ORIGINAL ARTICLE

Outcome of active anti-cancer treatment in elderly patients with advanced non-small cell lung cancer: A single center experience

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Abstract

Background: This study aimed to evaluate the characteristics of active anti-cancer treatment (AAT) compared with best supportive care (BSC) in elderly patients with advanced non-small cell lung cancer (NSCLC).

Methods: A retrospective analysis of 144 patients, aged 70 or older, with stage IIIb/IV NSCLC from 672 patients with confirmed lung cancer, was conducted.

Results: Median age at diagnosis was 77 years and median survival time was five months. On multivariate analysis, AAT independently contributed to a decreased hazard ratio of death ($P = 0.04$), whereas male gender ($P = 0.004$), a body mass index of less than 18.5 ($P = 0.004$), and a poor performance score were associated with an increased risk of death ($P < 0.001$). The 52 subjects receiving AAT experienced longer survival than the 92 subjects receiving BSC (median seven months [AAT] versus three months [BSC]; $P < 0.001$). When sub-classified into five-year age intervals, AAT was a significant advantage in overall survival (OS) to patients aged 70–74, but not to those ≥75 years old.

Conclusions: AAT for patients ≥70 years old with advanced NSCLC extended OS. However, care should be taken in decisions on active anti-cancer treatments for patients over 75 years old. A prospective multicenter trial is required in the near future.

Introduction

With the growing elderly population and the advance of industrialization and urbanization, the number of patients being diagnosed with lung cancer has increased, and the mean age at the time of diagnosis has gradually increased. Weiss and Langer reported that the median age at diagnosis for non-small cell lung cancer (NSCLC) was 71 years old.[1] Forty-three percent of patients with advanced NSCLC included in the current study were aged 70 years or over. In Korea, the mean age of individuals diagnosed with lung cancer was 63 years in 1997 and 65 years in 2005, indicating a trend of increasing age at diagnosis. It is expected that the proportion of the elderly population with lung cancer will continue to increase.[2] The likelihood of detecting lung lesions has also risen, as a result of more frequent health examinations provided by the Health Insurance Plan and the increased use of chest computed tomography (CT) scanning.[3,4] Anti-cancer programs in Korea are enabling access to a wider range of treatment by improving cancer management, as well as providing a national cancer screening process and comprehensive care of patients and their families to treat cancer more actively.[5]

However, these opportunities are more often used by younger patients, as older patients still seem to have negative concepts of examination and active anti-cancer treatment (AAT) because of concerns about adverse events and possible treatment complications.[6] Because 50% of NSCLC cases occur in individuals >65 years old, and about 40% of NSCLC patients are >70 years old,[7] an age-based assessment of AAT is needed. Previous studies and guidelines of lung cancer in older patients have been limited.[8,9] This study evaluated the characteristics of elderly patients with advanced stage IIIb and IV NSCLC in response to AAT compared with best supportive care (BSC).

Methods

Patients

The data were retrieved retrospectively from the medical records of elderly patients who were aged 70 years or older and were diagnosed with NSCLC at stage IIIb or IV by histological or cytological methods from January 2000 to December 2007 at Ewha Womans University Mokdong Hospital. The Institutional Review Board of the Hospital (IRB no: 12-11-06) approved the study.

Data collection

To determine disease status, serial clinical examinations were conducted. Staging was based on the 7th Tumor Node Metastasis (TNM) classification of the American Joint Committee on Cancer. In total, 672 patients >18 years old were confirmed to have lung cancer by histological or cytological methods. We excluded 157 subjects: for whom we could not acquire sufficient data for this study; who had only been treated with one chemotherapy cycle; underwent any surgery; received regional radiotherapy, excluding the chest area, with a palliative purpose; or who were lost to follow-up after diagnosis, leaving 515 patients. Of these, 144 patients were aged 70 or older with stage IIIb/IV NSCLC. The 144 elderly patients were grouped according to whether they received AAT or BSC. The clinical decision about the aims of treatment was based on multidisciplinary discussion, including group discussion of clinicians and opinions from the patient and their family. Patients who had received more than two cycles of chemotherapy or chest radiotherapy were placed in the AAT group, whereas those who had received only BSC without any kind of chemotherapy or radiotherapy were placed in the BSC group. Individuals' comorbidities were scored by Charlson index,[10] and computed by electronic application without age adjustments.[11] Overall survival (OS) time was measured from the date of histological or cytological diagnosis to the date of death from any cause or to 31 August 2012, whichever came first.

