

Effect of Second-Line Chemotherapy in Elderly Patients with Non-Small Cell Lung Cancer

Kobayashi H^{1*}, Kenmotsu H¹, Suzuki K¹, Omori S¹, Nakashima K¹, Wakuda K¹, Ono A¹, Naito T¹, Murakami H¹, Endo M², Ohde Y³ and Takahashi T¹

¹Division of Thoracic Oncology, Shizuoka Cancer Center, Shizuoka, Japan

²Division of Diagnostic Radiology, Shizuoka Cancer Center, Shizuoka, Japan

³Division of Thoracic Surgery, Shizuoka Cancer Center, Shizuoka, Japan

*Corresponding authors: Haruki Kobayashi, Division of Thoracic Oncology, Shizuoka Cancer Center, 1007 Shimonagakubo, Nagaizumi-cho Sunto-gun, Shizuoka 411-8777, Japan, Tel: +81-55-989-5222; E-mail: h.kobayashi@scchr.jp

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Abstract

Background: The effect of second-line chemotherapy in patients with non-small cell lung cancer (NSCLC) who received first-line chemotherapy at the age of ≥ 75 years is unclear.

Methods: Sixty-five elderly patients with NSCLC who received first-line chemotherapy at the age of ≥ 75 years and treated with second-line chemotherapy at Shizuoka Cancer Center between January 2005 and December 2014 were retrospectively reviewed.

Results: The overall response rate of the second-line chemotherapy was 9.2% [95% confidence interval (CI) 4-19]. The median progression-free survival at the second-line chemotherapy was 2.2 months. The median overall survival at the second-line chemotherapy was 7.5 months. Multivariate analysis of prognostic factors showed that an Eastern Cooperative Oncology Group performance-status score (PS 0-1/PS 2; HR, 0.396; 95% CI, 0.192-0.899; $p=0.03$) and histology (squamous/non-squamous; HR, 0.465; 95% CI, 0.228-0.884; $p=0.02$) were significantly independent prognostic factors. On the other hand, the number of treatment-related deaths was 2 (3.1%) due to pneumonitis. Moreover, the proportion of patients who received third-line chemotherapy was only 35.9%.

Conclusion: Our study suggests that elderly patients have difficulty moving on to the next line of chemotherapy; however, selected elderly patients well tolerated the adverse effects of second-line chemotherapy, and second-line chemotherapy might be effective for elderly patients with NSCLC who received first-line chemotherapy at the age of ≥ 75 years. Therefore, prospective study should be planned in order to demonstrate the efficacy of second-line chemotherapy for elderly patients with NSCLC.

Keywords Lung cancer; Non-small cell lung cancer; Elderly patient; Second-line chemotherapy

Introduction

Among the patients in Japan dying from lung cancer in 2014, those aged 75 years or older (age ≥ 75 years) accounted for approximately 60% [1]. On the other hand, the mortality rate of lung cancer in the United States in patients aged ≥ 80 years was equivalent to 25.4% in 2012 [2]. These results accounted for a large percentage of patients dying from lung cancer. Therefore, it is very important to develop the optimal treatment strategy for not only fit patients but also elderly patients with lung cancer.

In 1999, it was reported that vinorelbine as a first-line chemotherapy for elderly patients with non-small cell lung cancer (NSCLC) improves overall survival (OS) compared with best supportive care (BSC) patients [3]. Thereafter, according to the results of randomized phase III trials [4-6], the use of a single third-generation cytotoxic drug or carboplatin-based doublet chemotherapy has been considered as a standard treatment for elderly patients with NSCLC. However, there have been few reports on second-line chemotherapy in elderly patients with NSCLC. In Japan, according to

the guidelines published in the Japan Lung Cancer Society, the definition of young patients with NSCLC is patients <75 years of age at the time of first-line chemotherapy. Therefore, the objective of this study was to evaluate the efficacy of the second-line chemotherapy in elderly patients with NSCLC who received first-line chemotherapy at the age of ≥ 75 years by comparing with that in non-elderly patients who received first-line chemotherapy at the aged 70-74 years.

