研究成果の刊行に関する一覧表

雑誌

	発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
51	Yoshida, T., Okamoto, I., Iwasa, T., Fukuoka, M., Nakagawa, K.	The anti-EGFR monoclonal antibody blocks cisplatin-induced activation of EGFR signaling mediated by HB-EGF.	FEBS Lett	582(30)	4125-4130	2008
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研究代表者	田村　友秀	国立がんセンター中央病院
研究分担者	西條　長宏	国立がんセンター東病院
	西脇　　裕	国立がんセンター東病院
	森　　清志	栃木県立がんセンター
	岡本　浩明	横浜市立市民病院
	野田　和正	神奈川県立がんセンター
	横山　　晶	新潟県立がんセンター新潟病院
	樋田　豊明	愛知県がんセンター中央病院
	根来　俊一	兵庫県立がんセンター
	今村　文生	地方独立行政法人大阪府立病院機構 大阪府立成人病センター
	松井　　薫	地方独立行政法人大阪府立病院機構 大阪府立呼吸器・アレルギー医療センター
	中川　和彦	近畿大学医学部内科学教室腫瘍内科部門
	河原　正明	独立行政法人国立病院機構 近畿中央胸部疾患センター
	木浦　勝行	岡山大学大学院医歯薬学総合研究科

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Circulating Endothelial Cells in Non-small Cell Lung Cancer Patients Treated with Carboplatin and Paclitaxel

Makoto Kawaishi, MD, Yutaka Fujiwara, MD,† Tomoya Fukui, MD,* Terufumi Kato, MD,* Kazuhiko Yamada, MD,† Yuichiro Ohe, MD, PhD,† Hideo Kunitoh, MD, PhD,† Ikuo Sekine, MD, PhD,† Noboru Yamamoto, MD, PhD,† Hiroshi Nokihara, MD, PhD,† Takeshi Watabe, PhD,‡ Yuji Shimoda, PhD,‡ Tokuzo Arao, MD, PhD,§ Kazuto Nishio, MD, PhD,§ Tomohide Tamura, MD† and Fumiaki Koizumi, MD, PhD**

Introduction: Circulating endothelial cells (CECs) increase in cancer patients and play an important role in tumor neovascularization.
Methods: This study was designed to investigate the role of CEC as a marker for predicting the effectiveness of a carboplatin plus paclitaxel based first line chemotherapy in advanced non-small cell lung cancer (NSCLC).
Results: The CEC count in 4 ml of peripheral blood before starting chemotherapy (baseline value) was significantly higher in NSCLC patients, ranging from 32 to 4501/4 ml (n = 31, mean ± SD = 595 ± 832), than in healthy volunteers (n = 53, 46.2 ± 86.3). We did not detect a significant correlation between the CEC count and estimated tumor volume. CECs were significantly decreased by chemotherapy as compared with pretreatment values (175.6 ± 24 and 173.0 ± 24, day +8, +22, respectively). We investigated the correlation between baseline CEC and the clinical effectiveness of chemotherapy. CEC values are significantly higher in patients with clinical benefit (partial response and stable disease, 516 ± 458, 870.8 ± 1215, respectively) than in progressive disease patients (211 ± 150). Furthermore, a statistically significant decrease in CECs, on day 22, was observed only in patients with partial response. Patients who had a baseline CEC count greater than 400/4 ml showed a longer progression-free survival (>400, 271 days [range: 181–361] versus <400, 34 [range: 81–186], p = 0.019).
Conclusion: CEC is suggested to be a promising predictive marker of the clinical efficacy of the CBDCA plus paclitaxel regimen in patients with NSCLC.

Key Words: Circulating endothelial cell, NSCLC, Chemotherapy.

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*Shien-Lab; †Medical Oncology, National Cancer Center Hospital, Chuo-ku, Tokyo, Japan; ‡Center for Molecular Biology and Cytogenetics, SRL Inc., Shinmachi, Hino-shi, Tokyo; and §Department of Genome Biology, Kinki University School of Medicine, Osaka-Sayama-shi, Osaka, Japan.
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Address for correspondence: Fumiaki Koizumi, MD, PhD, Shien-Lab, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo, Japan. E-mail: fkoizumi@gan2.res.ncc.go.jp

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Angiogenesis plays a critical role in the growth and metastasis of solid tumors.[1] The clinical importance of angiogenesis in human tumors has been demonstrated by several reports indicating a positive relationship between the blood vessel density in the tumor mass and poor prognosis, i.e., survival, in patients with various types of cancers including non-small cell lung cancer (NSCLC).[2–6] Furthermore, Natsume et al.[7] reported the antitumor activities of anticancer agents to be less active against vascular endothelial growth factor-secreting cells (SBC-3/VEGF), in vivo as compared with its mock transfectant (SBC-3/Neo). In recent years, antiangiogenic agents have also been demonstrated to be active against a variety of malignancies, including lung, colorectal, and renal cancer.[8–10] Thus, angiogenesis is a promising target for cancer treatment and is related to the prognosis and efficacy of these drugs, though the tumor vessel biomarkers which predict the effectiveness of antiangiogenic agents and other anticancer agents are not always useful and have not become well-established.

Circulating endothelial cells (CECs) have been recognized as a useful biomarker for vascular damage. CECs are increased in cardiovascular disease, vasculitis, infectious disease, and various cancers.[11–14] Recently, CECs were found to be more numerous and viable in cancer patients than in healthy subjects.[14,15] Furthermore, elevated CECs in cancer patients were found to be nearly normalized when the tumor was removed surgically or with chemotherapy.[15] Therefore, most CECs are considered to be disseminated tissue endothelial cells in the tumors and the CEC number may reflect the extent of tumor angiogenesis. Indeed, the CEC level has been demonstrated to correlate with the plasma level of VEGF, one of the pivotal factors promoting tumor angiogenesis.[15] Mancuso et al. reported that CEC kinetics and viability are promising predictors of the response to chemotherapy with antiangiogenic activity in patients with advanced breast cancer.[16] Thus, CEC is likely to be a useful marker for predicting the effectiveness of chemotherapy as a noninvasive angiogenesis marker.

NSCLC is the leading cause of cancer-related death worldwide. NSCLC accounts for approximately 50% of patients presenting with unresectable advanced stage,[17] and platinum-based chemotherapy offers only a small improve-

ment in survival with advanced NSCLC.[18,19] Over the past decade, several new agents against NSCLC have become available, including the taxanes, gemcitabine, vinorelbine, and irinotecan. The combination of platinum and these new agents has resulted in a high response rate and prolonged survival compared with older chemotherapy regimens (e.g., vindesine, mitomycin, ifosfamide, with cisplatin). Therefore, these regimens are considered standard chemotherapy for advanced NSCLC.[20–26] Although new agents have different mechanisms of action, these combination regimens have not been administered based on the biologic characteristics of each tumor.

Paclitaxel inhibits several endothelial cell functions in vitro such as proliferation, migration, morphogenesis, and metalloprotease production.[27–29] These activities result in antiangiogenic activity in in vivo xenograft models.[27,30] Interestingly, human endothelial cells are more sensitive to paclitaxel than other cellular types.[29] We hypothesized that the CEC value is associated with tumor neovascularization, which is one of the targets of paclitaxel. In the present study, we investigated whether the CEC count at baseline is associated with the effectiveness of the CDDP plus paclitaxel regimen in patients with advanced-stage NSCLC.