Statistical analysis

SPSS version 18.0 was used for statistical analysis. Descriptive statistics were used to obtain frequency, median, and range (25–75 percentile) values. For analysis of basic characteristics and clinical profiles between groups, the chi-square test and Mann–Whitney U test were applied appropriately. The Kaplan–Meier test was applied for survival curves; the Mantel–Cox version of the log rank test was used for comparison of OS between two groups. A Cox proportional-hazards model was used to identify risk factors that affected survival. $P < 0.05$ was considered statistically significant.

Results

Basic patient characteristics

The age of the 144 patients included in the final analysis ranged between 70 and 95 years; the median age was 77 years. Survival time ranged between 0–79 months; the median was five months. The most common combined illness was respiratory or cardiovascular disease. Of the 144 patients, 52 were placed in the AAT group and 92 patients in the BSC group (Table 1). As the primary treatment for the AAT group, 42 patients were treated with chemotherapy: 26 cases with platinum-based combination regimens, 16 cases with a single chemotherapeutic, and 10 patients were treated with radiotherapy. Among the 42 patients who received chemotherapy, 31 patients received chemotherapy only, and 11 received chemotherapy plus radiotherapy.

When comparing the two groups, AAT was selected more often for males than BSC ($P = 0.01$). Among individuals aged 70 or older, the median age of the AAT group was lower than the BSC group ($P = 0.002$). There was no difference between the two groups in terms of body mass index, smoking history, lung function, weight loss, Charlson comorbidity index, or histological type. Also, there was no difference in the distribution of Eastern Cooperative Oncology Group (ECOG) scores between the two groups, although patients with scores of ECOG 0 tended to be in the AAT group, and those with ECOG 3 scores in the BSC group (Table 1).

Variables affecting survival

Significant variables affecting mortality were selected from univariate analyses by the Cox proportional-hazards model and analyzed. In the multivariate analysis, AAT independently contributed to a decrease in the hazard ratio of death ($P = 0.04$), whereas male gender ($P = 0.004$), a body mass index of less than 18.5 ($P = 0.004$), and a poor performance score were associated with increased risk of death ($P < 0.001$) (Table 2).

Overall survival

Among patients aged 70 or older, the median survival time of the AAT group was seven months (95% confidence interval [CI]: 5.2–8.8), which was significantly longer than that of the BSC group at three months (95% CI: 1.3–4.7, $P < 0.001$). The 12-month survival rate was 31% in the AAT group, compared with 22% in the BSC group; the 24-month survival rate was 12% for AAT and 4% for BSC according to the survival curves (Fig. 1a). When age was limited to 70–74 years, AAT resulted in a significantly increased survival rate compared with BSC ($P = 0.02$) (Fig. 1b). However, when age was limited to

Table 1 Demographic characteristics of patients aged 70 years or older

Variable	AAT (n† = 52)	BSC (n = 92)	P-value
Gender			
Male	43 (83)	57 (62)	0.01*
Age			
≥70 years old	75 (72~78)	77 (74~82)	0.002**
70–74 years old (n = 23 vs. 25)‡	72 (70~73)	72 (71~73)	0.74**
75–79 years old (n = 21 vs. 29)‡	77 (76~78)	77 (75~78)	0.26**
≥80 years old (n = 8 vs. 38)‡	81 (80~81)	82 (81~85)	0.01**
BMI, kg/m^2	21 (20~24)	21 (19~23)	0.72**
Low (<18.5)	6 (12)	14 (18)	
Normal (18.5~25)	36 (74)	54 (70)	
Overweight (≥25)	7 (14)	9 (12)	
Smoking Amount of smoking, pack-year	40 (2~50)	28 (0~50)	0.50**
Never	12 (24)	30 (33)	0.34*
Current or previous§	38 (76)	60 (67)	
Pulmonary function			
FVC, % predicted	73 (55~90)	79 (60~92)	0.44**
FEV$_1$, % predicted	64 (52~91)	79 (59~102)	0.09**
FEV$_1$/FVC, %	67 (60~76)	69 (63~78)	0.41**
ECOG			
0	17 (33)	18 (20)	0.13*
1	24 (46)	48 (52)	
2	7 (13)	9 (10)	
3	4 (8)	17 (18)	
Weight loss			
<5%	27 (66)	61 (77)	0.20*
≥5%	14 (34)	18 (23)	
Charlson comorbidity index¶			
0	20 (39)	41 (45)	0.44*
1	19 (36)	36 (39)	
≥2	13 (25)	15 (16)	
Pathology			
Squamous cell carcinoma	23 (44)	27 (29)	0.10*
Non-squamous cell carcinoma	29 (56)	65 (71)	

Data are presented as number (percentage) or median (25–75%). †Number of patients. ‡AAT versus BSC. §Previous smoker: patient stopped smoking at least 6 months prior to diagnosis of lung cancer. ¶Reference 10. *Chi-square test. **Mann–Whitney U test. AAT, active anti-cancer treatment; BMI, body mass index; BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group scale; FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity.

