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A multicenter, open-label, phase II trial of pemetrexed plus bevacizumab in elderly patients with previously untreated advanced or recurrent nonsquamous non-small cell lung cancer

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Abstract

Background: Although the incidence of lung cancer in elderly individuals has been increasing in recent years, the number of clinical trials designed specifically for elderly patients with advanced non-small cell lung cancer (NSCLC) is still limited. To fulfill this unmet medical need, we conducted a phase II study to elucidate the efficacy of pemetrexed (PEM) plus bevacizumab (Bev) combination chemotherapy in elderly patients with nonsquamous NSCLC.

Methods: A total of 29 elderly patients (≥75 years old) with nonsquamous NSCLC were enrolled in this multicenter, open-label, phase II study, and 27 patients were finally analyzed. PEM at 500 mg/m^2 on day 1 plus Bev at 15 mg/kg on day 1 were administered triweekly. The primary endpoint was the investigator-assessed objective response rate.

Results: The median age at initiating chemotherapy was 80 years old. Almost all patients (92.6%) had adenocarcinoma histology. The median number of cycles administered was 6, and the objective response rate was 40.7%. The median progression-free survival, overall survival and 1-year survival were 8.8 months, 27.2 months and 79%, respectively. The treatment was well-tolerated, and no treatment-related death was observed.

Conclusion: Combination chemotherapy with PEM plus Bev in elderly patients with previously untreated advanced non-squamous NSCLC exhibited favorable antitumor activity and tolerability, suggesting that a combination of PEM plus Bev might be a promising treatment option for this population.

KEYWORDS
bevacizumab, elderly patients, pemetrexed, previously untreated nonsquamous non-small cell lung cancer

INTRODUCTION

Lung cancer is the leading cause of cancer-related death worldwide. In recent years, the incidence of lung cancer in the elderly has been increasing, and approximately half of patients with stage III/IV lung cancer are ≥75 years old. Although molecular-targeted agents and immune checkpoint inhibitors (ICIs) have drastically expanded opportunities for the treatment of advanced non-small-cell lung cancer (NSCLC), even in elderly individuals, cytotoxic chemotherapies remain the mainstay for patients who are not suitable for treatment with targeted or immunotherapeutic drugs.

As single-agent chemotherapy, such as that with vinorelbine (VNR), gemcitabine (GEM) and docetaxel (DTX), has

demonstrated therapeutic benefits for elderly patients with advanced NSCLC in randomized phase III trials,[1–3] it has been established as a standard treatment for the indicated patients. In addition, recent clinical studies have demonstrated that the efficacy of carboplatin (CBDCA)-doublet chemotherapies is comparable to that of single-agent VNR, GEM or DTX in select elderly patients with advanced NSCLC.[4,5] As a consequence, CBDCA-doublet chemotherapies are also recommended regimens.

However, despite recent progress in the development of therapeutic strategies as described above, the number of clinical trials designed specifically for elderly patients with advanced NSCLC is still limited, and the efficacy of treatments is far from satisfactory. Therefore, more effective therapeutic strategies for elderly patients with advanced NSCLC are urgently needed.

Pemetrexed (PEM) is an antifolate that exerts antitumor effects by inhibiting multiple folate-metabolizing enzymes and de novo synthesis of purine and pyrimidine nucleotides. PEM is currently used in combination with cisplatin as a standard first-line chemotherapy regimen for advanced NSCLC. Furthermore, PEM exhibited equivalent efficacy and significantly fewer adverse events than DTX in patients with previously treated NSCLC.[6] Given its mild toxicity profile, PEM may be a promising agent as standard chemotherapy for elderly nonsquamous (Non-Sq) NSCLC. Bevacizumab (Bev) is a humanized antivascular endothelial growth factor (VEGF) monoclonal antibody that specifically binds to VEGF. The Eastern Cooperative Oncology Group (ECOG) demonstrated that the addition of Bev to paclitaxel (PTX) plus CBDCA in patients with advanced Non-Sq NSCLC had a significant survival benefit (ECOG4599 study).[7] In a randomized phase II study of advanced Non-Sq NSCLC patients in Japan, the addition of Bev to first-line PTX plus CBDCA significantly improved the progression-free survival (PFS) in patients <75 years old.[8]

