Efficacy of second-line treatment and importance of comorbidity scores and clinical parameters affecting prognosis in elderly patients with non-small cell lung cancer without epidermal growth factor receptor mutations

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Abstract. The present study investigated the importance of comorbidity scores and clinical parameters in elderly patients with non-small cell lung cancer (NSCLC) not harboring epidermal growth factor receptor (*EGFR*) mutations who received second-line chemotherapy. The present study also compared the efficacy of tyrosine kinase inhibitor and cytotoxic chemotherapy as second-line treatment in elderly patients. The present study retrospectively reviewed the treatment of elderly patients with NSCLC (≥70 years old) who received second-line chemotherapy at Korea University Guro Hospital. Patients who had an *EGFR* mutation were excluded from the analysis. Between 2005 and 2013, 126 patients were included in the present study. The median progression-free survival (PFS) and overall survival (OS) for all patients who received second-line treatment were 2.47 months [95% confidence interval (CI), 2.08-2.86] and 8.63 months (95% CI, 5.99-11.28), respectively. A total of 52 patients (41.3%) were treated with tyrosine kinase inhibitor (TKI) and 74 (58.7%) were treated with chemotherapy. No difference was observed in the median PFS and OS between the TKI and chemotherapy groups (P=0.287 for PFS and P=0.374 for OS). The Charlson comorbidity index was not associated with survival, whereas a simplified comorbidity score and clinical factors, including poor performance status, short PFS of first-line chemotherapy, presence of brain metastasis and low serum albumin and sodium levels were significant prognostic factors in these elderly patients. Second-line chemotherapy was not beneficial to patients who had at least 3 of these factors and a median OS of 1.73 months, whereas patients who had less than 2 of these factors had a median OS of 11.50 months. For elderly lung cancer patients without *EGFR* mutations, clinical parameters were the most important factors affecting survival, rather than the types of drugs.

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Introduction

Lung cancer is the most common cause of cancer-associated mortality, and according to the data from western countries, >50% of newly diagnosed patients with lung cancer are >70 years of age (1). With the advances in diagnostics and cancer treatment, an increasing number of elderly patients are being diagnosed with lung cancer and actively receiving treatment.

Second-line treatments are comparably efficacious in elderly as well as younger patients. For patients not harboring an epidermal growth factor receptor (*EGFR*) mutation, tyrosine kinase inhibitor (TKI) and cytotoxic chemotherapeutic agents are currently second-line treatment options. In a retrospective analysis performed on elderly patients (≥70 years old) enrolled in the BR.21 trials, elderly patients revealed a benefit from second-line erlotinib treatment compared with the best supportive care with similar overall survival (OS) and response rates to those of younger patients (2). Regarding cytotoxic chemotherapy, pemetrexed or docetaxel as second-line treatment demonstrated comparable efficacy and toxicity in elderly, and younger patients in a retrospective analysis of large randomized clinical trials (3).

In addition, predicting which elderly patients may or may not benefit from chemotherapy and investigating suitable chemotherapeutics is important. Treatment without these considerations cause unnecessary treatment-associated

toxicities, longer hospital stays, poor quality of life, economic burden and ultimately shorter survival times. As the majority of clinical trials have been performed in young and otherwise healthy people, there is insufficient knowledge regarding the efficacy and safety of drugs in elderly patients who are particularly prone to exclusion from clinical trials owing to comorbidities, coexisting multi-pharmacies or poor performance status (PS).

Comorbidities are assessed using the Charlson comorbidity index (CCI) and the simplified comorbidity score (SCS) (4-7). The CCI is one of the most widely used scoring systems and has been validated in a number of diseases and the SCS has been designed for lung cancer (4,7). In addition, there are no data comparing the efficacy of TKI and chemotherapeutic drugs in elderly patients without an *EGFR* mutation. Therefore, the present study compared the efficacy and toxicity of these two types of drugs in elderly patients.

Materials and methods

Patients. Elderly patients (≥70 years of age) with wild-type *EGFR* NSCLC who previously experienced chemotherapy failure and received second-line chemotherapy at the Korea University Guro Hospital (Seoul, Korea) between January 2005 and December 2013 were included in this retrospective study. For squamous cell carcinoma, *EGFR* mutation testing was not a routine practice due to a lack of possibility for *EGFR* mutation positivity (8). Therefore, the present study included patients with squamous cell carcinoma with unknown *EGFR* mutation status and confirmed wild-type *EGFR*. For other types of histology, only patients confirmed to have wild-type *EGFR* were included. *EGFR* mutation status was confirmed using direct sequencing or a peptide nucleic acid (PNA) clamping method using the PNA Clamp™ EGFR Mutation Detection kit (Panagene, Inc., Daejeon, Korea). Data were collected from electronic medical records. The present study was approved by the Institutional Review Board of the Korea University Guro Hospital (KUGH15250-001).