75 years or older, AAT had a similar survival rate to BSC (P = 0.08, Fig. 1c; P = 0.09, Fig. 1d).

Discussion

Our results showed that in elderly patients with lung cancer, AAT significantly extended overall survival compared with BSC in patients with advanced NSCLC ≥ 70 years old. To date, assessments of therapeutic effectiveness in elderly patients have been limited, especially in those older than 70 years.[1,9] Lewis *et al*. reported that 61% of all cancer patients were aged 65 years or older, but only 32% of these patients participated in phase II or phase III clinical studies.[12] A study of 6308 patients aged 65 or older with stage IV NSCLC reported that 27% of patients 65–74 years old had received anti-cancer treatments, but only 15% of patients 75–84 years old had

received anti-cancer treatments.[13] These trends correspond to our study, which showed that 36% of patients over 70 years of age and 30% of those aged over 75 years were actively treated. Nevertheless, the number of studies of treatments for elderly patients has gradually increased since 2000; age has not limited analysis of the effectiveness and/or safety of chemotherapy or radiotherapy.[7,14] Chemotherapy options with less cytotoxicity or molecularly targeted agents, recommended as a new option for maintenance-phase chemotherapy,[15,16] can also be recommended for elderly patients.

Other unfavorable risk factors being studied that affect survival include male gender, low body mass index, and poor performance, which were already established risk factors.[17–19]

In this study, the AAT group was slightly younger than the BSC group, which had little influence on the outcome, and as patients aged they showed a preference for BSC. This is

Table 2 Univariate and multivariate analyses by Cox regression for predictors of overall survival

Factor	HR†	95% CI	P-value	HR‡	95% CI	P-value
Treatment			0.016			0.04
Best supportive care	1			1		
Active anti-cancer treatment	0.65	0.45–0.92		0.66	0.44–0.98	
Gender			0.15			0.004
Female	1			1		
Male	1.32	0.91–1.92		1.89	1.22–2.93	
Age (year +1)	1.04	1.01–1.07	0.013	1.03	0.99–1.07	0.19
BMI (+1 kg/m^2)			0.009			0.004
≥18.5	1			1		
<18.5	1.92	1.18–3.13		2.07	1.26–3.41	
Smoking			0.10			
Never	1					
Ever	1.39	0.94–2.04				
ECOG (+1)	1.40	1.20–1.65	<0.001	1.49	1.25–1.79	<0.001
Charlson comorbidity index			0.25			
0	1					
1	0.86	0.54–1.37				
≥2	0.73	0.50–1.06				
Weight loss			0.20			
<5%	1					
≥5%	1.31	0.87–1.98				
Pathology			0.80			
Squamous cell carcinoma	1					
Non-squamous cell carcinoma	0.96	0.67–1.36				
FEV$_1$ (% predicted +1)	1.003	0.99–1.01	0.59			

HR†, hazard ratio on univariate analysis; HR‡, hazard ratio on multivariate analysis. BMI, body mass index; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group scale; FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity.

consistent with the negative views that some patients and their families have shown toward cancer treatment in terms of aging and may reflect the conditions of actual clinical practice. Regarding the oldest age at which a patient would be expected to demonstrate therapeutic effectiveness and safety, de Rijke *et al.*[20] reported that 75 years of age is an important selection criterion for determining guideline treatments for elderly patients, in addition to comorbidity. Tamiya *et al.*[21] suggested that even if a patient with advanced lung cancer was 80 years or older, chemotherapy could be relatively successful with proper guidelines for selection. We subdivided our results, using five-year age intervals to evaluate survival according to the influence of age between the two groups. The superiority of AAT to BSC was maintained in patients aged younger than 75, but was lost in those aged over 75, consistent with de Rijke's results.[20] The activity and opinion of the doctor may be very important for determining the treatment of the patient or for participation in a clinical trial.[22]

The limitations of this study include the sample size, which was relatively small, and the data source, which was a single institution. The age of the AAT group was relatively lower than the control group and we sub-analyzed survival between

the two groups by dividing into five-year age intervals to minimize age difference, as previously discussed.

