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Trends in chemotherapy for elderly patients with advanced non–small-cell lung cancer

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This manuscript includes 18 text pages, 6 tables, and 1 figure.

Running Title: Chemotherapy for NSCLC in the elderly

Keywords: non-small-cell lung cancer, elderly, chemotherapy, third-generation, second-line

ABSTRACT

BACKGROUND. In approximately the year 2000, the results of a number of important studies of non–small-cell lung cancer (NSCLC) were published.

METHODS. Between July 1992 and December 2003, 223 patients with NSCLC aged ≥70 years received chemotherapy alone as their initial treatment at the National Cancer Center Hospital East. These patients were divided into 2 groups: those that began treatment between 1992 and 1999 (group A) and between 2000 and 2003 (group B). The details of chemotherapy regimens and outcomes were compared.

RESULTS. In group A, 83% of patients received platinum-based chemotherapy, two-thirds of these regimens comprised platinum plus second-generation combination chemotherapy. In contrast, although 55% of patients received platinum-based chemotherapy in group B, 41% of patients received non-platinum-based chemotherapy. Among patients in group B, performance status was significantly associated with the selection of platinum-based or non-platinum-based chemotherapy; age was marginally associated with this selection. Median survival time (MST), 1-year survival rate, and 2 year-survival rate were 6.7 months, 14%, and 7%, respectively, in group A, and 8.1 months, 35%, and 20% in group B (p = 0.0109). Multivariate analysis revealed that clinical stage and administration of salvage chemotherapy were independent prognostic

factors.

CONCLUSIONS. In and after the year 2000, chemotherapy regimens changed greatly and survival of elderly patients significantly improved in our institute, and this improvement appears to be attributable mostly to the effect of salvage chemotherapy. These results suggest that even elderly patients should be offered salvage chemotherapy regardless of age, if possible.

INTRODUCTION

Lung cancer is the leading cause of cancer-related death in many industrialized countries. Non-small cell lung cancer (NSCLC) accounts for approximately 80% to 85% of all lung cancers, and the majority of patients have metastatic disease at the time of diagnosis[1]. Previous data indicate that more than 50% of advanced NSCLC are diagnosed in patients aged ≥65 years and about 30% to 40% are diagnosed in patients ≥70 years of age[2]. NSCLC can therefore be regarded as a disease of the elderly, and the proportion of older adults among NSCLC patients is expected to progressively increase due to the aging of the populations of most developed countries.

Platinum-based combination chemotherapy improves survival and quality-of-life (QOL) in patients with advanced NSCLC, and is now widely accepted as the standard in chemotherapy[3, 4]. However, platinum-based chemotherapy is often contraindicated in elderly patients because of patient deficits in functional status and organ function. In addition, elderly patients have approximately twice as many comorbidities as the general population[5, 6]. Past studies on the effect of age on treatment choices for advanced NSCLC have revealed that elderly patients were less likely to receive active treatments[7-9]. Until recently, clinical trials for NSCLC have not specifically examined the importance of chronological age or the desirability of an

upper age limit for treatment. Indeed, it has been reported that elderly patients are under-represented in those trials. In fact, according to a survey conducted by the Southwest Oncology Group, only 39% of patients enrolled in lung cancer trials between 1993 and 1996 were older than age 65, even though such patients represent 66% of the overall cancer patient population[10].

The lack of clinical data on elderly NSCLC patients encouraged physicians to carry out elderly-specific clinical trials. In the 1990s, third-generation cytotoxic agents, such as vinorelbine (VNR), gemcitabine, docetaxel (DOC), paclitaxel, and irinotecan, were developed, and single-agent chemotherapy regimens using these agents were investigated in many phase II trials. In 1999, the results of the first elderly-specific phase III trial comparing VNR to best supportive care were published [11]. In that study, a significant survival benefit was seen in patients receiving VNR. Furthermore, VNR was well tolerated and QOL scores were better in patients treated with VNR. Then, in 2000, 2 phase III trials revealed a survival benefit for DOC when used as second-line chemotherapy agent, which was the first evidence for the effectiveness of second-line chemotherapy for NSCLC[12, 13]. In addition, in 2002, as compared to other countries, approval for gefitinib, epidermal growth factor tyrosine kinase inhibitor (EGFR-TKI), was granted early in Japan.

These results should have a significant impact on clinical practice relating to advanced NSCLC in the elderly. In this study, we reviewed data on chemotherapy regimens used in the treatment of elderly NSCLC patients at our institute, and compared regimens and patient outcomes before and after year 2000.

