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Research paper

Stage IV non-small cell lung cancer patients aged 75 years and older



T. Tamura^a, K. Kurishima^b, H. Watanabe^a, K. Nakazawa^a, H. Ishikawa^b,
 H. Satoh^{c,*}, N. Hizawa^a

^a Division of Respiratory Medicine, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan

^b Division of Respiratory Medicine, Tsukuba Medical Center, Tsukuba, Japan

^c Division of Respiratory Medicine, Mito Medical Center, University of Tsukuba, Miya-machi 3-2-7, Mito, 310-0015 Ibaraki, Japan

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ABSTRACT

Objectives: The purpose of this study is to examine clinical and pathological features and chemotherapy in the elderly with metastatic non-small cell lung cancer (NSCLC), especially in patients aged 75 years and older.

Methods: From the databases at two teaching hospitals during the period from January 1999 to December 2013, medical records of lung cancer patients were retrospectively reviewed. The patient population was divided into two age groups: 75 years or older (the ≥ 75 age group) and less than 75 years (the < 75 age group). Time trends were also studied in three time periods: 1999–2003, 2004–2008, and 2009–2013. The years 2004 and 2009 were chosen as cutoff points because of the introduction of gefitinib and bevacizumab, respectively around these years to treat NSCLC patients.

Results: Patients aged 75 years and older comprised 27.3% of 772 consecutive stage IV NSCLC patients; there was an increase in the proportion of ≥ 75 age patients treated with chemotherapy; a trend of improvement in survival of these patients was found. No statistical difference was found in survival between the two age groups of patients treated with chemotherapy ($P = 0.883$). Age ≥ 75 was not an unfavorable prognostic factor in multivariate analysis.

Conclusion: In order to improve survival, detection of appropriate candidates for effective chemotherapy is indeed essential even for the ≥ 75 age group of stage IV NSCLC patients.

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1. Introduction

Lung cancer in the elderly is an increasingly common problem faced by chest physicians and thoracic surgeons [1–5]. Elderly patients tend to tolerate toxic medical treatments poorly compared to their younger counterparts, because of the comorbid diseases related to age. Clinical trials of platinum-based chemotherapy for selected “fit” elderly patients in good condition have been conducted, attracting attention to the utility of such therapy for the elderly [6–14]. Especially in non-small cell lung cancer (NSCLC), the development of new drugs such as epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) and vascular endothelial growth factor (VEGF) inhibitors, higher standards of medical care, and wider availability of health services may change survival rates of elderly stage IV NSCLC patients.

To address the question of whether the overall survival of lung cancer patients 75 years of age or older has improved, we performed a retrospective study using clinical data from consecutive patients with NSCLC diagnosed at our two tertiary hospitals. We also focused on the role of performance status (PS), comorbid disease, and treatment modalities including chemotherapy on survival of the elderly patients aged 75 years or older.

2. Patients and methods

Clinicopathological data for all the consecutive patients with NSCLC were obtained by retrospective review from the databases at University of Tsukuba Hospital and Tsukuba Medical Center Hospital and Regional Cancer Center. All the patients were diagnosed pathologically and treated between 1999 and December 2013 at these two tertiary hospitals. Pathological diagnosis was defined by the WHO classification [15]. Staging was recorded for patients with NSCLC according to TNM classification [16]. Demographic data, including age, gender, and PS, were retrieved from their medical records along with the specific details of their cancer.

* Corresponding author.

E-mail address: hirosato@md.tsukuba.ac.jp (H. Satoh).

Table 1

Comparison of clinicopathological features between aged ≥ 75 and < 75 years stage IV non-small lung cancer patients.

Variables	Patients aged ≥ 75	Patients aged < 75
Number of patients	211	561
Male patients	147 (69.7%)	388 (69.2%)
Smoking habit: present	154 (73.0%)	412 (73.4%)
Performance status: 2–4	137 (64.9%)	210 (37.4%)**
Non-adenocarcinoma	62 (29.4%)	124 (22.1%)*
Comorbidity		
Respiratory disease	63 (29.9%)	121 (21.6%)*
Cardiovascular disease	123 (58.3%)	176 (31.4%)**
Neurological disease	30 (14.2%)	33 (5.9%)**
Diabetes mellitus	44 (20.9%)	91 (16.2%)
Malignant disease ^a	34 (16.1%)	51 (9.1%)**
Serum albumin (< 3.5 g/dL)	95 (45.0%)	190 (33.9%)**
Serum CRP (> 1.0 mg/dL)	314 (58.7%)	91 (38.4%)**

* $P < 0.05$.

** $P < 0.01$.

^a Malignant disease included past and concurrent diseases.