Between January 2005 and December 2013, 943 patients with lung cancer received palliative chemotherapy at Korea University Guro Hospital. Among them, 365 patients were >70 years of age and 203 of these patients received second-line chemotherapy. Following exclusion of patients harboring an *EGFR* mutation, 126 patients were included in the analysis. The patient characteristics are presented in Table I. The median age was 75 (range, 70-85) years. There were 101 males (80.2%) and 25 females (19.8%). Of the 126 patients, 58 (46.0%) were diagnosed with adenocarcinoma, 63 (50.0%) were diagnosed with squamous cell carcinoma and 5 (4.0%) were diagnosed with another histology (3 with undifferentiated carcinoma, 1 with sarcomatoid carcinoma and 1 with large-cell carcinoma).

Data collection. The following data were collected and analyzed for each patient: Age, sex, tumor histology, stage at diagnosis, site(s) of metastasis, comorbidities, previous chemotherapy prior to second-line treatment, Eastern Cooperative Oncology Group (ECOG) PS, plasma hemoglobin levels, serum sodium and albumin levels at the beginning of the second-line chemotherapy, difference in body surface area difference (BSA) between day 1 of first-line chemotherapy and day 1 of second-line chemotherapy and the subsequent treatment following failure of second-line chemotherapy.

In addition, the present study analyzed the following data: Type of chemotherapy regimen, start and end dates of chemotherapy and response and best response to the second-line chemotherapy according to the Response Evaluation Criteria in Solid Tumors version 1.1 guidelines (9). The responses of all patients were assessed at 2- to 3-month intervals by enhanced computed tomography. Magnetic resonance imaging, fluorodeoxyglucose positron emission tomography and bone scanning were performed at the physician's discretion. Treatment-related toxicity data were collected via medical records based on the National Cancer Institute Common Terminology Criteria for Adverse Events version 3 (10).

Comorbidity assessment. For assessment of comorbidities, the present study investigated the CCI and SCS at the day of second-line chemotherapy initiation. The CCI has 19 and the SCS has 7 different descriptors, with a maximum score of 35 for the CCI, and 20 for the SCS (Tables II and III) (4,7). The presence of comorbidities was assessed by reviewing electronic medical charts for individual descriptors of both comorbidity-scoring systems.

Chemotherapy regimens. Chemotherapy regimens were classified as TKI or chemotherapy, with the TKI group including patients who received an EGFR TKI, and the chemotherapy group including patients who received any type of cytotoxic chemotherapy regimen. EGFR TKIs included erlotinib and gefitinib and the cytotoxic chemotherapy regimen included docetaxel, pemetrexed, a combination of gemcitabine and vinorelbine, and platinum doublets.

Statistical analyses. All patients who received at least 1 cycle of second-line chemotherapy were included in the efficacy analysis. Rates were compared using the χ^2 test. The Kaplan-Meier method was used to estimate the OS and progression-free survival (PFS). PFS was evaluated from the initiation of the second-line chemotherapy until the first occurrence of progression, mortality from any cause or the final follow-up visit if none of the preceding events had occurred. OS was determined as the interval between the first day of first-line treatment and mortality or the final follow-up visit. Differences between the curves were analyzed using the log-rank test. Following univariate analyses using the Kaplan-Meier method, variables significantly associated with poor survival time ($P<0.05$) were selected, and a Cox proportional hazards regression was performed for multivariate analyses using the 'ENTER' method in SPSS. SPSS for Windows version 20.0 (IBM Corp., Armonk, NY, USA) was used for all statistical analyses. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. Among the 126 patients included in the present study, 52 (41.3%) were treated with TKIs and 74 (58.7%) were treated with cytotoxic chemotherapy. In the TKI group, 21 patients (40.4%) were treated with

Table I. Patient characteristics.