MATERIALS AND METHODS

Patients

Patients with histologically or cytologically documented advanced NSCLC were eligible for this study. Each patient was required to meet the following criteria: (1) no prior treatment including chemotherapy, surgery, irradiation, or any fluid drainage; (2) no prior general anesthesia for diagnostic procedures including mediastinoscopy or thoracoscopy; (3) no concomitant diseases including ischemic heart diseases, systemic vasculitis, pulmonary hypertension, or serious complications including infectious disease or diabetes; (4) written informed consent. The trial document was approved by the institutional review board. The clinical characteristics of the patients are shown in Table 1.

TABLE 1. Baseline Characteristics of the Patients

Characteristic	$N = 31$ No. (%)
Gender	
Male	17 (55)
Female	14 (45)
Median age (yr)	60
Range	43–71
ECOG performance status	
0	18 (58)
1	13 (42)
Stage	
IIIA	2 (6)
IIIB	7 (23)
IV	22 (71)
Histology	
Adenocarcinoma	23 (74)
Squamous cell carcinoma	4 (13)
Others	4 (13)

Treatment Schedule and Response Evaluation

All patients were treated according to the following chemotherapeutic regimen: paclitaxel at 200 mg/m^2 over a 3-hour period followed by carboplatin at a dose with an area under the curve of 6 on day 1, repeated every 3 weeks. The treatment was repeated for three or more cycles unless the patients met the criteria for progressive disease (PD) or experienced unacceptable toxicity.

The major axis (a) and minor axis (b) of the tumor mass in each patient were measured with computed tomography. Estimated tumor volume (ETV) was calculated using the following formula; ETV = $4/3 \times \pi\ (a/2 \times b/2) \times (a/2 + b/2)/2$. Computed tomography examinations were performed before treatment and with every one or two cycles of chemotherapy. Response was evaluated according to the RECIST, and tumor markers were excluded from the criteria.[31]

Assay for CEC

Blood samples from NSCLC patients and healthy volunteers were drawn into a 10-ml Cellsave Preservative Tube (Immunicon Corp. Huntingdon Valley, PA) for CEC enumeration. The CEC protocol used was approved by the Institutional Review Board and written informed consent was obtained from each subject. Samples from NSCLC were obtained before (baseline) and 8 and 22 days after starting chemotherapy. Samples were kept at room temperature and processed within 42 hours after collection. All evaluations were performed without knowledge of the clinical status of the patients. The CellTracks system (Immunicon Corp) which consists of CellTracks AutoPrep system and the CellSpotter Analyzer system was used for endothelial cell enumeration.[32,33] In this system, CD146+/DAPI+/CD105-PE+/CD45APC- cells are defined as CECs. Briefly, cells which express CD146 were immunomagnetically captured using ferrofluids coated with CD146 antibodies. The enriched cells were then labeled with the nuclear dye 4V,6-diamidino-2-phenylindole (DAPI), CD105 antibodies conjugated to phycoerythrin (CD105-PE), and the pan-leukocyte antibody CD45 conjugated to allophycocyanin (CD45-APC). In this system, the CD146-enriched, fluorescently labeled cells were identified as CECs when the cells exhibited the DAPI+/CD105+/CD45- phenotype. We performed CEC enumeration twice, using the same sample, and calculated the mean value.

Statistical Analyses

This study was carried out as exploratory research for detecting CECs from NSCLC patients. The number of enrolled patients was therefore not precalculated. Spearman's correlation analysis was performed to investigate the correlation between CEC count and ETV. Between-group comparisons were made using the t test. The association between CEC count and progression free survival (PFS) was estimated using the Kaplan-Meier method. The log-rank test was used to assess the survival difference between strata. Differences were considered statistically significant at $p < 0.05$.

RESULTS

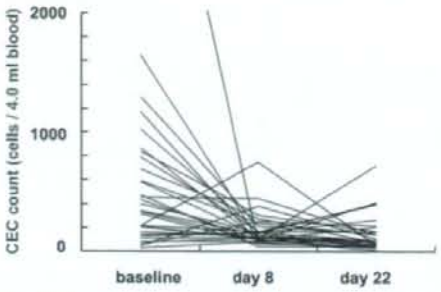
Patient Characteristics

A total of 32 patients were enrolled in the study between August 2005 and March 2006 (Table 1). One patient withdrew consent to participate. Table 1 summarizes the characteristics of the study population. The median age of the patients was 60 years (range, 43–71). The histologic and/or cytologic diagnosis was adenocarcinoma in 23 patients (74.2%), squamous cell carcinoma in 4 (12.9%), and unclassified NSCLC in 4 (12.9%). There were 17 males (54.8%). The clinical stage was IIIA in 2 patients (6.5%), IIIB in 7 (22.6%), and IV in 22 (71.0%).

Ninety-two CEC samples from 31 patients (three samples per patient) were obtained and analyzed. One sample, obtained 22 days after treatment, was not examined because of inadequate collection.

Quantification of CEC

In 31 advanced NSCLC patients, CECs ranged from 32 to 4501 cells/4.0 ml of blood, mean ± SD = 595 ± 832 at baseline. CEC counts were elevated in a large portion of patients with NSCLC as compared with healthy volunteers (n = 53, mean ± SD = 46.2 ± 86.3/4 ml). Case 21 had an exceptionally high CEC count (4501 at baseline). We did not detect a significant correlation between the CEC count and ETV in the 28 assessable patients (p = 0.84, Figure 1). The analysis of CECs during the first course of treatment showed CEC levels to be reduced by CBDCA plus paclitaxel chemotherapy as compared with pretreatment values (176 ± 141 at 8 days and 173 ± 189 at 22 days after treatment) (Figure 2). These reductions were significant (p = 0.011 on day 8 and p = 0.04 on day 22), but there was no significant difference between CEC amounts on day 8 versus day 22 (p = 0.476). There was no difference in the amount of CEC at baseline when patients were subgrouped according to characteristics, such as sex, smoking history, histologic type, and clinical stage. Furthermore, there was no correlation of CEC amounts with the blood examination data (e.g., number of white blood cells, neutrophils, lymphocytes, hemoglobin, platelets, albumin, LDH, CRP, CEA, CYFRA).



	baseline	day 8	day 22
mean ± SD	595± 832	176± 141 *	173 ± 189 *

FIGURE 2. Circulating endothelial cell (CEC) levels during the first course of CDDP plus paclitaxel chemotherapy. *p < 0.05 versus values at baseline.

CEC Amounts and Objective Tumor Response to Chemotherapy

Thirteen (41.9%) of the 31 patients who received carboplatin and paclitaxel therapy showed a partial response (PR) and 12 (38.7%) showed stable disease (SD). The other 6 patients (19.4%) showed PD. The amounts of CEC at baseline in the patients who showed PR and SD were 516 ± 458/4 ml and 871 ± 1215/4 ml, respectively, and these values were significantly higher than in PD patients (211 ± 150/4 ml, p = 0.023 and p = 0.044, respectively) (Figure 3*A*). Although CEC decrements during chemotherapy were observed in all three subgroups, the extent of the decrements tended to be greater in

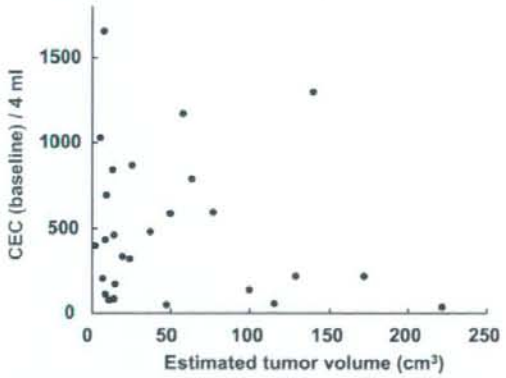


FIGURE 1. Scatter plot analysis to determine the correlation between the number of circulating endothelial cell (CEC) and estimated tumor volume (ETV). ETV is calculated with computed tomography (CT) examination. Case 21 is not included.