MATERIALS AND METHODS

Patients

Between July 1992 and December 2003, 223 NSCLC patients aged ≥70 years received chemotherapy alone as their initial treatment at the National Cancer Center Hospital East. These patients were divided into 2 groups: those that began treatment between 1992 and 1999 (group A) and those that began treatment between 2000 and 2003 (group B). Chemotherapy regimens and outcomes were then compared between groups. Group B patients were then subdivided into 2 groups—the platinum-based chemotherapy group and the non-platinum-based chemotherapy group—and the clinical factors responsible for treatment choice were then analyzed. In addition, Group B patients were subdivided into another two groups; EGFR-TKI treated group or not-treated group. All patient data were obtained from our database.

Tumor evaluation and statistical analysis

Survival time was measured from the start of chemotherapy to either the time of death from any cause or the date patients were last known to be alive. The survival curve was estimated using the Kaplan-Meier method, and compared by using the log-rank test. Comparisons between individual clinical factors were performed using the χ^2 test.

Multivariate analysis was conducted according to the Cox proportional hazards model. $P<0.05$ was considered to denote statistical significance. All statistical analyses were performed using StatView, Version 5.0 (Abacus Concepts, Berkley, CA).

RESULTS

Patient characteristics

Patient characteristics are listed in Table 1. There were 74 patients in group A and 149 in group B. Median age was almost identical, but the proportion of patients aged ≥75 years was significantly higher in group B (p = 0.0182). Other clinical factors, including sex, performance status (PS), tumor histology, disease stage, and smoking history, were not significantly different between the groups.

First-line chemotherapy

Details of first-line chemotherapy are shown in Table 2. In group A, 83% of patients received platinum-based chemotherapy; two-thirds of these were platinum-based plus second-generation combination chemotherapy regimens. In group B by contrast, although 55% of patients received platinum-based chemotherapy, 41% received non-platinum-based chemotherapy and 4% received epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI). EGFR-TKI as first-line treatment was all clinical trial settings. In group B, second-generation agents were no longer used, and the most frequently administered third-generation single-agent chemotherapy was VNR.

Clinical factors influencing selection of platinum-based and non-platinum-based chemotherapy

In group B, 143 patients (96%) received platinum-based or non-platinum-based chemotherapy; only 6 patients (4%) received EGFR-TKI. In order to determine the clinical factors that affected the selection of platinum-based and non-platinum-based chemotherapy, relevant clinical factors were individually compared between these 2 patient subgroups. As shown in Table 3, only PS significantly differed between groups: patients with a PS of 0 or 1 tended to receive platinum-based chemotherapy; those with a PS of 2 tended to receive non-platinum-based chemotherapy (p = 0.004). Other clinical factors did not significantly differ between the groups; however, the proportion of patients aged ≥75 years was marginally higher in the non-platinum-based chemotherapy group (p = 0.0596).

EGFR-TKI treatment

In group B, 34 patients received EGFR-TKI treatment during entire treatment period, while no patients in group A. In group B, the proportion of patients who received EGFR-TKI was significantly higher in female, adenocarcinoma, and never-smoked patients (Table 4).

Second-line chemotherapy and beyond

The characteristics of patients who underwent multiple-line chemotherapy are shown in Table 5. In group A, second-line chemotherapy was administered to only 4 patients (5%) and no patients underwent third-line chemotherapy. In group B by contrast, second-line and third-line chemotherapy was administered to 62 (42%) and 22 (15%) patients, respectively. DOC was the agent most frequently used in second-line chemotherapy; EGFR-TKI was the most common agent for third-line chemotherapy.

Survival

Median survival time (MST) was 6.7 months in group A and 8.1 months in group B (p = 0.0109). The 1-year-survival rate and 2-year-survival rate were 14% and 7%, respectively, in group A, and 35% and 20% in group B. Survival curves are shown in Figure 1. The relationships between clinical variables and survival are shown in Table 6. Univariate analysis revealed that female, stage ≤IIIB, never-smoker, EGFR-TKI treatment, and the administration of salvage chemotherapy were associated with better survival. However, multivariate analysis demonstrated that only clinical stage and the administration of salvage chemotherapy were independent prognostic factors.