Characteristics	All patients	TKI	Chemotherapy	P-value[a]
No. patients (%)	126 (100.0)	52 (41.3)	74 (58.7)	
Age, years (range)	75 (70-85)	73 (70-85)	75 (70-81)	
Age, years (%)				0.456
<75	80 (63.5)	35 (67.3)	45 (60.8)	
≥75	46 (36.5)	17 (32.7)	29 (39.2)	
Sex (%)				0.845
Male	101 (80.2)	42 (80.8)	59 (79.7)	
Female	25 (19.8)	10 (19.2)	15 (20.3)	
Histology (%)				<0.001
Non-squamous	63 (50.0)	38 (73.1)	25 (33.8)	
Squamous	63 (50.0)	14 (26.9)	49 (66.2)	
Smoking history (%)				0.413
Never smoker	27 (21.4)	13 (25.0)	14 (18.9)	
Ever smoker	99 (78.6)	39 (75.0)	60 (81.1)	
Stage at diagnosis (%)				0.360
I-IIIA	22 (17.5)	11 (21.2)	11 (14.9)	
IIIB-IV	104 (82.5)	41 (78.8)	63 (85.1)	
Stage at second-line chemotherapy (%)				0.549
M0/M1a	79 (62.7)	31 (59.6)	48 (64.9)	
M1b	47 (37.3)	21 (40.4)	26 (35.1)	
PFS of first-line line chemotherapy (%)				0.383
<4 months	64 (50.8)	24 (46.2)	40 (54.1)	
≥4 months	62 (49.2)	28 (53.8)	34 (45.9)	
ECOG PS at second-line chemotherapy (%)				0.412
0-1	87 (69.0)	38 (73.1)	49 (66.2)	
2-3	39 (31.0)	14 (26.9)	25 (33.8)	
Subsequent treatment following failure of second-line chemotherapy (%)				0.036
Second-line	51 (40.5)	15 (28.8)	36 (48.6)	
Third-line	39 (31.0)	22 (42.3)	17 (23.0)	
Fourth-line or more	36 (28.6)	15 (28.8)	21 (28.4)	
BSA change between first- and second-line treatment (%)				0.963
Not decreased	73 (57.9)	30 (57.7)	43 (58.1)	
Decreased	53 (42.1)	22 (42.3)	31 (41.9)	
Plasma Hb at the second-line chemotherapy, g/dl (%)				0.153
<10	43 (34.1)	14 (26.9)	29 (39.2)	
≥10	83 (65.9)	38 (45.8)	45 (54.2)	
Serum sodium at the second-line chemotherapy, mmol/l (%)				0.482
<135	68 (54.0)	30 (57.7)	38 (51.4)	
≥135	58 (46.0)	22 (42.3)	36 (48.6)	
Serum albumin at the second-line chemotherapy, g/dl (%)				0.224
<3.5	25 (19.8)	13 (25.0)	23 (16.2)	
≥3.5	101 (80.2)	39 (75.0)	62 (83.8)	

[a]Statistical analyses were conducted using χ^2 tests. TKI, tyrosine kinase inhibitor; ECOG, Eastern Cooperative Oncology Group; PS, performance status; PFS; progression-free survival; SCS, simplified comorbidity score; BSA, body surface area; Hb, hemoglobin; HR, hazard ratio; CI, confidence interval.

gefitinib and 31 (59.6%) were treated with erlotinib. In the chemotherapy group, docetaxel was the most common agent, which was administered to 34 patients (45.9%). Pemetrexed was administered to 20 patients (27.0%). A total of 9 patients

(12.2%) were treated with a combination of gemcitabine and vinorelbine, and 7 patients (9.4%) were treated with a platinum doublet combination. A total of 4 patients (5.4%) were treated with a singlet agent other than docetaxel or pemetrexed (3 with gemcitabine and 1 with vinorelbine). A greater percentage of patients had non-squamous cell carcinoma in the TKI group, and more patients had squamous cell carcinoma in the chemotherapy group (P<0.001). The number of patients who received further treatment was not balanced between the 2 treatment groups. In the TKI group, 71.1% of patients received subsequent chemotherapy following failure of second-line treatment. Conversely, 51.4% of patients in the chemotherapy group received further treatment, including patients who received more than third-line chemotherapy (P=0.036). Except for histology and subsequent chemotherapy, there were no significant differences in the clinical characteristics of the patients between the two treatment groups (Table I).

Comorbidities of patients. The distribution of comorbidities in the included patients is presented in Table IV. A total of 69 patients (54.8%) had hypertension, 33 (26.2%) had diabetes and 46 (36.5%) had chronic pulmonary disease, including chronic obstructive pulmonary disease and interstitial lung disease. A history of solid tumor prior to second-line chemotherapy for lung cancer was observed in 15 patients; all cases were localized tumors. There were no patients with hemiplegia, dementia or acquired immune deficiency syndrome. A total of 20 patients (15.9%) had no underlying disease except metastatic lung cancer. The CCI scores of all patients ranged between 9 and 12 (median, 10) points. The SCS of all patients ranged between 1 and 15 (median, 8) points. There were no significant differences in the distribution of CCI scores and SCSs between the TKI, and chemotherapy groups.