Patients and methods

Patients

The medical records of patients with NSCLC treated with first-line chemotherapy at Shizuoka Cancer Center between January 2005 and December 2014 were retrospectively reviewed. All patients met the following inclusion criteria: 1) histologically or cytologically confirmed NSCLC, 2) diagnosis of stage III or IV NSCLC as per the 7th TNM lung cancer staging system or recurrent NSCLC after radiation therapy or surgical resection, 3) previously underwent first-line chemotherapy, 4) ≥ 70 years at the start of first-line chemotherapy, 5) an Eastern Cooperative Oncology Group (ECOG) performance-status score (PS) of 0-2 at the second-line chemotherapy. The exclusion criteria were the use of epidermal growth factor receptor tyrosine kinase inhibitors

(EGFR-TKIs) or anaplastic lymphoma kinase (ALK) inhibitors at any line of treatment.

In addition, continuation maintenance therapy, which is the administration of part of the initial chemotherapy regimen, was considered as first-line chemotherapy, and on the other hand, switch maintenance therapy, which is the administration of a new chemotherapy agent that was not part of the original chemotherapy regimen, was not included as first-line chemotherapy. Moreover, chemotherapy for recurrence during or within 6 months of completion of the adjuvant chemotherapy and readministration after the failure of regimen were counted as one regimen for advanced disease.

The patients were divided into two groups based on the age at the start of first-line chemotherapy: aged 75 years or older (age \geq 75 group) and aged 70–74 years (age 70–74 group), and the efficacy of second-line chemotherapy was compared between the two groups.

The age 70–74 group received the standard second-line chemotherapy, which is docetaxel with or without anti-vascular endothelial growth factor-targeted therapy. On the other hand, the age \geq 75 group received no standard second-line chemotherapy. Therefore, in this study, second-line chemotherapy was limited to docetaxel with or without anti-vascular endothelial growth factor-targeted therapy in the age 70–74 group, whereas chemotherapy regimens were selected based on the physician's choice in the age \geq 75 group.

Evaluation of efficacy and tolerability of second-line chemotherapy

The objective tumor response was assessed in accordance with the Response Evaluation Criteria in Solid Tumors guidelines (version 1.1) [7]. Tolerability was examined in median number of cycles delivered per patient.

OS was calculated from the start of second-line chemotherapy to the date of death from any cause or last follow-up. Progression-free survival (PFS) was calculated from the start of second-line chemotherapy to the date of disease progression or death from any cause.

Statistical analysis

OS and PFS were estimated using the Kaplan–Meier curves with two-sided log-rank test. To identify prognostic factors for elderly patients with NSCLC, univariate and multivariate analyses were conducted. All categorical variables were analyzed using Fisher's exact test or chi-squared test, as appropriate. Continuous variables were analyzed using Wilcoxon/Kruskal–Wallis test. Multivariate analyses were conducted using Cox proportional hazards model to assess the relationship between various factors and the prognosis of elderly patients with NSCLC. The overall response rate (ORR) was compared between groups using the Fisher's exact test. All statistical analyses were performed using the Software Packages JMP 11.2.0 Software. Survival analyses were assessed until February 1, 2016. The study protocol was approved by the Institutional Review board of Shizuoka Cancer Center (Nagaizumi-cho Sunto-gun, Japan).

Results

Patient characteristics

Between January 2005 and December 2014, among the 276 patients with NSCLC of \geq 70 years treated with first-line chemotherapy, 145 patients received the second-line chemotherapy at our institution. Of them, 65 patients (45%) of 143 who received first-line chemotherapy were treated with second-line chemotherapy in the age \geq 75 group.

| Patient Characteristics | Age \geq 75 | Age 70-74 | p value |
|---|---------------|-----------|---------|
| No. of patients | 65 | 41 | |
| Age at the 2nd-line chemotherapy (year) | | | |
| Median | 79 | 72 | |
| Range | (75-85) | (70-75) | |
| Sex (% of patient) | | | |
| Male | 82 | 85 | 0.7915 |
| Female | 18 | 15 | |
| ECOG- Performance status at the 2nd-line chemotherapy (% of patient) | | | |
| 0-1 | 85 | 93 | 0.3622 |
| 2 | 15 | 7 | |
| Pathological subtype (% of patients) | | | |
| Squamous | 25 | 34 | 0.3763 |
| Non-squamous | 75 | 66 | |
| Clinical Stage at the 1 st -line chemotherapy (% of patient) | | | 0.0855 |
| | 28 | 12 | |
| | 68 | 76 | |
| Recurrent | 4 | 12 | |
| Smoking status (% of patients) | | | |
| current smoker or ever smoked | 83 | 85 | 1.000 |
| never smoked | 17 | 15 | |
| Platinum-based at the 1st-line chemotherapy (% of patients) | | | |
| Yes | 28 | 100 | <0.0001 |
| No | 72 | 0 | |