DISCUSSION

In approximately the year 2000, the results of large phase III trials of treatments for advanced NSCLC were published. The findings of these studies were of great importance in understanding how to treat elderly patients with NSCLC. In the present retrospective study, we attempted to evaluate the impact of those trials by reviewing the records of 223 patients aged ≥70 years who began chemotherapy between 1992 and 2003 at our institute and comparing treatment details between those who began chemotherapy between 1992 and 1999 (group A) and those who began treatment between 2000 and 2003 (group B).

As we anticipated, the proportion of patients who received non-platinum-based chemotherapy, with either 1 or 2 agents, was higher in group B; however, more than 50% of patients in group B still received platinum-based chemotherapy. We further investigated group B to determine what clinical factors were associated with the selection of platinum-based or non-platinum-based chemotherapy. The results were unsurprising: patients with a PS of 2 aged ≥75 tended to receive non-platinum-based chemotherapy. Several sub-group analyses from phase III trials indicated that, when PS was not impaired, platinum-based chemotherapy was equally safe and effective in patients aged over and under 70 years[14-17]. The first elderly-specific trial comparing

platinum-based and non-platinum-based chemotherapy regimens also indicated that patients aged 70 to 74 years might derive more benefit from platinum-based chemotherapy than from non-platinum -based chemotherapy[18]. However, it is unclear whether platinum-based chemotherapy is safe and effective for patients aged ≥75 years.

In the present study, the proportion of patients who received salvage chemotherapy was also higher in group B. While only 5% of patients received second-line chemotherapy in group A, 42% received second-line chemotherapy in group B. In 15% of patients in group B, third-line chemotherapy was also administered.

Overall survival time was significantly longer in group B, as compared with group A, and multivariate analysis revealed that clinical stage and the administration of salvage chemotherapy were independent prognostic factors. Between group A and B, the difference of clinical stage was not significant. Therefore, these results seem to be the effect of salvage chemotherapy and suggest that even elderly patients should be offered salvage chemotherapy regardless of age, if possible. To date, several agents, such as docetaxel, gefitinib, erlotinib, and pemetrexed, have been approved as salvage chemotherapy worldwide, including Japan[19]. Physicians should not miss a chance to offer these effective agents to elderly patients.

In conclusion, in our institute, chemotherapy regimens changed considerably after

the year 2000. In addition, survival time significantly improved after 2000, and this improvement appears to be attributable mostly to the effect of salvage chemotherapy.

Conflict of Interest Statement

None of the authors have a conflict of interest to declare in relation to this work.

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Figure legends

Figure 1. Kaplan-Meier curve of overall survival in all patients (n = 232). Median survival time, 1-year-survival rate, and 2-year-survival rate were 6.7 months, 14%, and 7%, respectively, in group A , and 8.1 months, 35%, and 20% in group B.