Clinical parameters associated with treatment outcomes. The median PFS and OS for all patients who received second-line treatment was 2.47 months [95% confidence interval (CI), 2.08-2.86] and 8.63 months (95% CI, 5.99-11.28), respectively (Fig. 1A). Univariate analysis demonstrated that the OS for all patients was significantly associated with the following factors: Histology (squamous vs. non-squamous), stage at diagnosis (stage I-IIIA vs. stage IIIB-IV), PS (0-1 vs. 2-3), SCS (<13 vs. ≥13), PFS of first-line treatment (<4 months vs. ≥4 months), change of BSA between first-line and second-line treatment (not decreased vs. decreased), subsequent treatment after failure of second-line chemotherapy (at least third-line chemotherapy vs. no chemotherapy), brain metastasis (no vs. yes), distant lymph node metastasis (no vs. yes), number of metastatic organs (<3 vs. ≥3), plasma hemoglobin at the start of second-line chemotherapy (<10 vs. ≥10 g/dl), serum albumin at the start of second-line chemotherapy (<3.5 vs. ≥3.5 g/dl) and serum sodium at the start of second-line chemotherapy (<135 vs. ≥135 mmol/l). CCI, response to second-line treatment or adrenal gland, liver or bone metastasis were not associated with OS. The present study then performed multivariate analysis using a Cox proportional hazards regression model. Histology (squamous vs. non-squamous), good PS (ECOG 0-1), lower SCS (<13), no brain metastasis, longer PFS of previous chemotherapy (≥4 months), higher serum sodium level (>135 mmol/l) and higher serum albumin level (>3.5 g/dl) were associated with prolonged OS (Table V).

The present study subsequently performed survival analysis of patients who exhibited poor prognostic factors to identify patients who did not benefit from second-line chemotherapy. As the present study surmised that histology was not yet validated as prognostic markers to decide second-line treatment, a subgroup was constructed that did not include histology, but

Table II. Charlson comorbidity index and weighting of comorbidities.

Score	Comorbid condition
1	Myocardial infarction
	Congestive heart failure
	Cerebral vascular disease
	Peripheral vascular disease
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Peptic ulcer disease
	Mild liver disease
	Age[a]
2	Diabetes
	Hemiplegia
	Moderate/severe renal disease
	Diabetes with end-organ damage
	Any solid tumor
	Leukemia
	Lymphoma
3	Moderate/severe liver disease
6	Metastatic solid tumor
	Acquired immunodeficiency syndrome

Scores were obtained using the Charlson comorbidity index (4). [a]For each decade after 40 years, a point is added (1 point for age group 41-50, 2 points for age group 51-60, 3 points for 61-70 and 6 points for 71 or older).

Table III. Simplified comorbidity score and weighting of comorbidities.

Score	Comorbidity
7	Tobacco consumption
5	Diabetes mellitus
4	Renal insufficiency
1	Respiratory comorbidity
1	Neoplastic comorbidity
1	Cardiovascular comorbidity
1	Alcoholism

Comorbidities were assessed according to the simplified comorbidity score (7).

Table IV. Comorbidities and comorbidity scores of the patients included in the present study.

Cormorbity	Number	%
Comorbidities		
Diabetes mellitus	33	26.2
Chronic pulmonary disease	46	36.5
Congestive heart failure	5	4.0
Cerebrovascular disease	9	7.1
Peripheral vascular disease	10	7.9
Ulcer disease	6	4.8
Myocardial infarction	5	4.0
Liver disease	3	2.4
Chronic kidney disease	2	1.6
None except lung cancer	20	15.9
Charlson comorbidity index		
9	38	30.2
10	56	44.4
11	21	16.7
12	11	8.7
Total	126	100
Simplified comorbidity score		
1	12	9.5
2	3	2.4
3	6	4.8
6	5	4.0
7	1	0.8
8	53	42.1
9	18	14.3
13	13	10.3
14	10	7.9
15	5	4.0
Total	126	100

Comorbidities were assessed according to Charlson's comorbidity index and the simplified comorbidity score (4,7).