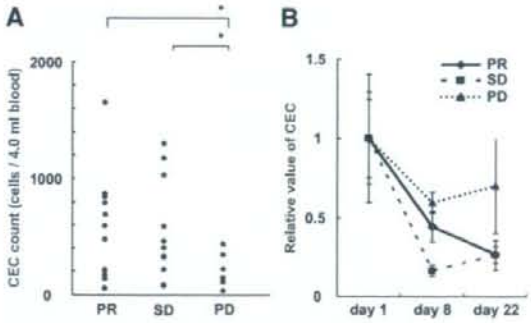


FIGURE 3. *A*, Comparison of circulating endothelial cell (CEC) amount at baseline in non-small cell lung cancer (NSCLC) patients with different clinical responses to CBDCA plus paclitaxel chemotherapy. *p < 0.05 versus values of patients with progressive disease (PD). Case 21 is not included. *B*, Relative change in CEC amount in patients with partial response (PR), stable disease (SD), and PD.

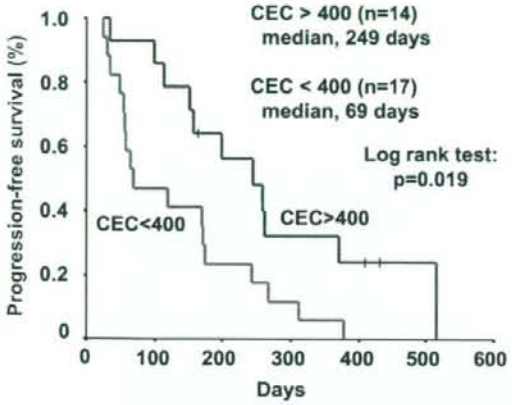


FIGURE 4. Progression-free-survival according to circulating endothelial cell (CEC) count at baseline. The median duration of progression-free survival was greater in patients whose CEC count exceeded 400 (median, 244 days) than in patients whose CEC count was less than 400 (69 days).

patients with PR and SD than in those with PD (Figure 3*B*). In the subgroup analysis, a significant decrease in CECs was observed on day 22 only in PR patients ($p = 0.018$).

CEC Amounts and PFS

For all 31 patients, the median PFS was 154 days (range, 81–361 days). Univariate analysis indicated that patients who had a CEC count of more than 400/4 ml at baseline showed a significantly improved PFS ($n = 14$, median; 244 days) (Log-rank test, $p = 0.019$, Figure 4). A CEC count below 400 at baseline was associated with a poorer PFS ($n = 17$, median; 69 days). The CEC count did not exceed the value of 400/4 ml in any of the healthy volunteers. When we compared the patients whose CEC counts exceeded 200 with those whose counts were less than 200, a consistent difference in PFS was observed between the two groups (>200; $n = 22$, median 227, <200; $n = 9$, median 116, $p < 0.039$).

DISCUSSION

In the present study, we investigated the number of CEC during the first course of CBDCA plus paclitaxel chemotherapy. To our knowledge, this is the first report of CEC in NSCLC patients before treatment. Our findings demonstrated CEC counts in advanced NSCLC at baseline level to be much higher than those in healthy subjects (595 ± 832/4.0 ml versus 32.6 ± 29.5/4.0 ml). Because the NSCLC patients had not yet received anticancer therapy, these increased CECs are likely to be mostly derived from the tumor site. In a previous study, it was found that the amounts of CECs correlate strongly with tumor volume in vivo in an animal model[34]. Nevertheless, we did not find a significant correlation between CECs and ETV. Because the number of CECs could be influenced by many factors related to tumor vasculature, neovascularization, and localization of the tumor, our failure to identify a strong correlation in this study is not surprising. We were also unable to detect a significant direct correlation between CEC amounts and various blood examination data including tumor markers such as CEA and CYFRA. It is unclear at present what biologic characteristics of the tumor or clinical features the CEC number most closely reflects as a biomarker. Mancuso et al. reported that CECs are strongly associated with plasma levels of VCAM-1 and VEGF in breast cancer and lymphoma patients.[15,34] Because VCAM-1 and VEGF are crucial factors for tumor angiogenesis, the variability in CEC values among NSCLC patients might indicate a difference in the neovascularization of each tumor.

We were further able to demonstrate that elevated CECs decreased dramatically after CBDCA plus paclitaxel treatment, but did not reach the level of healthy subjects. Decreased CEC values did not rise again during the first cycle of chemotherapy. Although myelosupression was observed on day 8 and recovered on day 22 in many patients (data not shown), CEC kinetics do not parallel those of WBC, indicating that CEC kinetics might not be influenced by myelopoiesis. Several clinical studies in the field measuring CEC found chemotherapy to be associated with either an increase or a decrease in CECs.[35–39] The different tumor types, stages, prior therapy or not, the anticancer drugs used, measuring points and quantification methods of CEC might have influenced the CEC results after treatment. In the present study, the pretreatment CEC value was much higher than that in lung cancer with metastasis (mean ± SD = 146 ± 270/4 ml), as reported elsewhere.[33] Although the details of the prior therapy in patients with metastatic carcinoma were not provided,[33] chemotherapy can eventually decrease the CEC count.

Schiller et al. compared four standard chemotherapy regimens, cisplatin plus paclitaxel, cisplatin plus gemcitabine, cisplatin plus docetaxel, and carboplatin plus paclitaxel and found no significant difference in survival.[25] Despite the different modes of action of each nonplatinum agent against tumors and different biologic characteristics of each tumor, we could not select the regimen based on these characteristics. In our small study, the patients with PR/SD and longer PFS had higher baseline CEC values. Therefore, it seems that the baseline CEC count is a promising predictor of clinical response to the CBDCA plus paclitaxel regimen and survival in advanced NSCLC. If CEC is a marker for angiogenesis and reflects tumor neovascularization, it is likely that a high CEC is associated with a poor prognosis and lower effectiveness of antiangiogenic therapy. Paclitaxel and docetaxel are categorized as mitotic spindle agents with potent antiangiogenic properties.[27–30] This is why a paclitaxel based regimen might be more effective against tumors with high CEC values. Nevertheless, CEC counts have also been reported to be increased in several clinical syndromes, such as cardiovascular diseases, infectious diseases, and vasculitides.[11–13] The CEC counts in patients with vasculitides have been reported to be dozens of fold higher than those in healthy subjects,[12] therefore, we have to consider the patient condition carefully while interpreting the CEC counts in individual patients, although there were no patients with vasculitis in the present study. Further clinical investigation, with a similar approach, including other nonplatinum anticancer agents, such as

CDDP plus gemcitabine, is essential for the clinical application of CEC for made-to-order chemotherapy in NSCLC.