Figure1

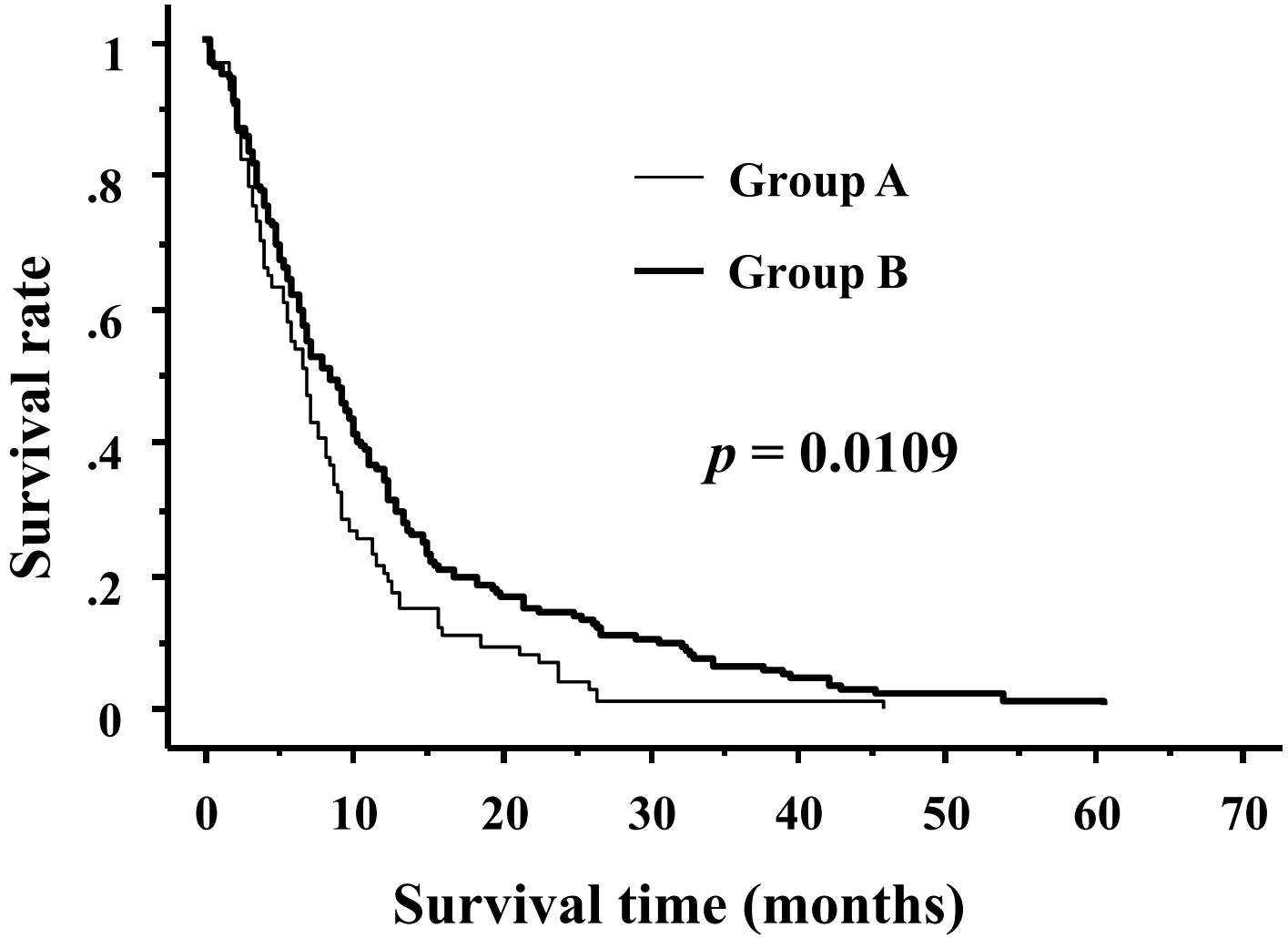

Fig. 1

Table1

Table 1. Patient characteristics (n=223)

	Group A ('92-'99)	Group B ('00-'03)
No. of patients	**74**	**149**
Age		
Median	**73**	**74**
<75	**55 (75%)**	**86 (58%)**
≥75	**19 (25%)**	**63 (42%)**
Sex		
Male	**62 (84%)**	**115 (78%)**
Female	**12 (16%)**	**34 (22%)**
ECOG PS		
0-1	**69 (93%)**	**136 (91%)**
2	**5 (7%)**	**13 (9%)**
Histology		
Ad	**52 (70%)**	**84 (56%)**
Non-Ad	**22 (30%)**	**65 (44%)**
Stage		
≤IIIb	**25 (34%)**	**55 (37%)**
IV	**49 (66%)**	**94 (63%)**
Smoking history		
Current/former	**62 (84%)**	**119 (80%)**
Never	**12 (16%)**	**30 (20%)**

ECOG, Eastern Clinical Oncology Group; PS, performance status

Table2

Table 2. First-line chemotherapy

	Group A ('92-'99)		Group B ('00-'03)	
Platinum based				
Pltinum + 2nd-generation	**41**	**(56%)**	**0**	**(0%)**
CDDP+VDS+MMC	**26**		**0**	
CDDP+VDS	**14**		**0**	
254S+VDS	**1**		**0**	
Pltinum + 3rd-generation	**20**	**(27%)**	**83**	**(55%)**
CDDP+VNR	**3**		**44**	
CDDP+DOC	**15**		**15**	
CBDCA+PTX	**0**		**12**	
CDDP+VNR+GEM	**0**		**5**	
CDDP+GEM	**0**		**4**	
CDDP+CPT-11	**2**		**3**	
Non-platinum based				
2nd-generation	**3**	**(4%)**	**0**	**(0%)**
ETP	**3**		**0**	
3rd-generation (mono)	**7**	**(10%)**	**29**	**(20%)**
VNR	**2**		**23**	
DOC	**0**		**5**	
GEM	**0**		**1**	
PTX	**3**		**0**	
CPT-11	**2**		**0**	
3rd-generation (doublet)	**2**	**(3%)**	**31**	**(21%)**
GEM+VNR	**2**		**31**	
EGFR-TKI	**0**	**(0%)**	**6**	**(4%)**
Gefitinib	**0**		**6**	