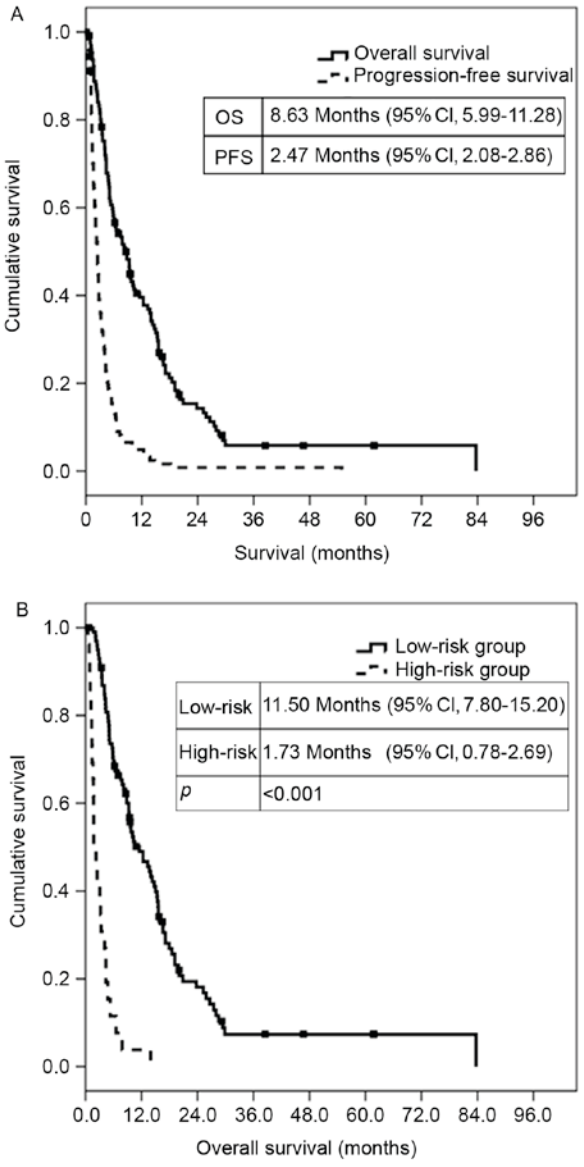

Figure 1. Survival of patients. (A) Overall survival and progression-free survival of second-line treatment in all patients. (B) Overall survival of second-line treatment according to the risk group. CI, confidence interval; OS, overall survival; PFS, progression-free survival.

prognostic factors showing statistical significance in the Cox proportional hazards regression model were weighted 1 score for each factor. The present study then divided the patients into 2 groups: Low-risk and high-risk. The low-risk group included patients who had ≤2 factors and the high-risk group included those who had ≥3 factors. There were 26 patients (20.6%) in the high-risk group. The median OS of patients in the low-risk group who received second-line treatment was 11.50 months (95% CI, 7.80-15.20), whereas the median OS of the high-risk group was 1.73 months (95% CI, 0.78-2.69). The difference in survival was statistically significant (P<0.001; Fig. 1B).

Efficacy of TKI and chemotherapy. The results of efficacy analysis are presented in Table VI. Of the 126 patients, there was no case of complete remission. The best responses were partial remission (PR) in 11 patients (15.5%) and stable disease (SD) in 51 patients (40.5%). In the TKI group, no patient exhibited PR. A total of 25 patients (50.0%) revealed SD as the best response. However, 11 patients (15.5%) demonstrated PR and 26 patients (36.6%) demonstrated SD in the chemotherapy group. Therefore, the overall response rate, which is defined as the proportion of PR and CR, was statistically different between the two groups (P=0.029).

No difference was observed in the median PFS and OS of second-line chemotherapy between the TKI, and chemotherapy groups (P=0.287 for PFS and P=0.374 for OS). The survival curves for PFS and OS are presented in Fig. 2.

Drug delivery and toxicities. The median treatment duration was 3.8 months. Of the 126 patients, 32 patients (25.4%) underwent dose reduction during second-line chemotherapy, 6 in the TKI group and 26 in the chemotherapy group. A total of 13 patients (10.3%) underwent initial dose reduction. The causes of dose reduction were chemotherapy-associated toxicity (n=18)

Table V. Multivariate analysis of prognostic factors.