Table 1: Baseline Characteristics of the patients (N=106); ECOG Eastern Cooperative Oncology Group.

Further, 80 patients (60%) of 133 who received first-line chemotherapy were treated with second-line chemotherapy in the age

70-74 group. Among them, 41 patients received docetaxel as the second-line chemotherapy. The baseline characteristics of patients are presented in Table 1.

The median age at the start of second-line chemotherapy was 79 (range, 75-85) years in age ≥ 75 group and 72 (range, 70-75) years in age 70-74 group. There were significant differences in frequency of platinum-based chemotherapy as first-line chemotherapy between the groups. On the other hand, there were no significant difference between the groups in terms of sex, performance status, pathological subtype, clinical staging, and smoking status.

Second-line chemotherapy regimens in age ≥ 75 group are shown in Table 2. Pemetrexed monotherapy was the most frequently used regimen.

| Regimens | N (%) |
|-------------|---------|
| Pemetrexed | 23 (35) |
| Gemcitabine | 14 (22) |
| Docetaxel | 11 (17) |
| S1 | 8 (12) |
| Vinorelbine | 7 (11) |
| Nedaplatin | 2 (3) |

Table 2: Frequency of Second-line chemotherapy regimens in age ≥ 75 group (N=65).

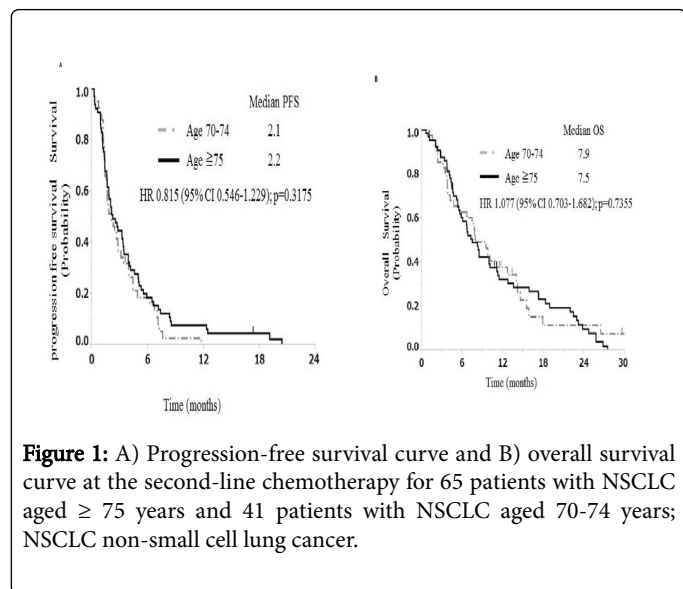


Figure 1: A) Progression-free survival curve and B) overall survival curve at the second-line chemotherapy for 65 patients with NSCLC aged ≥ 75 years and 41 patients with NSCLC aged 70-74 years; NSCLC non-small cell lung cancer.

Efficacy

ORR of the second-line chemotherapy was 9.2% [95% confidence interval (CI), 4-19] in age ≥ 75 group and 12.2% (95% CI, 5-26) in age 70-74 group. There was no significance difference between the groups ($p=0.75$). The median PFS at the second-line chemotherapy was 2.2 months in age ≥ 75 group and 2.1 months in age 70-74 group. There was no statistical significant difference in PFS (hazard ratio (HR), 0.815; 95% CI, 0.546-1.229; $p=0.32$) between the groups (Figure 1A). The median OS at the second-line chemotherapy was 7.5 months in

the age ≥ 75 group compared with 7.9 months in the age 70-74 group. There was no statistically significant difference in OS (HR, 1.077; 95% CI, 0.703-1.682; $p=0.74$) between the groups (Figure 1B).