Antiangiogenic therapy targeting the VEGF pathway such as bevacizumab and VEGFR inhibitors have shown promise in the treatment of solid tumors.[8,39] These agents inhibit endothelial cells through inhibition of the VEGF pathway. It was recently demonstrated that the addition of bevacizumab to CBDCA plus paclitaxel in advanced NSCLC patients produces a significant survival benefit as compared with chemotherapy alone.[40] Considering the outstanding clinical trial and our present study, it would be of great interest to investigate the role of CEC in this regimen.

In conclusion, CECs were measured in NSCLC patients before treatment. Our small clinical study indicates that the CEC count at baseline is a potential biomarker for predicting the response to chemotherapy and PFS, but further clinical evaluation is needed. In the near future, we will start a clinical investigation, using a similar approach, to examine other chemotherapeutic regimens.

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Gender Differences in Treatment Outcomes among Patients with Non-Small Cell Lung Cancer Given a Combination of Carboplatin and Paclitaxel

Harukaze Yamamoto Ikuo Sekine Kazuhiko Yamada Hiroshi Nokihara
Noboru Yamamoto Hideo Kunitoh Yuichiro Ohe Tomohide Tamura

Division of Internal Medicine and Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan

Key Words
Non-small cell lung cancer · Chemotherapy, carboplatin and paclitaxel

Abstract
Objectives: It was the aim of this study to investigate gender differences in the outcomes of carboplatin and paclitaxel chemotherapy in patients with unresectable stage IIIB-IV non-small cell lung cancer (NSCLC). ***Methods:*** Gender, age, performance status, histology, hematological toxicity, tumor responses and survival parameters obtained retrospectively by medical chart review were analyzed. ***Results:*** A total of 227 patients (147 males and 80 females) were included. The median lowest leukocyte count was 2,900 (range 1,200–12,400)/μl in males and 2,200 (range 600–6,500)/μl in females ($p < 0.001$). Grade 3–4 leukopenia was noted in 15% of male and in 39% of female patients ($p < 0.001$). In both genders, the response rate in evaluable patients was 39%. The median progression-free survival was 4.4 months for men and 5.3 months for women ($p = 0.0081$). After progression of the disease, gefitinib was administered in 64 (44%) male and 45 (56%) female patients, with a median treatment of 35 and 144 days, respectively. The median survival time was 11.9 months for men and 22.2 months for women ($p < 0.001$). ***Conclusion:*** Female gender was associated with a favorable prognosis in patients with NSCLC who received carboplatin and paclitaxel chemotherapy, although the response rates did not differ between the genders. Of note, hematological toxicity was more severe in female patients.

Introduction

Lung cancer remains a major cause of cancer-related death, with an increasing incidence in Japan, as well as world-wide. Non-small cell lung cancer (NSCLC) accounts for more than 80% of lung cancer. Systemic chemotherapy is appropriate for patients with NSCLC if they have extrathoracic metastases or locally advanced disease with a malignant effusion. The standard first-line chemotherapy is a platinum-based doublet regimen, even though it is associated with increased toxicity [1]. Although cisplatin-based regimens are slightly more effective than carboplatin-based regimens, carboplatin is often used due to its more favorable toxicity profile and the fact that it does not require a large intravenous infusion [2]. Among several carboplatin-based regimens, the combination of carboplatin and paclitaxel is frequently used for advanced NSCLC in Japan.

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Ikuo Sekine
Division of Internal Medicine and Thoracic Oncology
National Cancer Center Hospital, Tsukiji 5-1-1, Chuo-ku
Tokyo 104-0045 (Japan)
Tel. +81 3 3542 2511, Fax +81 3 3542 3815, E-Mail isekine@ncc.go.jp

Lung cancer in women differs from that in men with respect to its incidence, association with smoking and histological distribution [3]. Prospective cohort studies and a population-based study have consistently shown that female gender is a favorable prognostic factor in NSCLC patients; however, these studies included patients of all stages, and their therapy was not specified [4–6]. The presence of a gender difference in survival remains controversial among patients with advanced NSCLC who are treated with systemic chemotherapy; some studies involving multivariate analysis showed better survival in women [7–12], but others showed no difference between men and women [4, 13, 14]. In addition, only a few studies have reported gender differences in tumor responses to chemotherapy [7, 11, 12] and toxicity other than nausea and vomiting [7], which have been reported to be more severe in women [15]. Thus, in the present study, gender differences in survival, tumor responses and toxicity were analyzed in patients with advanced NSCLC who were treated with carboplatin and paclitaxel.

Patients and Methods

Study Population

Patients with unresectable stage IIIB-IV NSCLC who received first-line chemotherapy of carboplatin (AUC = 6, day 1) and paclitaxel (200 mg/m^2, day 1) every 3 weeks at the National Cancer Center Hospital were eligible for this study. A total of 227 patients were identified from January 2001 to July 2005. All patients underwent a systematic pretreatment evaluation and standardized staging procedures. Gender, age, smoking history, performance status, stage, histology, treatment delivery, hematological toxicity, sensory neuropathy, tumor responses and survival parameters were obtained from a retrospective medical chart review. The clinical stage was assigned based on the results of physical examination, chest X-rays, CT scans of the chest and abdomen, CT scans or MRI of the brain and bone scintigrams. The histological classification of the tumor was based on the criteria of the World Health Organization [16]. Toxicity was graded according to the Common Terminology Criteria for Adverse Events version 3.0. Objective tumor responses were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) [17].

Statistical Methods

The demographic, clinical and histopathologic characteristics were compared between the genders. The χ^2 and Mann-Whitney tests were used to evaluate differences in categorical and continuous variables, respectively. Survival curves were calculated according to the Kaplan and Meier method. Cox proportional hazards models were used to adjust potential confounding factors such as smoking history, histology, tumor stage and performance status [18]. All of the above mentioned analyses were performed using the Dr. SPSS II 11.0 for Windows software package (SPSS Japan Inc., Tokyo, Japan).

Table 1. Patient characteristics

Characteristics	Males (n = 147)	Females (n = 80)	p value
Age, years			
Median	61	61	0.60
Range	29–80	27–79	
Smoking history			
All patients			
Smoker	128 (87.1)	22 (27.5)	<0.001
Never-smoker	19 (12.9)	58 (72.5)	
Patients with adenocarcinoma			
Smoker	78 (83.0)	17 (23.9)	<0.001
Never-smoker	16 (17.0)	54 (76.1)	
Patients with non-adenocarcinoma			
Smoker	50 (94.3)	5 (55.6)	0.001
Never-smoker	3 (5.7)	4 (44.4)	
Stage			
IIIB	50 (34.0)	21 (26.3)	0.23
IV	97 (66.0)	59 (73.8)	
Performance status			
0	43 (29.3)	22 (27.5)	0.78
1	104 (70.7)	58 (72.5)	
Histology			
Adenocarcinoma	94 (63.9)	71 (88.8)	<0.001
Squamous cell	27 (18.4)	3 (3.8)	
Others	26 (17.7)	6 (7.5)	

Figures in parentheses are percentages.

Results

Patient Demographics

Of the 227 patients, 147 (65%) were males and 80 (35%) were females (table 1). Smoking history was closely associated with both gender and tumor histology. Eighty-three percent of the male patients with adenocarcinoma had a smoking history compared with only 24% of the female patients. Among patients with non-adenocarcinoma, a gender difference in smoking history was apparent, although the difference was smaller than in adenocarcinoma patients. No significant differences were seen between the genders with respect to age, stage and performance status (table 1).