Our study showed the characteristics of management in patients aged 70 years or older with advanced NSCLC and compared AAT with BSC.

Conclusions

AAT in elderly patients aged 70 years or older extended survival longer than BSC. For patients 70–74 years old, active treatment should be considered. However, in patients' ≥75 years, great care must be taken in the decision of active anti-cancer treatment. A prospective multicenter trial is required in the near future.

Acknowledgment

Disclosure

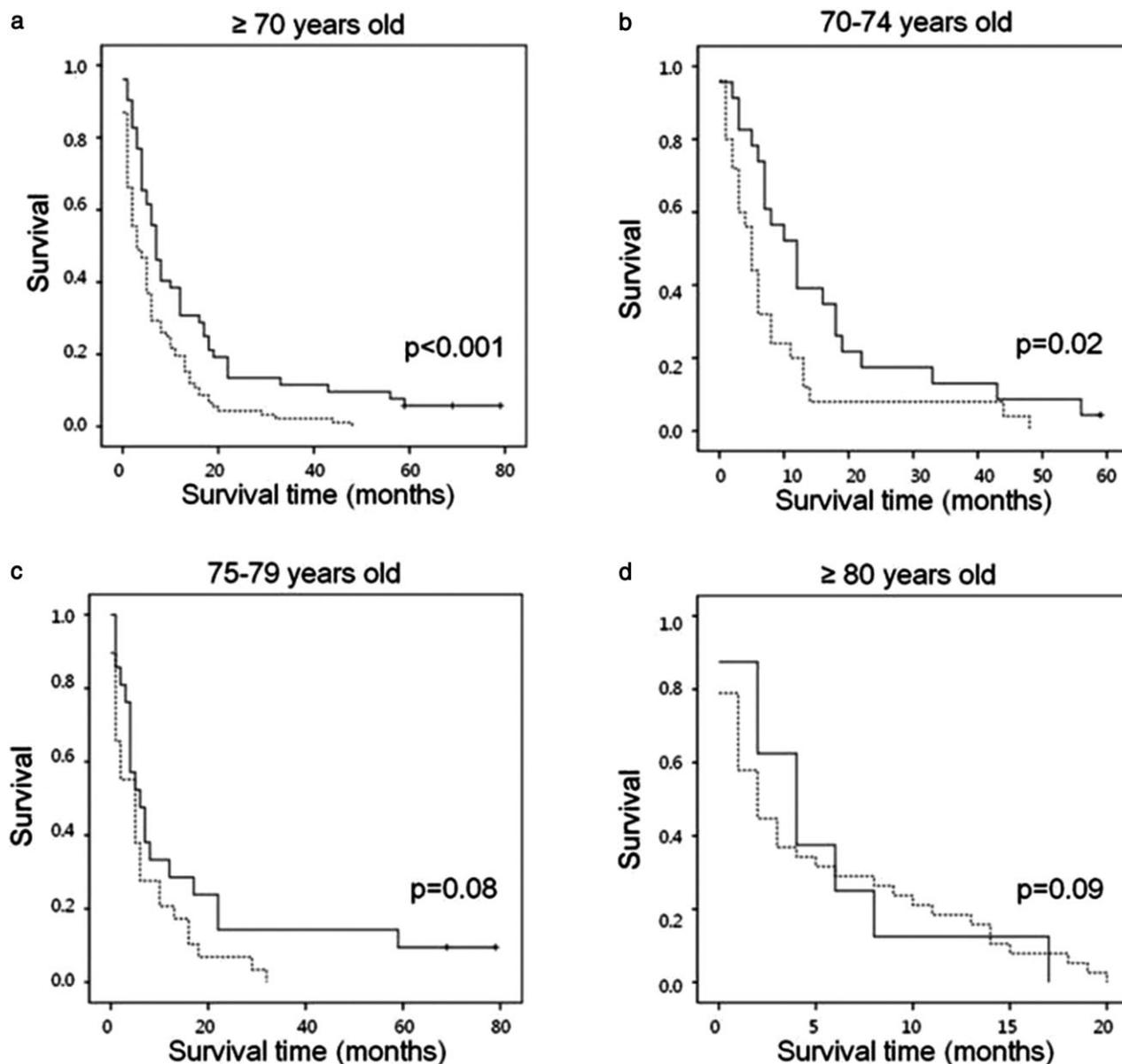No authors report any conflict of interest.

Figure 1 Kaplan-Meier estimates of overall survival in each age group according to treatment arm. AAT: active anti-cancer treatment; BSC: best supportive care. —, AAT; - - -, BSC.

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