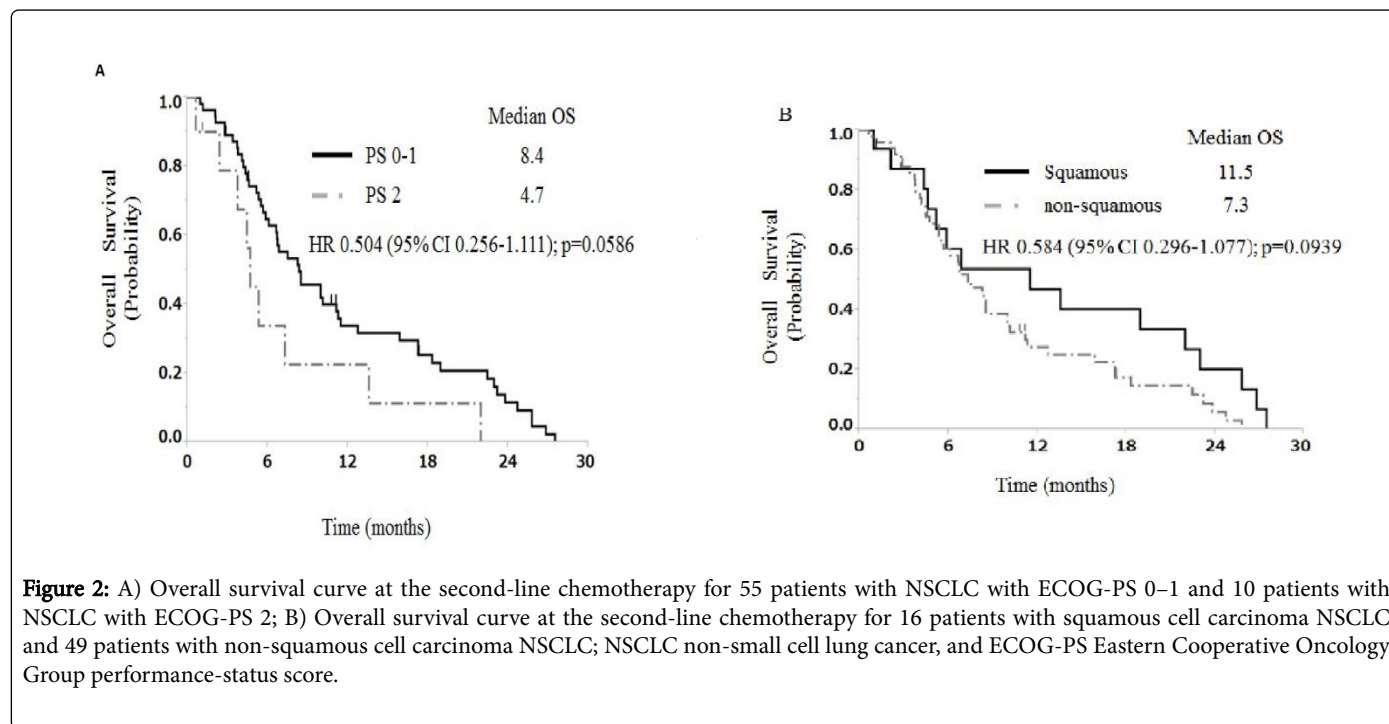
The univariate and multivariate analyses results of survival in age ≥ 75 group are shown in Table 3.