Chemotherapy Treatment Delivery

The median number of chemotherapy cycles was 3 (range 1–8) in males and 3 (range 1–6) in females (p = 0.21).

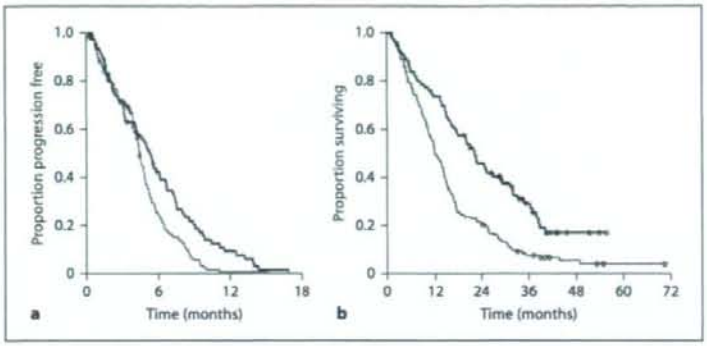

Fig. 1. PFS (**a**) and overall survival (**b**) in all patients. Thick line = Female patients; thin line = male patients.

Table 2. Toxicity

Toxicity	Males (n = 147)	Females (n = 80)	p value
Leukocytopenia			
Median	2,900	2,200	<0.001
Range	1,200–12,400	600–6,500	
Grade 0–2	125 (85.0)	49 (61.3)	<0.001
Grade 3	22 (15.0)	29 (36.3)	
Grade 4	0	2 (2.5)	
Neutropenia			
Median	700	700	0.289
Range	100–11,500	16–3,800	
Grade 0–2	42 (28.6)	20 (25.0)	0.39
Grade 3	56 (38.1)	26 (32.5)	
Grade 4	49 (33.3)	34 (42.5)	
Thrombocytopenia			
Median	13.2	12.4	0.086
Range	2.4–37.3	1.5–34.2	
Grade 0–1	139 (94.6)	73 (91.3)	0.46
Grade 2	7 (4.8)	5 (6.3)	
Grade 3	1 (0.7)	2 (2.5)	
Neurotoxicity			
Grade 0	81 (55.1)	47 (58.8)	0.869
Grade 1	64 (43.5)	32 (40.0)	
Grade 2	2 (1.4)	1 (1.2)	

Figures in parentheses are percentages.

Toxicities

Leukocytopenia during all the chemotherapy cycles was more severe in females than in males (median 2,200/mm^3 vs. 2,900/mm^3, respectively; $p < 0.001$); grade 4 leukocytopenia developed in 39% of females and 15% of males ($p < 0.001$). Grade 4 neutropenia was noted in 43% of females and 33% of males, but this difference was not statistically significant. No gender difference was noted in the frequency of grade 3–4 thrombocytopenia. The severity of neurosensory toxicity was also the same in men and women (table 2).

Response and Treatment after Failure of Initial Chemotherapy

There were 2 complete responses, 52 partial responses, 62 stable diseases and 21 progressive diseases among the 137 male patients evaluable for response, and 1 complete response, 28 partial responses, 33 stable diseases and 12 partial diseases among the 74 female patients evaluable for response; there was no difference in the response rates between male and female patients (39 vs. 39%; $p = 0.999$).

After recurrence or progression of the disease, 64 of the 147 (44%) male patients and 45 of the 80 (56%) female patients received gefitinib monotherapy ($p = 0.067$). The median days of gefitinib treatment was 35 (range 8–803) days in male patients and 144 (range 16–1,325) days in female patients ($p < 0.001$).

Survival

Median progression-free survival (PFS) was longer in females (5.3 months) than in males (4.4 months; $p = 0.0081$) (fig. 1). As of December 2007, 128 deaths had occurred among the male patients and 54 deaths among the female patients. The cause of death was progression of NSCLC, a treatment-related cause, other disease and unknown in 128 (95%), 3 (2.3%), 2 (1.6%) and 2 (1.6%) male and in 50 (93%), 0 (0%), 2 (3.7%) and 2 (3.7%) female patients, respectively. The median survival time (MST) was better in females (22.5 months) than in males (12.5 months; $p < 0.001$). After adjusting for stage, performance status, histology

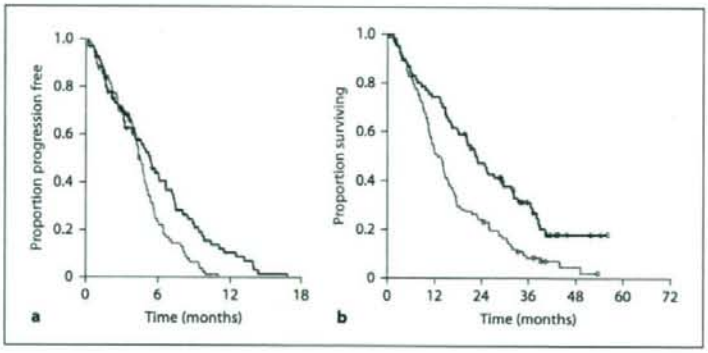

Fig. 2. PFS (**a**) and overall survival (**b**) in patients with adenocarcinoma. Thick line = Female patients; thin line = male patients.

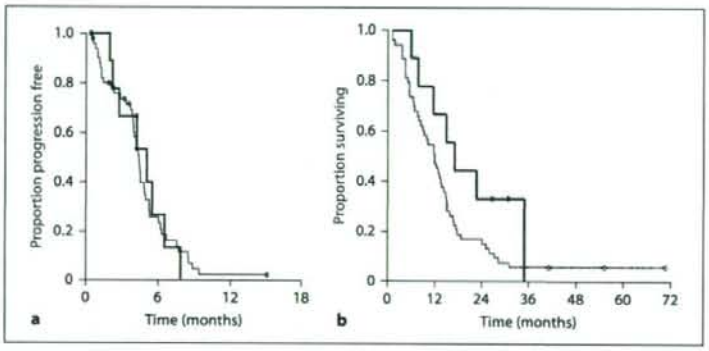

Fig. 3. PFS (**a**) and overall survival (**b**) in patients with non-adenocarcinoma. Thick line = Female patients; thin line = male patients.

and smoking status, female gender was a significant factor for a favorable prognosis (hazard ratio 0.49, 95% confidence interval 0.33–0.73; table 3). In the subset analyses, among patients with adenocarcinoma, PFS and MST were better in females than in males (fig. 2), whereas among patients with non-adenocarcinoma, there was no gender difference in PFS or MST (fig. 3).