Factor	All patients		
	HR	95% CI	P-value[a]
ECOG PS (0-1 vs. 2-3)	2.139	1.348-3.395	0.001
Brain metastasis (negative vs. positive)	3.177	1.288-7.839	0.012
PFS of first-line treatment, months (≥4 vs. <4)	2.860	1.837-4.452	<0.001
Serum sodium, mmol/l (≥135 vs. <135)	3.228	1.685-6.186	<0.001
Serum albumin, g/dl (≥3.5 vs. <3.5)	1.802	1.029-3.156	0.039
SCS (<13 vs. ≥13)	1.776	1.502-2.996	0.031
Histology (non-squamous vs. squamous)	1.908	1.206-3.017	0.006
Distant lymph node metastasis (negative vs. positive)	2.229	0.968-5.135	0.060
Metastatic organ (M1a vs. M1b)	1.561	0.923-2.641	0.097
Number of metastasis organs (<3 vs. ≥3)	0.475	0.184-1.226	0.124
Stage at diagnosis (I-IIIA vs. IIIB-IV)	0.865	0.490-1.527	0.617
Subsequent treatment (third-line or more chemotherapy vs. no chemotherapy)	1.278	0.819-1.996	0.280
BSA change between first- and second-line treatment (not decreased vs. decreased)	1.265	0.809-1.978	0.303
Plasma Hb, g/dl (≥10 vs. <10)	0.983	0.613-1.575	0.942

[a]Cox proportional hazards regression was conducted for multivariate analyses. ECOG, Eastern Cooperative Oncology Group; PS, performance status; PFS, progression-free survival; SCS, simplified comorbidity score; BSA, body surface area; Hb, hemoglobin; HR, hazard ratio; CI, confidence interval.

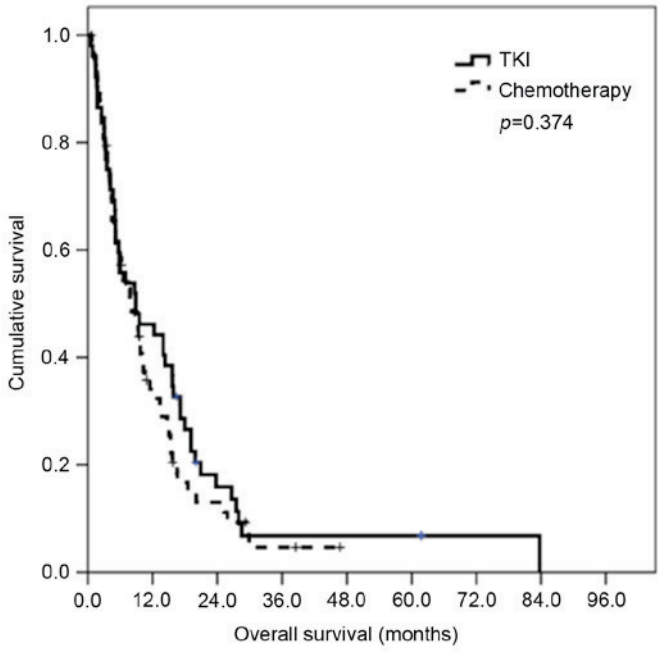

Figure 2. Overall survival of second-line treatment in TKI and chemotherapy groups. TKI, tyrosine kinase inhibitor.

and decreased PS (n=11). A total of 7 patients (5.5%) stopped chemotherapy owing to toxicity and 7 patients (5.5%) stopped treatment due to decreased PS. A total of 3 patients (2.4%) stopped chemotherapy because they refused further treatment. A total of 6 patients (11.5%) in the TKI group and 7 patients (9.4%) in the chemotherapy group stopped chemotherapy because of toxicity and poorer PS.

The frequencies of hematologic and non-hematologic adverse events are presented in Table VII. In the TKI group, non-hematological toxicities, including skin rash (54.9%), emesis (27.5%) and fatigue (27.5%), were common. In terms of hematological toxicities, anemia (47.1%) was the most common. Grade 3/4 toxicities included anemia, neutropenia, thrombocytopenia, diarrhea, emesis and fatigue, each occurring in <3.9% of patients. In the chemotherapy group, hematological toxicities were more common. Anemia (85.1%), neutropenia (36.5%), thrombocytopenia (16.2%) and febrile neutropenia (10.8%) were observed. Regarding non-hematological toxicities, emesis and fatigue were common, occurring in 44.6, and 41.9% of patients, respectively. Grade 3/4 toxicities included neutropenia (20.3%), febrile neutropenia (10.8%), anemia (8.1%), thrombocytopenia, (8.1%), emesis (6.8%) and fatigue (6.8%). There were no treatment-associated mortalities in either group.

Discussion

In the present study, clinical factors, including comorbid conditions is the most important factor affecting survival in elderly patients with lung cancer without EGFR mutations receiving second-line treatment. Additionally, clinical factors, including PS, PFS of first-line chemotherapy, presence of brain metastasis, serum albumin levels and serum sodium levels, were strong prognostic factors for elderly patients in the present study. A good PS is a well-known prognostic factor and a long PFS of previous chemotherapy reflects the less aggressive nature of the cancer (3,11). Brain metastasis is also a well-known risk factor with a poor outcome. In particular, brain metastasis in elderly patients may affect tolerability to

Table VI. Efficacy analysis of TKI and chemotherapy groups.