| | Univariate analysis | | Multivariate analysis | |
|---|------------------------|----------------|------------------------|----------------|
| | HR (95% CI) | p value | HR (95% CI) | p value |
| Age | | | | |
| <80 | HR 0.921 (0.537-1.635) | $p=0.76$ 99 | HR 0.946 (0.540-1.711) | $p=0.8$ 507 |
| ≥ 80 | | | | |
| Gender | | | | |
| Male | HR 1.199 (0.644-2.440) | $p=0.58$ 58 | HR 1.364 (0.714-2.839) | $p=0.3$ 601 |
| Female | | | | |
| ECOG- Performance status | | | | |
| 0-1 | HR 0.504 (0.256-1.111) | $p=0.05$ 86 | HR 0.396 (0.192-0.899) | $p=0.0$ 284 |
| 2 | | | | |
| Histology | | | | |
| Squamous | HR 0.584 (0.296-1.077) | $p=0.09$ 39 | HR 0.465 (0.228-0.884) | $p=0.0$ 187 |
| non-Squamous | | | | |
| Clinical Stage | | | | |
| A-B | HR 0.842 (0.457-1.476) | $p=0.55$ 74 | HR 0.830 (0.445-1.476) | $p=0.5$ 344 |
| recurrence after surgical resection or radiotherapy | | | | |
| Smoking status | | | | |
| never smoked | HR 0.908 (0.431-1.727) | $p=0.78$ 05 | | |
| current smoker or ever smoked | | | | |
| Platinum-based at the 1st-line chemotherapy | | | | |
| No | HR 0.750 (0.431-1.353) | $p=0.31$ 80 | | |
| Yes | | | | |

Table 3: Univariate and multivariate analysis of prognostic factors in age ≥ 75 group (N=65); ECOG Eastern Cooperative Oncology Group, HR hazard ratio, and CI confidence interval.

On univariate analyses, patients with ECOG-PS 0-1 showed better survival than those with ECOG-PS 2 (median OS, 8.4 vs. 4.7 months, $p=0.06$, Figure 2A). Moreover, patients with squamous cell carcinoma showed better survival than those with non-squamous cell carcinoma (median OS, 11.5 vs. 7.3 months, $p=0.09$, Figure 2B). Multivariate

analysis of prognostic factors showed that ECOG-PS (0–1: HR, 0.396; 95% CI, 0.192–0.899; $p=0.03$) and histology (squamous: HR, 0.465; 95% CI, 0.228–0.884; $p=0.02$) were significantly independent prognostic factors.



Tolerability

There was no difference in number of treatment cycles of second-line chemotherapy between groups [median three (range, 1–21) in age ≥ 75 group and two (range, 1–12) in age 70–74 group; $p=0.45$]. The number of patients unable to continue treatments with the exception of progressive disease was 21 (32%) in age ≥ 75 group compared with 9 (22%) in age 70–74 group ($p=0.28$). The number of treatment-related deaths in the age ≥ 75 group was 2 (3.1%) compared with 2 (4.9%) in the age 70–74 group ($p=0.64$). Two patients experiencing treatment-related death in the age ≥ 75 group showed pneumonitis due to chemotherapy. The proportion of patients who received third-line chemotherapy was significantly higher in the age 70–74 group than in the age ≥ 75 group (35.9% in the age ≥ 75 group, 57.5% in the age 70–74 group; $p=0.04$). In the age ≥ 75 group, the actual reasons for not performing next line of chemotherapy were PS deterioration due to disease progression or toxicity of pretreatment (73.2%), patient refusal of chemotherapy (12.2%), cognitive decline (4.9%), other complications (4.9%), and death during second-line chemotherapy (4.9%). On the other hand, in the age 70–74 group, they were PS deterioration (82.4%), other complications (5.9%), and death during second-line chemotherapy (11.8%).

Discussion

In most clinical trials, the majority of patients with NSCLC are <75 years of age; therefore, there are little data on the prognosis of patients age ≥ 75 years, especially for second-line or subsequent chemotherapy. In this study, we evaluated the prognosis of elderly patients with NSCLC treated with second-line chemotherapy. The previous trials of docetaxel as second-line chemotherapy in younger patients with NSCLC showed that median PFS and OS were 2.8–3.2 months and 6.0–14.8 months, respectively [8–15]. In this study, there was no statistically significant difference in PFS and OS at the second-line

chemotherapy between the age ≥ 75 group and the age 70–74 group. Furthermore, the median PFS and OS of patients aged ≥ 75 years with ECOG-PS 0–1 were similar to those reported in previous trials. In contrast, the prognosis of patients aged ≥ 75 years with ECOG-PS 2 was poor.