Discussion

The present study and other previous studies have shown that female gender is a favorable prognostic factor in patients with stage IIIB or IV NSCLC who receive combination chemotherapy [7–12]. The reasons for this gender difference are currently unknown, but there are 5 possibilities. First, men may not have received sufficient cycles and doses of chemotherapy, since they develop more severe toxicity during chemotherapy than women. How-

Table 3. Multivariate analysis of baseline characteristics for overall survival in all patients

Variables	Patients	Hazard ratio
Sex		
Male	147	1
Female	80	0.49 (0.33–0.73)
Stage		
IIIB	71	1
IV	156	1.37 (1.00–1.89)
Performance status		
0	65	1
1	162	1.31 (0.95–1.81)
Histology		
Adenocarcinoma	165	1
Non-adenocarcinoma	72	1.03 (0.73–1.45)
Smoking		
Never-smoker	77	1
Smoker	150	0.96 (0.65–1.42)

Figures in parentheses are 95% confidence intervals.

ever, in the present study, the number of chemotherapy cycles was the same for both male and female patients, and hematological toxicity was more severe in females than in males. Of note, treatment-related death was observed only in male patients, but the number of deaths was very small (2.7%). The second possibility may be that chemotherapy was more effective in females than in males. However, there was no difference in the response rates by gender in the present study and in previous studies [7, 11, 12]. In 1 study, the duration of response was also found to be the same in male and female patients [11]. The PFS was longer in females than in males in this and in 1 previous study [7], but the PFS can be affected by several factors other than chemotherapy-induced responses. Thus, the second scenario is not likely. The third reason may be that more men die from diseases other than lung cancer. However, in the present study, 95% of male patients and 93% of female patients died of lung cancer progression.

The fourth possibility is that males may have a more aggressive tumor that grows more rapidly than in females. In the present study, there was a higher percentage of never-smokers among female compared with male patients, especially in patients with adenocarcinoma. Large case series studies have found that patients with lung adenocarcinoma who had never smoked had a better survival than those who had a smoking history [19, 20]. Thus, the higher frequency of never-smokers among female patients may explain the better prognosis of female patients in the present study. Recent developments in the molecular pathogenesis of lung cancer suggest that the origins of adenocarcinomas may involve different pathways: a K-RAS mutation-dependent pathway in smokers and an epidermal growth factor receptor mutation-dependent pathway in never-smokers [21]. Lung adenocarcinomas arising by these distinct pathways may have a different potential for progression. Thus, adenocarcinoma in females arising through the epidermal growth factor receptor mutation-dependent pathway may be less aggressive than adenocarcinoma in males, which may arise mainly through the K-RAS mutation-dependent pathway. Carcinogenesis pathways in NSCLC other than adenocarcinoma are unknown, but they are not likely to differ by gender because these tumors are associated with a heavy smoking habit in both genders. These hypotheses are consistent with the results of the present study that there are gender differences in patients with adenocarcinoma, but that the gender differences were small, if any, in those with non-adenocarcinioma.

Finally, gefitinib administration may be associated with a gender difference in overall survival. In the present study, more female patients received gefitinib monotherapy, and the treatment duration was 4 times longer in female than in male patients. Thus, gefitinib treatment probably contributed to the improved survival of female patients.

The present study found that females had more chemotherapy-related hematological toxicity than males during treatment, while there was no gender difference in neurological toxicity. More severe hematological toxicity in females was also noted among patients with SCLC treated with combinations of cyclophosphamide, vincristine, doxorubicin, etoposide and cisplatin [22]. This can be explained by decreased clearance of cyclophosphamide, vincristine, doxorubicin and etoposide due to a 2.4-fold lower expression of hepatic P-glycoprotein, which is a transporter of these agents [23]. The mechanism that could explain the gender difference in toxicity associated with carboplatin and paclitaxel in the present study is unknown, but decreased clearance of paclitaxel is not likely, because neurological toxicity did not differ by gender. Since DNA repair capacity measured using peripheral blood lymphocytes is lower in female lung cancer patients than in male patients [24], increased susceptibility to carboplatin-induced DNA damage may be one factor related to increased chemotherapy-related toxicities in female patients. A recent large-scale study did not show an association between the severity of toxicity and polymorphisms of 16 key genes for drug-metabolizing enzymes, transporters and DNA repair in 914 patients with ovarian cancer who received combination chemotherapy consisting of carboplatin with paclitaxel or docetaxel [25]. However, our understanding of the true regulation of chemotherapy action is very limited at present, and the possibility remains that gender differences in chemotherapy outcome may be based on pharmacogenomic differences between the genders. The lower DNA repair capacity in females may also influence tumor DNA repair after exposure to cytotoxic chemotherapy, and therefore, it may have implications for the significantly longer PFS in female patients after first-line chemotherapy with carboplatin and paclitaxel.

In conclusion, female gender was associated with a favorable prognosis in patients with NSCLC who received combination carboplatin and paclitaxel chemotherapy, even though response rates did not differ by gender. Hematological toxicity was more severe in female patients.

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thus influenced the results including those assessed (overall survival) and not assessed (disease free survival and time to progression). Future studies on the efficacy of docetaxel as a second line agent should serve to address issues like the optimal dose regimen and intensity as well as adjust for potential confounders.

Navneet Singh, MD, DM, FCCP
Ashutosh N. Aggarwal, MD, DM, FCCP
Department of Pulmonary Medicine
Postgraduate Institute of Medical Education and Research (PGIMER)
Chandigarh
India

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Reply: Higher Intensity Does Not Necessary Yield Better Survival in Second-Line Chemotherapy for NSCLC

To the Editor:

We would like to thank Singh et al. for suggesting that the dose of docetaxel and previous treatment modality may have an impact on second-line therapy in non-small cell lung cancer (NSCLC). Herein, we discuss the dose of docetaxel and the influence of previous chemotherapy in relation to second-line treatment of NSCLC.

In second-line chemotherapy for NSCLC, whether a higher dose of an anticancer agent would inevitably yield a longer survival is open to question. In a study comparing docetaxel 100 mg/m^2, docetaxel 75 mg/m^2 and best supportive care, the overall survivals were 5.9, 7.5, and 7.0 months, respectively.[1] Docetaxel 100 mg/m^2 was also found to be inferior to docetaxel 75 mg/m^2 in terms of the 1-year survival rate in another phase III study.[2] A similar tendency was also observed for another agent in the second-line setting; pemetrexed 500 mg/m^2 and 900 mg/m^2 were compared, and the overall median survivals were 6.7 and 6.9 months, respectively, and the hazard ratio was 1.013 (95% confidence interval, 0.837–1.226).[3] Even the response rate in the 900 mg/m^2 arm did not exceed that in the 500 mg/m^2. Thus, finding the optimal dose of docetaxel or other agents for second-line chemotherapy may be an intriguing issue.[4]

Meanwhile, docetaxel 60 mg/m^2 is the standard therapeutic dose in Japan, since a Japanese phase I trial determined the maximum tolerated dose to be 70 mg/m^2.[5] Even though this dose of docetaxel is lesser than that used in other countries, this may be the optimal dose for Japanese. In a phase II study of docetaxel for previously untreated NSCLC conducted in Japan, the response rate to docetaxel 60 mg/m^2 was 19%, no less than that to the higher doses used in other countries.[6] A retrospective study evaluating docetaxel 60 mg/m^2 for previously treated NSCLC also showed a response rate of 18.5%, comparable with that reported for higher doses.[7] This difference in the dose requirement in Japanese may be attributed to ethnic differences between the Japanese and other populations, but the issue remains under debate.

