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第３次対がん総合戦略研究事業

新しい薬物療法の導入とその最適化に関する研究

研究成果の刊行物・別刷

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

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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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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).

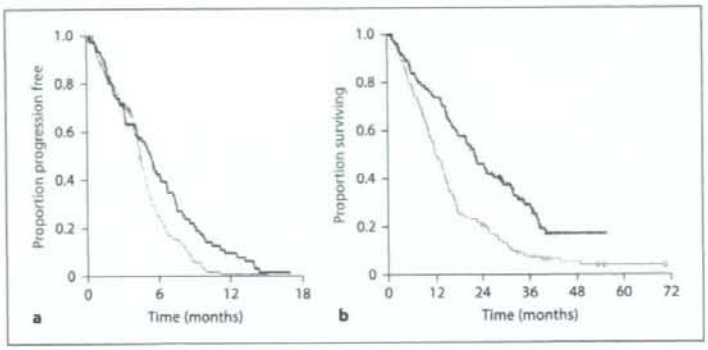

Fig. 1. PFS (**a**) and overall survival (**b**) in all patients. Thick line = Female patients; thin line = male patients.

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