Factor	TKI (n=50)	Chemotherapy (n=73)
Response to second-line chemotherapy, n=123[a] (%)		
Complete remission	0 (0.0)	0 (0.0)
Partial remission	0 (0.0)	11 (15.5)
Stable disease	25 (50.0)	26 (36.6)
Progressive disease	25 (50.0)	34 (47.9)
Response rate	0.0%	15.5%
Disease control rate	50.0%	52.1%
Survival of second-line chemotherapy		
Progression-free survival (months), median (95% CI)	2.57 (2.18-3.00)	2.33 (1.75-2.92)
Overall survival (months), median (95% CI)	8.83 (1.26-16.4)	7.83 (4.80-10.87)

[a]Patients without measurable lesions (n=3, 2 in the TKI group and 1 in the chemotherapy group) were excluded. CI, confidence interval; TKI, tyrosine kinase inhibitor.

Table VII. Treatment-associated adverse events of TKI and chemotherapy groups.

	TKI (n=52)				Chemotherapy (n=74)			
	All		Grade 3-4		All		Grade 3-4	
Adverse event	n	(%)	n	(%)	n	(%)	n	(%)
Hematologic								
Anemia	24	47.1	1	2.0	63	85.1	6	8.1
Neutropenia	1	2.0	1	2.0	27	36.5	15	20.3
Thrombocytopenia	1	2.0	1	2.0	12	16.2	6	8.1
Febrile neutropenia	0	0.0	0	0	8	10.8	8	10.8
Non-hematologic								
Diarrhea	10	19.6	1	2.0	6	8.1	0	0
Emesis	14	27.5	1	2.0	33	44.6	5	6.8
Constipation	1	2.0	0	0	6	8.1	0	0
Fatigue	14	27.5	2	3.9	31	41.9	5	6.8
Neuropathy	0	0	0	0	3	4.1	0	0
Skin rash	28	54.9	1	2.0	1	1.4	0	0
ILD	2	3.9	1	2.0	0	0	0	0

TKI, tyrosine kinase inhibitor; ILD, interstitial lung disease; n, number.

chemotherapy, quality of life and neurotoxicities depending on the surgery or radiotherapy of the brain (12,13). Furthermore, numerous studies evaluated low serum albumin and sodium levels as independent poor prognostic factors in patients with cancer (14-16). Serum albumin is a commonly used marker for assessing a patient's nutritional status, inflammation and hepatic function. Serum albumin is decreased in cases of malnutrition due to cancer cachexia, treatment-associated poor oral intake or response to acute inflammation as these situations are major causes of albumin synthesis suppression (17). Hyponatremia is caused by inappropriate antidiuretic hormone secretion syndrome, diuretic drugs and salt-wasting conditions in patients with brain metastases, meningitis, and salt-losing nephropathy following cisplatin use (16). Furthermore, poor oral intake accompanying hypovolemia may induce hyponatremia in numerous patients with cancer (16). Therefore, serum albumin and sodium are reliable factors representing nutritional status, inflammatory conditions or cancer activities. Clinicians should pay close attention to these laboratory findings when treating elderly patients with cancer.

In the present study, patients with non-squamous cell histology without an *EGFR* mutation demonstrated better survival, compared with the patients with squamous cell histology. The OS in lung adenocarcinoma patients has been

reported to be higher compared with that in patients with lung squamous cell carcinoma owing to the introduction of EGFR TKI therapy (18). However, the reasons for the survival difference between patients with lung adenocarcinoma not harboring *EGFR* mutations and patients with squamous cell carcinoma in the present study remain unclear. Further investigations of survival according to histology in patients with lung cancer with or without target therapy options may aid in explaining this difference.

The present study divided patients into subgroups to investigate reliable clinical factors to predict which patients do not benefit from second-line chemotherapy. Therefore, the present study identified low-risk and high-risk groups according to the six factors that revealed statistical significance in the multivariate analysis. The OS of the high-risk group revealed ≥3 risk factors were 1.73 months, a very short duration compared with the OS of the low-risk group patients (11.50 months). Therefore, the present study concluded that second-line treatment is not beneficial and may even be harmful to patients with numerous risk factors.