The previously employed treatment modality differed between those who had received a combination of carboplatin and paclitaxel (group P) and those who had received a combination of a platinum and an agent other than paclitaxel [group nonpaclitaxel (NP)] in our study. We consider, however, that this difference had only a small impact on our study results, for three reasons. Firstly, all the patients in our study had metastatic disease at the time of recurrence and start of docetaxel therapy. Secondly, although 29% of patients in group NP had received radiotherapy, the response rate to the previous treatment in group NP was the same as that in group P (45.0 versus 44.9%, respectively). In general, the response rate to chemoradiotherapy is higher than that to chemotherapy alone. This difference may have disappeared in our study, probably because we only recruited patients who developed recurrence after chemoradiotherapy. Finally, no previous studies of second-line chemotherapy for NSCLC have dealt with these issues. Even though multiple modalities may have been used in previous treatment, we can only evaluate the integrated result of the treatment. It is impossible to distinguish between the efficacy of chemotherapy and radiotherapy if both are undertaken simultaneously.

In conclusion, further investigation of the optimal dose of chemotherapeutic agents for second-line chemotherapy of NSCLC is warranted. The efficacy of previous chemotherapy, whether or not administered in combination with radiotherapy, is a useful reference for subsequent docetaxel therapy.

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Address for correspondence: Ikuo Sekine, MD, PhD, Division of Internal Medicine and Thoracic Oncology, National Cancer Center Hospital, Tsukiji 5-1-1, Chuo-ku, Tokyo 104-0045, Japan. E-mail: isekine@ncc.go.jp

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Yasushi Goto, MD
Ikuo Sekine, MD, PhD
Tomohide Tamura, MD
Division of Internal Medicine and Thoracic Oncology
National Cancer Center Hospital
Chuo-ku, Tokyo
Japan

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Tracheo-Esophageal Fistula with Bevacizumab after Mediastinal Radiation

To the Editor:

We report here a case of a young man who developed a trachea-esophageal fistula 4 months following thoracic radiation while being treated with bevacizumab and chemotherapy. A 28-year-old gentleman was diagnosed with non-small cell lung cancer (NSCLC) when he presented with a large right sided mediastinal mass. Transbronchial biopsy results were consistent with adenocarcinoma. Staging evaluation with computerized tomography, flourodeoxyglucose positron emission tomography, and mediastinoscopy confirmed stage IIIB (T2N2M0) disease. He was treated with definitive radiation (74 gray) and concurrent cisplatin with etoposide. One month after completing radiotherapy, he developed progressive disease with enlargement of cervical lymph nodes. Biopsy of a cervical lymph node was consistent with adenocarcinoma. Two months after radiotherapy had been completed, he began systemic treatment with carboplatin, paclitaxel, and bevacizumab (15 mg/kg) every 3 weeks. After two cycles, he had a partial response.

One week prior to his third cycle, he developed progressive odynophagia, then severe coughing with swallowing. An endobronchial evaluation was performed with visualization of a fistulous communication between the esophagus and the trachea, extending into the right mainstem bronchus. An endotracheal stent was placed, but after 2 weeks he had no relief of his respiratory symptoms and was referred to our institution. Bronchoscopy revealed a persistent tracheoesophageal fistula which was not excluded by the endotracheal stent. This endotraheal stent was removed and the fistula was visualized as seen in Figure 1*A*. At that time, a covered esophageal stent (18-mm diameter, 120-mm length, Alveolus) was placed in the esophagus to exclude gastric and oral secretions from the airway (Figure 1*B*). Biopsies of the fistulous tract showed no evidence of malignancy. As the computed tomography scan of the chest and abdomen revealed progressive disease in the mediastinum and liver, an attempt at surgical correction was not considered appropriate. A jejunal feeding tube was placed for nutrition, and he was discharged home with supportive care.

Bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF), has been approved for the treatment of advanced NSCLC in combination with paclitaxel and carboplatin.[1,2] Bevacizumab has been associated with bleeding complications, hypertension and gastrointestinal tract perforation.[2] When administered in combination with thoracic radiation, bevacizumab has recently been associated with tracheo-esophageal fistulas. The manufacturer issued a warning based on the development of tracheo-esophageal fistulas in 3 of 29 patients with limited stage small cell lung cancer being treated with definitive radiation, concurrent with irinotecan, carboplatin, and bevacizumab. Data from the manufacturer (as of March 2007) refer to six other instances in which patients with lung and esophageal malignancies developed tracheo-esophageal fistulas while being treated with bevacizumab.[3] A black box warning regarding this complication was mandated by the Food and Drug Administration in April 2007;[2] however, no such reports are available at this time

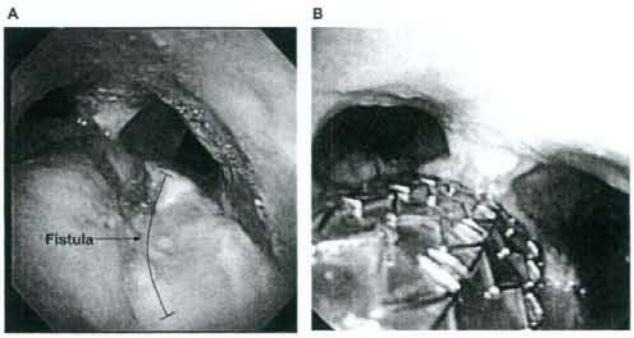

FIGURE 1. *A*, Tracheo-esophageal fistula in patient treated with bevacizumab. *B*, Coated stent in the esophagus, as visualized through the large posterior airway defect.

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Address for correspondence: Ramaswamy Govindan, MD, Division of Oncology, 4960 Children's Place St Louis, MO 63021. E-mail: rgovinda@im.wustl.edu

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Influence of Previous Chemotherapy on the Efficacy of Subsequent Docetaxel Therapy in Advanced Non-small Cell Lung Cancer Patients

Yasushi Goto, MD, Ikuo Sekine, MD, PhD, Kazuhiko Yamada, MD, Hiroshi Nokihara, MD, PhD, Noboru Yamamoto, MD, PhD, Hideo Kunitoh, MD, PhD, Yuichiro Ohe, MD, PhD, and Tomohide Tamura, MD

Purpose: To identify factors, particularly the previous use of paclitaxel, that might influence the efficacy of subsequent docetaxel therapy.

Patients and Methods: The patient characteristics, responses, and survivals were compared between the two groups that had received a combination of carboplatin and paclitaxel (group P), and a combination of a platinum and an agent other than paclitaxel (group NP).

Results: A total of 227 patients (127 in group P, and 100 in group NP) were recruited from a hospital-based registry. Two hundred twenty patients were evaluated for the survival, and 210 patients were evaluated for the response of docetaxel therapy. The response rate to docetaxel therapy (14.2% versus 16.0%, $p = 0.702$) or the median survival time (10.9 months versus 11.1 month, $p = 0.567$) did not differ between groups P and NP. The results of multivariate analysis, adjusted for sex, age, and performance status at the start of docetaxel therapy, showed that not the regimen per se, but the response to previous chemotherapy significantly influenced the response rate of docetaxel therapy (odds ratio [OR]: 1.38, 95% confidential interval [CI]: 0.63–3.01; and OR: 2.93, 95% CI: 1.28–6.72, respectively). As for the overall survival, neither the response to nor the previous chemotherapy regimen had any impact (hazard ration [HR]: 0.90, 95% CI 0.66–1.22; HR 0.88, 95% CI 0.65–1.20, respectively).

Conclusion: The previous use of paclitaxel had no impact on the response or survival to subsequent docetaxel therapy. In contrast, the response to previous chemotherapy had a predictive value in relation to responses to subsequent docetaxel therapy in patients with advanced non-small cell lung cancer.