CDDP, cisplatin; VDS, vindesine; MMC, mitomycin C; 254S, nedaplatin; VNR, vinorelbine; DOC, docetaxel; CBDCA, carboplatin; PTX, paclitaxel; GEM, gemcitabine; CPT-11, irinotec ETP, etoposide

Table3

Table 3. Patient characteristics of Group B (platinum vs non-platinum)

	Platinum based	Non-platinum based	*P*
No. of patients	**83**	**60**	
Age			
Median	**73**	**74**	
<75	**55 (66%)**	**28 (47%)**	**0.0596**
≥75	**30 (34%)**	**32 (53%)**	
Sex			
Male	**66 (80%)**	**47 (78%)**	**>0.9999**
Female	**17 (20%)**	**13 (22%)**	
Performance status			
0-1	**81 (98%)**	**50 (83%)**	**0.0040***
2	**2 (2%)**	**10 (17%)**	
Histology			
Ad	**51 (61%)**	**29 (48%)**	**0.1283**
Non-Ad	**32 (39%)**	**31 (52%)**	
Stage			
≤IIIb	**33 (40%)**	**21 (35%)**	**0.6032**
IV	**50 (60%)**	**39 (65%)**	
Smoking history			
Current/former	**66 (80%)**	**49 (82%)**	**0.8326**
Never	**17 (20%)**	**11 (18%)**	

Ad, adenocarcinoma

Table4

Table 4. Patient characteristics of Group B (EGFR-TKI treated vs not EGFR-TKI treated)

	EGFR-TKI(+)	EGFR-TKI(-)
No. of patients	**34**	**115**
Age		
Median	**73**	**74**
<75	**25 (74%)**	**61 (53%)**
≥75	**9 (26%)**	**54 (47%)**
Sex		
Male	**19 (56%)**	**96 (83%)**
Female	**15 (44%)**	**19 (17%)**
Performance status		
0-1	**30 (88%)**	**106 (92%)**
2	**4 (12%)**	**9 (8%)**
Histology		
Ad	**27 (79%)**	**57 (50%)**
Non-Ad	**7 (21%)**	**58 (50%)**
Stage		
≤IIIb	**11 (32%)**	**44 (38%)**
IV	**23 (68%)**	**71 (62%)**
Smoking history		
Current/former	**21 (62%)**	**98 (85%)**
Never	**13 (38%)**	**17 (15%)**

Ad, adenocarcinoma

Table5

Table 5. The number of patients receiving multiple chemotherapies (n=223)

		Group A ('92-'99)		Group B ('00-'03)	
2nd-line	yes	4	(5%)	62[a]	(42%)
	no	70	(95%)	87	(58%)
3rd-line	yes	0	(0%)	22[b]	(15%)
	no	74	(100%)	127	(85%)
4th-line	yes	0	(0%)	9	(6%)
	no	74	(100%)	140	(94%)

a, docetaxel 27; EGFR-TKI 12; platinum-based 12; others 11
b, EGFR-TKI 14; docetaxel 1; others 7

Table6

Table 6. Multivariate analysis for survival

Variables	Category	MST (months)	Univariate	Multivariate	
			p	Risk ratio	95%CI
Age	<70	7.6	0.6031	1.0930	0.815-1.465
	≥70	7.0			
Sex	Female	9.7	0.0012*	1.4060	0.798-2.476
	Male	7.0			
PS	0-1	7.5	0.1509	1.3030	0.783-2.169
	2	4.0			
Histology	Ad	7.5	0.0564	0.8300	0.623-1.106
	non-Ad	6.7			
Stage	≤IIIB	9.3	0.0094*	0.6120	0.524-0.949
	IV	6.8			
Smoking history	(-)	9.2	0.0062*	0.8510	0.634-2.044
	(+)	7.0			
Platinum-doublet	(-)	7.3	0.8551	1.1260	0.829-1.529
	(+)	7.1			
3rd-generation agent	(-)	6.7	0.2715	0.8640	0.596-1.252
	(+)	7.3			
EGFR-TKI	(-)	6.7	<0.0001*	0.7900	0.453-1.379
	(+)	15.0			
Salvage chemotherapy	(-)	5.8	<0.0001*	0.5100	0.335-0.776
	(+)	12.6			

EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; Ad, adenocarcinoma