This study conformed to the Ethical Guidelines for Clinical Studies by the Ministry of Health, Labor and Welfare of Japan. The entire patient population was divided into two age groups: 75 years or older (the ≥ 75 age group) at diagnosis, and less than 75 years (the < 75 age group) [17–19]. The median survival time (MST) was compared between the two age groups as defined by gender, histologic subtype, stage, and therapy. Three predefined time periods, that is patients presenting between 1999 and 2003, between 2004 and 2008, and between 2009 and 2013 were used for comparison of survival. The years 2004 and 2009 were chosen as cutoff points because of the introduction of gefitinib and bevacizumab, respectively around these years to treat NSCLC patients.

Differences in distribution of subpopulations between the two age groups and three time periods were analyzed using a Chi-square test. The Kaplan–Meier method was used to assess survival curves and the log-rank test to evaluate the statistical significance of differences between the two groups [20,21]. Length of survival was defined as the interval in months from date of initial therapy or supportive care until date of death or date of last follow-up. The Cox proportional hazard model was used to study the effects of age on survival while adjusting for other important factors. A probability value less than 0.05 was considered to be significant.

3. Results

3.1. Demographics

A total of 772 patients with NSCLC were registered during the 15-year period. As shown in Table 1, 211 patients (27.3%) were 75 years or older, and 72.7% of patients were younger than

75 years. Men constituted 69.7% in the ≥ 75 age group and 69.2% in the < 75 age group. Non-adenocarcinomas accounted for 29.4% in the ≥ 75 age group and 22.1% in the < 75 age group. Poor PS (2–4) accounted for 64.9% in the ≥ 75 age group and 37.4% in the < 75 age group ($P < 0.001$). The ≥ 75 age group had higher incidences of comorbid disease (respiratory, cardiovascular, neurological, and malignant disease) than those in the < 75 age group. Incidences of lower serum albumin (< 3.5 g/dL) and elevated serum C-reactive protein (CRP) level (> 1.0 mg/dL) at the time of NSCLC diagnosis in the ≥ 75 age group were higher than in the < 75 age group. Best supportive care without chemotherapy or radiotherapy was also higher in the ≥ 75 age group than in the < 75 age group. Table 2 shows the details regarding the first-line medical treatment. There were no apparent trends among the three time periods.

3.2. Ratio of the elderly patients who received chemotherapy and survival

Among the ≥ 75 age group of patients, 12 (26.1%) of 46 patients received chemotherapy in 1999 to 2003, 37 (40.7%) of 91 patients received chemotherapy in 2004 to 2008, and 37 (50%) of 74 patients received chemotherapy in 2009 to 2013. The ratio of the elderly patients who received chemotherapy increased significantly ($P = 0.034$). Fig. 1 shows the survival curves of the ≥ 75 age group of patients. Median survival of the patients during 1999 to 2003, 2004 to 2008, and 2009 to 2013 was 4.7, 5.7, and 6.1 months, respectively. Fig. 2 shows the survival curves of the ≥ 75 age group of patients who were treated with chemotherapy. Median survival of the patients during 1999 to 2003, 2004 to 2008, and 2009 to 2013 was 9.0, 11.9, and 13.5 months, respectively. There was improvement in survival but it was not statistically significant in the log-rank test.

3.3. Comparison of survival between the elderly and the younger patients

Fig. 3 shows the comparison of survival between the two age groups of patients with chemotherapy. There was no statistically significant difference between them (11.9 months vs 12.5 months, $P = 0.883$), although the elderly patients in all had poorer survival than younger patients (5.4 months vs 8.8 months, $P < 0.001$). There was no statistically significant difference in survival between the two age groups of patients with supportive care only (3.0 months vs 2.6 months, $P = 0.560$).

3.4. Prognostic factors

Table 3 summarizes the relationship between clinical variables and survival. In univariate analysis, age more than 75 years old, male gender, smoking habit, poor PS (PS 2–4), non-adenocarcinoma, comorbid respiratory and neurological disease, lower level of serum albumin, elevated serum CRP level, and no chemotherapy as initial therapy were unfavorable prognostic factors. In multivariate

Table 2

Detail of 1st line treatment given in each time period.

Treatment	1999–2003		2004–2008		2009–2013	
	< 75	≥ 75	< 75	≥ 75	< 75	≥ 75
Platinum doublet	74 (46.5%)	2 (4.3%)	131 (63.3%)	13 (14.3%)	133 (68.2%)	15 (20.3%)
With bevacizumab	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (5.6%)	1 (1.4%)
Single-agent	4 (2.5%)	3 (6.5%)	10 (4.8%)	21 (23.1%)	6 (3.1%)	11 (14.9%)
EGFR-TKI	15 (9.4%)	6 (13.0%)	12 (5.8%)	2 (2.2%)	29 (14.9%)	11 (14.9%)
Other	2 (1.3%)	1 (2.2%)	1 (0.5%)	1 (1.1%)	0 (0.0%)	0 (0.0%)
Supportive care only	64 (40.3%)	34 (73.9%)	53 (25.6%)	54 (59.3%)	27 (13.8%)	37 (50.0%)

EGFR-TKI: epidermal growth factor receptor-tyrosine kinase inhibitor.

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