Key Words: Non-small cell lung cancer, Second-line chemotherapy, Docetaxel.

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Division of Internal Medicine and Thoracic Oncology, National Cancer Center Hospital, Chuo-ku, Tokyo, Japan.

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Address for correspondence: Ikuo Sekine, MD, PhD, Division of Internal Medicine and Thoracic Oncology, National Cancer Center Hospital, Tsukiji 5-1-1, Chuo-ku, Tokyo 104-0045, Japan. E-mail: isekine@ncc.go.jp

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Lung cancer is a leading cause of cancer-related deaths worldwide.[1] Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all cases of lung cancer. For chemotherapy-naive, patients with advanced NSCLC, with a good performance status (PS), platinum -based chemotherapy has been shown to offer a modest survival benefit over best supportive care alone.[2,3] A high proportion of patients, however, shows disease relapse after initial clinical responses, or progress during the chemotherapy. Thus, a large percentage of patients is moved on to second-line chemotherapy, even though it should only be considered in selected patients with a good PS.[4]

In the landmark study by Shepherd et al., second-line docetaxel thearpy was demonstrated to improve the outcome over best supportive care alone in patients with a history of previous chemotherapy.[5] Since then, a number of agents have been introduced as effective agents for the second-line setting[6–8]; however, the impact of previous chemotherapy on the efficacy of subsequent chemotherapy has not been established.

In relation to small-cell lung cancer, the response of tumors to first-line therapy and recurrence more than 3 months after completion of the initial therapy is often referred to as "sensitive relapse," and absence of tumor response, tumor progression through treatment, or tumor recurrence within 3 months of discontinuation of initial therapy is termed "refractory" disease. Although both are grouped together in most second-line clinical trials, their prognosis and response to salvage therapy have been shown to be different.[9,10] Therefore, in patients with small-cell lung cancer, the efficacy of previous chemotherapy has a significant impact on selection of the subsequent chemotherapy. Whether this relationship between first-and second-line chemotherapy would also apply to cases of NSCLC has not yet been clarified.

In this study, we attempted to identify factors, particularly the previous use of paclitaxel, that might influence the response to subsequent docetaxel therapy in patients with NSCLC. Towards this objective, we divided our patients into two groups according to the previous regimen received.

PATIENTS AND METHODS

We evaluated the patients with histologically or cytologically proven unresectable locally advanced or metastatic

NSCLC, who had received a platinum-containing chemotherapy, and subsequently received docetaxel therapy. The following baseline pretreatment demographic and prognostic information was extracted: age, sex, PS (Eastern Cooperative Oncology Group scale), clinical stage at diagnosis, histology, interval between the final administration of the previous chemotherapy and the start of docetaxel, and response to previous chemotherapy. The platinum-containing therapy was continued for as long as clinical benefit could be observed. Docetaxel was administered at the dose of 60 mg/m^2 and repeated every 3 weeks or longer. We divided these patients into two groups by the initial regimen that they received, namely, combined carboplatin and paclitaxel (group P), or combination of a platinum and an agent other than paclitaxel (group NP).

Objective responses were evaluated using standard bidimensional measurements.[11] Overall survival was measured from the first day of docetaxel treatment until death or the final day of the follow-up period, analyzed using the Kaplan-Meier method, and compared using the log-rank test. Other comparisons were made by χ^2 test, Fisher exact test, and Wilcoxon's test. Factors potentially associated with the efficacy of docetaxel therapy were assessed by univariate and multivariate analysis using the logistic regression model and Cox proportional hazards model. All variables were entered in a single step. Variables tested were sex (male versus female), age (continuous variable), PS at the start of docetaxel therapy (0 versus 1 and 2), regimen of previous chemotherapy (group P versus NP), interval between previous therapy and the start docetaxel chemotherapy (continuous variable), and response to previous chemotherapy (SD/PD versus CR/PR). Differences were considered to be significant at $p < 0.05$. All analyses were performed with Dr. SPSS II (SPSS Japan Inc.).

RESULTS

Patient Characteristics and Docetaxel Delivery

A total of 227 consecutive patients were recruited from a hospital-based registry who were treated with docetaxel after previous platinum-containing chemotherapy between January 2001 and April 2006 at the National Cancer Center Hospital. Of these 127 patients were classified into group P, and 100 into group NP. Seven patients were excluded for the analysis of survival because there was no measurable lesion for the evaluation of response in the previous chemotherapy. Of these 220 patients, another 10 patients were excluded for the analysis of response to docetaxel therapy, because there was no measurable lesion for the evaluation of response in the subsequent docetaxel therapy. By the time of the analysis, 187 out of the 227 patients had died. The median follow-up duration was 10.2 months (range, 0.3–66.9 months) for all patients, and 18.9 months (range, 0.8–66.9 months) for patients who had lost for follow up or alive at the time of analysis.

The patient characteristics are listed in Table 1. The sex and age distributions were similar in the two groups. Stage III disease and a history of previous radiation therapy were slightly predominant in group NP, because concurrent chemoradiotherapy was only administered with the cisplatin (CDDP) and vinorelbine regimen. The response to initial therapy did not differ between the two groups.

TABLE 1. Patient and Disease Characteristics in the Two Groups

Characteristics	Group P (N = 127) No.	(%)	Group NP (N = 100) No.	(%)	p
Sex					
Male	90	(70.9)	79	(79.0)	0.161
Female	37	(29.1)	21	(21.0)	
Age, yr					
Median	58		60		0.072
Range	30–77		34–75		
Performance status at the start of docetaxel therapy					
0	22	(17.3)	26	(26.0)	0.262
1	101	(79.5)	72	(72.0)	
2	4	(3.2)	2	(2.0)	
Stage at diagnosis					
III	34	(26.8)	51	(51.0)	0.002
IV	72	(56.7)	39	(39.0)	
Recurrence	21	(16.5)	10	(10.0)	
Histology					
Adenocarcinoma	90	(70.9)	68	(68.0)	0.262
Squamous cell carcinoma	23	(18.1)	15	(15.0)	
Large cell carcinoma	2	(1.6)	0	(0)	
Other	12	(9.4)	17	(17.0)	
Interval between the final administration of the previous chemotherapy and the start of docetaxel (wk)					
Median	17		17		0.285
Range	3–134		2–141		
Response to previous chemotherapy					
CR	0	(0)	2	(2.0)	0.031
PR	57	(44.9)	43	(43.0)	
SD	49	(38.6)	46	(46.0)	
PD	17	(13.4)	6	(6.0)	
NE	4	(3.1)	3	(3.0)	
Other treatment					
Radiation	0	(0)	29	(29.0)	<0.001
Surgery	21	(16.5)	10	(10.0)	0.149

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable.

In group NP, the regimens used for the prior chemotherapy and the number of patients treated were as follows; CDDP and vinorelbine (n = 35), combined carboplatin and gemcitabine (n = 24), CDDP and gemcitabine (n = 19), CDDP and irinotecan (n = 18), and others (n = 4).

The median (range) number of cycles of docetaxel chemotherapy administered was 3 (1–17) in group P and 3 (1–13) in group NP.

Efficacy

The response data to docetaxel therapy are summarized in Table 2. There were no significant differences between group P and group NP in terms of the overall response rate (15.1% versus 17.6%), "clinical benefit rate" (79.8% versus 75.6%), or median survival time (6.1 month versus 6.0