The definition of elderly patients with NSCLC is still controversial. The American Society of Clinical Oncology and European Society for Medical Oncology Clinical Practice Guidelines released that decisions on the selection of chemotherapy should not be made or altered based on age alone [16,17]. The reason is that carboplatin-based doublet chemotherapy was associated with survival benefits in patients with NSCLC >80 years of age in the French multicenter randomized phase III trial, IFCT- 0501 [6]. However, treatment-related death was 4.4% for patients with NSCLC >70 years of age undergoing carboplatin-based doublet chemotherapy and remained a serious problem. On the other hand, in Japan, although there was a phase III trial that was designed to clarify whether the addition of cisplatin to monotherapy could improve survival for elderly patients, this study showed cisplatin-based doublet chemotherapy could not significantly associate with survival benefits in patients with NSCLC ≥ 75 years of age [18]. Moreover, elderly patients have been defined as patients aged ≥ 75 years in ongoing clinical trials, including in the JCOG1210/WJOG7813L study (UMIN000011460) of docetaxel versus carboplatin plus pemetrexed followed by pemetrexed as a first-line treatment in elderly patients with advanced non-squamous NSCLC in Japan. Therefore, we defined elderly patients as patients ≥ 75 years of age in this study.

Second-line chemotherapy and third-line chemotherapy were administered in 45.5% and 16.2% of patients, respectively, who received first-line chemotherapy in the age ≥ 75 group in this study, which were lower in frequency compared with the age 70–74 group in this study and previous reports [10–12,19,20]. The possible cause of not

moving on to next line of therapy in the age ≥ 75 group is that older patients had more adverse events during chemotherapy than younger patients [21]. Therefore, elderly patients might be unable to receive subsequent lines of therapy because of ECOG-PS deterioration caused by adverse events of previous chemotherapy.

To the best of our knowledge, the present study is the first report to evaluate prognostic factor concerning with second-line chemotherapy in patients with NSCLC who received cytotoxic agents with or without bevacizumab at the age of ≥ 75 years and were excluded from the use of EGFR-TKIs or ALK inhibitors during their treatment. The results of this study showed that ECOG-PS and pathological subtype were independent prognostic factors. Patients with ECOG-PS 0-1 had better prognosis, of which median PFS and OS were similar to the results of the past trials of docetaxel arm as second-line chemotherapy for younger patients with NSCLC [8-14]. On the other hand, patients with non-squamous cell carcinoma tended to have a shorter survival than those with squamous cell carcinoma in this study, and they had a shorter survival than those in previous studies [12,22]. The possible reason why patients with non-squamous cell carcinoma showed shorter survival was that patients with NSCLC harboring wild-type EGFR who received EGFR-TKI at any point during their treatment were excluded from this study. Therefore, patients who could receive subsequently long-term chemotherapy might be excluded from this study.

There was no statistically significant difference in the number of second-line chemotherapy cycles between the age ≥ 75 group and the age 70-74 group. In addition, the median number of cycles of docetaxel as second-line chemotherapy in previous trials in younger patients with NSCLC was 3-4 cycles [10-12], which was equivalent to the age ≥ 75 group in this study. In addition, the proportion of discontinued second-line chemotherapy in the age ≥ 75 group, with the exception of progressive disease, was not statistically significantly different from that in the age 70-74 group in this study, and it was almost equal to the previous trial of docetaxel as second-line chemotherapy in younger patients with NSCLC [10]. Therefore, it seems reasonable to suppose that adverse effects of second-line chemotherapy were well tolerated by patients who could start second-line chemotherapy.

Several limitations of this study should be considered. Firstly, this study was a retrospective, non-randomized study performed at a single center; however, this is the first report to evaluate second-line chemotherapy for patients with NSCLC who received cytotoxic agents with or without bevacizumab at the age of ≥ 75 years and were excluded from the use of EGFR-TKIs or ALK inhibitors during their treatment. Furthermore, this study included as many as 65 patients. Second, chemotherapy regimens of second-line chemotherapy were not unified but only cytotoxic agents during their treatment were received. Therefore, it is possible to evaluate the efficacy of the second-line chemotherapy in defiance of the oncogene mutation.

