Furthermore, many elderly patients have not been referred

to medical oncologists and have been under-treated in oncologic practice because of concerns over toxicity.<sup>5-9</sup> Frequencies and severities of toxicity associated with cancer chemotherapy are higher in elderly patients than in younger patients.<sup>10-14</sup> 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.<sup>15-18</sup> In addition, few studies have focused on the alterations of