In general, comorbid conditions of patients with cancer are associated with poorer survival (19,20). The present study evaluated CCI and SCS to analyze the association of comorbidities and efficacy of chemotherapy. CCI was not associated with survival, whereas SCS was associated with OS in univariate and multivariate analyses. SCS was suggested to be more sensitive to validate comorbidities. In other studies, the SCS represented an independent prognostic factor for NSCLC as well as small-cell lung cancer (7,21) and was more informative compared with CCI to predict outcomes in patients with NSCLC (7), although this is still debated. Numerous studies reported that SCS did not provide prognostic information in patients with lung cancer (6,5). To more precisely predict the outcome of patients with lung cancer with underlying disease, more validation is required.

For patients with lung cancer without *EGFR* mutations, second-line treatment includes cytotoxic agents, such as docetaxel, pemetrexed, gemcitabine and EGFR TKIs (gefitinib and erlotinib). A number of studies reported that EGFR TKI treatment in second-line treatment had similar efficacy to cytotoxic chemotherapy in patients with NSCLC (22-25). Patients with squamous cell carcinoma or NSCLC who do not harbor an *EGFR* mutation revealed a benefit from TKI compared with the best supportive care as second-line treatment (25-28). However, previous meta-analyses reported that cytotoxic chemotherapy is better compared with TKI for patients without *EGFR* mutations (29-31).

Numerous factors other than survival alone have to be considered to select therapies for elderly patients who failed previous chemotherapy as they are regarded as having a poorer physical status compared with younger patients. Physicians should take into account a number of factors in addition to age, including the patient's life expectancy, functional status and comorbidities. Therefore, TKI is an attractive choice for elderly patients as TKIs are convenient to take and require less frequent hospital visits. Furthermore, TKIs have less severe toxicities compared with cytotoxic chemotherapeutic agents. However, the treatment choice for more than second-line treatment of elderly patients with wild-type *EGFR* remains unclear, as there have been no reports on this patient group to date.

The present study was performed with elderly patients with NSCLC not harboring *EGFR* mutations in order to determine a solution for the practical treatment of these patients. In the present study, TKI produced a poor response rate compared with chemotherapy. However, PFS and OS were not different between the two treatment groups. As expected, severe toxicities exceeding grade 3 were more common in the chemotherapy group and dose reduction was also more common in the chemotherapy group, compared with the TKI group. Therefore, the results of the present study suggested that TKI may be an appropriate second-line treatment option for elderly patients. Furthermore, the present study suggested that careful dose adjustment is necessary during cytotoxic chemotherapy treatment in this age group. Hematologic toxicities are generally more common with chemotherapy compared with TKI therapy, and these toxicities affect the quality of life as well as the dose intensity during chemotherapy. In addition, elderly patients frequently have numerous comorbidities and these comorbidities also affect the dose of drugs. A low dose intensity may result in shorter survival times and hematologic toxicities may sometimes cause treatment-associated mortality. Therefore, physicians should administer well-managed chemotherapy and pay careful attention to elderly patients.

As studies of the parameters associated with treatment outcomes of second-line therapy in this clinical setting are scarce, the prognostic factors identified in the present study should be useful for designing prospective, randomized clinical trials on the efficacy of second-line chemotherapy in these patients. In addition, the present study investigated the usefulness of comorbidity scores, including the CCI and SCS, as prognostic factors. Comorbidity analysis is important in studies of elderly patients, but few such studies have been reported to date (32,33). Based on the results of the present study, it is suggested that clinical factors as well as comorbidity factors have a strong predictive value with respect to survival. To the best of our knowledge, this is the first study comparing second-line TKI and chemotherapy treatment in elderly patients with NSCLC and wild-type *EGFR*. Although the findings were limited by the small number of patients evaluated and the retrospective study design, they provide a practical guide for selecting second-line chemotherapy in elderly patients without *EGFR* mutations.

Previously, novel immunotherapeutics, including programmed death ligand-1 immune check point blockade revealed high efficacy in patients with lung cancer. Nivolumab, pembrolizumab and atezolizumab demonstrated benefits in terms of survival compared with docetaxel as second-line treatment. Furthermore, these agents revealed good safety profiles (34) and therefore would be more beneficial to elderly patients. Further investigation of immunotherapeutics is required.

In conclusion, significant prognostic factors affecting survival identified in the current study were squamous histology, poor PS, higher SCS, short PFS of first-line

treatment, presence of brain metastasis, low serum albumin level and hyponatremia. Careful consideration should be given in deciding second-line treatment for patients having ≥3 of these factors, except histology. TKI and cytotoxic chemotherapy as second-line treatment revealed similar survival results and different toxicity profiles. Both are good options for elderly patients with NSCLC not harboring *EGFR* mutations if careful management is provided. Therefore, physicians should consider clinical conditions of each patient as the most important factors affecting survival in the second-line treatment of elderly patients.

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