Conclusion

In conclusion, these results from this study indicate that elderly patients have difficulty moving on to next line of chemotherapy because there were patient refusal of chemotherapy and cognitive decline in addition to PS deterioration due to disease progression or toxicity of pretreatment; however, selected patients well tolerated the adverse effects of second-line chemotherapy. Furthermore, second-line chemotherapy might be effective for elderly patients with NSCLC who received first-line chemotherapy at the age of ≥ 75 years. Therefore,

prospective study should be planned in order to demonstrate the efficacy of second-line chemotherapy for elderly patients with NSCLC.

Conflict of Interest Statement

HK reports honoraria from Eli Lilly and Taiho Pharmaceutical. SO reports honoraria from Chugai Pharmaceutical, Ono Pharmaceutical, AstraZeneca, Boehringer Ingelheim, and Taiho Pharmaceutical. KN reports honoraria from Eli Lilly, Ono Pharmaceutical, Mochida Pharmaceutical, and Taiho Pharmaceutical. KW reports honoraria from Taiho Pharmaceutical, Boehringer Ingelheim, and Ono Pharmaceutical. AO reports honoraria from Taiho Pharmaceutical, Chugai Pharmaceutical, and Takeda Pharmaceutical. HK reports honoraria from Ono Pharmaceutical, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Chugai Pharmaceutical, Bristol-Myers, Taiho Pharmaceutical, and Kyowa Hakko Kirin and research funding from AstraZeneca and Boehringer Ingelheim. TN reports honoraria from Ono Pharmaceutical. HM reports honoraria from Chugai Pharmaceutical, Pfizer, Novartis, Boehringer Ingelheim, Taiho Pharmaceutical, AstraZeneca, Eli Lilly, Ono Pharmaceutical, Bristol-Myers, and Astellas. EM reports honoraria from Ono Pharmaceutical. TT reports honoraria from Ono Pharmaceutical, AstraZeneca, Boehringer Ingelheim, Pfizer, Eli Lilly, and Chugai Pharmaceutical and research funding from Ono Pharmaceutical, AstraZeneca, Eli Lilly, Chugai Pharmaceutical, Pfizer, Takeda Pharmaceutical, Taiho Pharmaceutical, and MSD.

Author Contributions

Dr Kobayashi is the guarantor of the article.

Dr Kobayashi: Contributed to conceiving the study concepts and design, performing the data analysis, and producing the initial draft of the manuscript; participated in data generation, interpretation of the analysis, final preparation of the manuscript; and read and approved the final manuscript.

Dr Kenmotsu: Contributed to conceiving the study design and producing the initial draft of the manuscript; participated in the interpretation of the analysis and final preparation of the manuscript; and read and approved the final manuscript.

Dr Suzuki: Contributed to conceiving the study design and performing the data analysis; participated in data generation, interpretation of the analysis, and final preparation of the manuscript; and read and approved the final manuscript.

Dr Omori: Contributed to the interpretation of the analysis and final preparation of the manuscript and read and approved the final manuscript.

Dr Nakashima: Contributed to the interpretation of the analysis and final preparation of the manuscript and read and approved the final manuscript.

Dr Wakuda: Contributed to the interpretation of the analysis and final preparation of the manuscript and read and approved the final manuscript.

Dr Ono: Contributed to the interpretation of the analysis and final preparation of the manuscript and read and approved the final manuscript.

Dr Naito: Contributed to the interpretation of the analysis and final preparation of the manuscript and read and approved the final manuscript.

Dr Murakami: Contributed to the interpretation of the analysis and final preparation of the manuscript and read and approved the final manuscript.

Dr Endo: Contributed to the interpretation of the analysis and final preparation of the manuscript and read and approved the final manuscript.

Dr Ohde: Contributed to the interpretation of the analysis and final preparation of the manuscript and read and approved the final manuscript.

Dr Takahashi: Contributed to the interpretation of the analysis and final preparation of the manuscript and read and approved the final manuscript.

