Chemotherapy: Open Access

Kobayashi et al., Chemo Open Access 2017, 6:2
DOI: 10.4172/2167-7700.1000236

Research Article OMICS International

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

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Received date: May 11, 2017; **Accepted date:** June 12, 2017; **Published date:** June 19, 2017

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 ≥ 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 ≥ 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 ≥ 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 ≥ 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 ≥ 75 group.

Patient Characteristics	Age ≥ 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 1st-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).

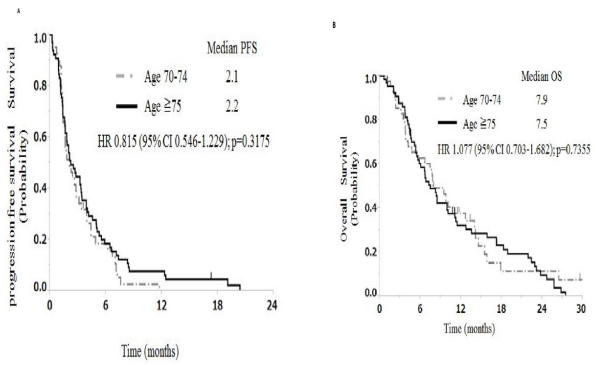

Figure 1: A) Progression-free survival curve and B) overall survival curve at the second-line chemotherapy for 65 patients with NSCLC aged ≥ 75 years and 41 patients with NSCLC aged 70-74 years; NSCLC non-small cell lung cancer.

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=0.7699	HR 0.946 (0.540-1.711)	p=0.8507
≥ 80				
Gender				
Male	HR 1.199 (0.644-2.440)	p=0.5858	HR 1.364 (0.714-2.839)	p=0.3601
Female				
ECOG- Performance status				
0-1	HR 0.504 (0.256-1.111)	p=0.0586	HR 0.396 (0.192-0.899)	p=0.0284
2				
Histology				
Squamous	HR 0.584 (0.296-1.077)	p=0.0939	HR 0.465 (0.228-0.884)	p=0.0187
non-Squamous				
Clinical Stage				
A-B	HR 0.842 (0.457-1.476)	p=0.5574	HR 0.830 (0.445-1.476)	p=0.5344
recurrence after surgical resection or radiotherapy				
Smoking status				
never smoked	HR 0.908 (0.431-1.727)	p=0.7805		
current smoker or ever smoked				
Platinum-based at the 1st-line chemotherapy				
No	HR 0.750 (0.431-1.353)	p=0.3180		
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.

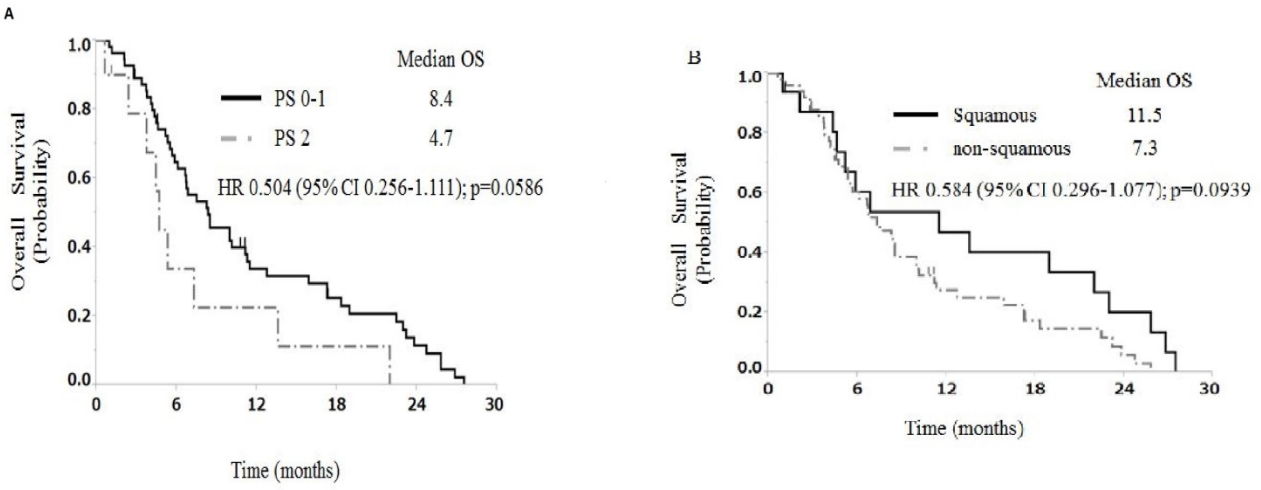

Figure 2: A) Overall survival curve at the second-line chemotherapy for 55 patients with NSCLC with ECOG-PS 0–1 and 10 patients with NSCLC with ECOG-PS 2; B) Overall survival curve at the second-line chemotherapy for 16 patients with squamous cell carcinoma NSCLC and 49 patients with non-squamous cell carcinoma NSCLC; NSCLC non-small cell lung cancer, and ECOG-PS Eastern Cooperative Oncology Group performance-status score.

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 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.

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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.

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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.

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