References

1. <http://ganjoho.jp/public/index.html>
2. Siegel RL, Miller KD, Jemal A (2016) Cancer statistics, 2016. *CA Cancer J Clin* 66: 7-30.
3. The Elderly Lung Cancer Vinorelbine Italian Study Group (1999) Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small-cell lung cancer. *J Natl Cancer Inst* 91: 66-72.
4. Gridelli C, Perrone F, Gallo C, Cigolari S, Rossi A, et al. (2003) Chemotherapy for elderly patients with advanced non-small-cell lung cancer: the Multicenter Italian Lung Cancer in the Elderly Study (MILES) phase III randomized trial. *J Natl Cancer Inst* 95: 362-372.
5. Kudoh S, Takeda K, Nakagawa K, Takada M, Katakami N, et al. (2006) Phase III study of docetaxel compared with vinorelbine in elderly patients with advanced non-small-cell lung cancer: results of the West Japan Thoracic Oncology Group Trial (WJTOG 9904). *J Clin Oncol* 24: 3657-3663.
6. Quoix E, Zalcman G, Oster JP, Westeel V, Pichon E, et al. (2011) Carboplatin and weekly paclitaxel doublet chemotherapy compared with monotherapy in elderly patients with advanced non-small-cell lung cancer: IFCT-0501 randomised, phase 3 trial. *Lancet* 378: 1079-1088.
7. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, et al. (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 45: 228-247.
8. Shepherd FA, Dancey J, Ramlau R, Mattson K, Gralla R, et al. (2000) Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol* 18: 2095-2103.
9. Hanna N, Shepherd FA, Fossella FV, Pereira JR, De Marinis F, et al. (2004) Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol* 22: 1589-1597.
10. Garon EB, Ciuleanu TE, Arrieta O, Prabhaskar K, Syrigos KN, et al. (2014) Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet* 384: 665-673.
11. Brahmer J, Reckamp KL, Baas P, Crino L, Eberhardt WE, et al. (2015) Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. *N Engl J Med* 373: 123-135.
12. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, et al. (2015) Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. *N Engl J Med* 373: 1627-1639.
13. Garassino MC, Martelli O, Broggin M, Farina G, Veronese S, et al. (2013) Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type EGFR tumours (TAILOR): a randomised controlled trial. *Lancet Oncol* 14: 981-988.
14. Kawaguchi T, Ando M, Asami K, Okano Y, Fukuda M, et al. (2014) Randomized phase III trial of erlotinib versus docetaxel as second- or third-line therapy in patients with advanced non-small-cell lung cancer: Docetaxel and Erlotinib Lung Cancer Trial (DELTA). *J Clin Oncol* 32: 1902-1908.
15. Maruyama R, Nishiwaki Y, Tamura T, Yamamoto N, Tsuboi M, et al. (2008) Phase III study, V-15-32, of gefitinib versus docetaxel in previously treated Japanese patients with non-small-cell lung cancer. *J Clin Oncol* 26: 4244-4252.
16. Masters GA, Temin S, Azzoli CG, Giaccone G, Baker S, et al. (2015) Systemic Therapy for Stage IV Non-Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol* 33: 3488-3515.
17. Reck M, Papat S, Reinmuth N, De Ruysscher D, Kerr KM, et al. (2014) Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 25: 27-39.
18. Tsukada H, Yokoyama A, Goto K, Shinkai T, Harada M, et al. (2015) Randomized controlled trial comparing docetaxel-cisplatin combination with weekly docetaxel alone in elderly patients with advanced non-small-cell lung cancer: Japan Clinical Oncology Group (JCOG) 0207 dagger. *Jpn J Clin Oncol* 45: 88-95.
19. Shukuya T, Yamanaka T, Seto T, Daga H, Goto K, et al. (2015) Nedaplatin plus docetaxel versus cisplatin plus docetaxel for advanced or relapsed squamous cell carcinoma of the lung (WJOG5208L): a randomised, open-label, phase 3 trial. *Lancet Oncol* 16: 1630-1638.
20. Ohe Y, Ohashi Y, Kubota K, Tamura T, Nakagawa K, et al. (2007) Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. *Ann Oncol* 18: 317-323.
21. Chrischilles EA, Pendergast JF, Kahn KL, Wallace RB, Moga DC, et al. (2010) Adverse events among the elderly receiving chemotherapy for advanced non-small-cell lung cancer. *J Clin Oncol* 28: 620-627.
22. Scagliotti G, Hanna N, Fossella F, Sugarman K, Blatter J, et al. (2009) The differential efficacy of pemetrexed according to NSCLC histology: a review of two Phase III studies. *Oncologist* 14: 253-263.