With the emerging role of PEM plus Bev in the treatment of Non-Sq NSCLC being recognized and given the moderately good tolerability of these drugs, there is an interest in evaluating PEM in combination with Bev for elderly patients with advanced Non-Sq NSCLC. We therefore conducted a multicenter, phase II study of treatment with PEM plus Bev in cytotoxic chemotherapy-naïve patients ≥75 years old with advanced Non-Sq NSCLC.

METHODS

Patient population and study design

The criteria for patient eligibility included histologically or cytologically confirmed Non-Sq NSCLC; stage IIIB/IV or postoperative recurrent diseases; no prior chemotherapy except for epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) and postoperative uracil and tegafur; ECOG performance status (PS) of 0 or 1; ≥1 measurable lesion in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST) criteria (version 1.1); an age ≥ 75 years old; adequate bone marrow, hepatic, and renal functions; and a projected life expectancy of at least 3 months. The main exclusion criteria were a history of hemoptysis within 3 months, cavitary lesions of the lung, direct invasion of the tumor into the large blood vessels, visible tumor on bronchoscopy, serious concomitant diseases, pleural effusion, ascites and pericardial effusion necessitating treatment, active concomitant malignancy, a history of drug allergy and uncontrollable peptic ulcers.

This study was conducted in accordance with the Declaration of Helsinki and approved by the institutional ethics committee of each of the participating institutions. Written informed consent was obtained from all of the patients. This study was registered in the UMIN Clinical Trials Registry, and the clinical trial registration number was UMIN000008764.

Treatment plan

PEM was administered intravenously at 500 mg/m^2 on day 1. To avoid adverse effects, folate and vitamin B12 were given at least 7 days before PEM administration. Bev was also administered intravenously at 15 mg/kg on day 1. The treatment regimen was repeated every 3 weeks unless at least one of the following discontinuation criteria were met: progressive disease (PD), ≥21 days of rest to recover from PEM toxicity, ≥42 days of rest to recover from Bev toxicity, requiring 2-step dose reduction, a thromboembolic event of grade ≥3, bleeding of grade ≥3, hemoptysis of grade ≥3 or grade 2 requiring treatment with hemostatic agents, hypertension of grade 4, pneumonitis of grade ≥2 or other serious toxicities. Subsequent therapeutic cycles were withheld if at least one of the following criteria were met: a leukocyte count of <1000/mm^3 or a neutrophil count of <500/mm^3, a platelet count of <50 000/mm^3, a fever of ≥38°C suspected of involving infection, proteinuria of ≥ + 2 by urine qualitative test or other nonhematological toxicities of grade ≥3. The dose of PEM was reduced to 375 mg/m^2 if the at least one of following criteria were met: a minimum neutrophil count of <500/mm^3 and a minimum platelet count of ≥50 000/mm^3, a minimum platelet count of <50 000/mm^3, nonhematological toxicity of grade ≥3 except for mucositis or diarrhea of grade ≥3 or requiring hospitalization. The dose of PEM was reduced to 250 mg/m^2 if the following criteria were met: a minimum platelet count of <50 000/mm^3 with bleeding and mucositis of grade ≥3.

Baseline and follow-up assessments

Prior to enrollment in the study, all patients provided their medical history and underwent a complete physical examination, clinical laboratory testing, chest X-ray, chest and abdominal computed tomography (CT), head CT or magnetic resonance imaging and bone scintigraphy or fluorodeoxyglucose-positron emission tomography.

The patients' weight, height, and ECOG PS were also determined. Chest X-ray was performed every week until 3 weeks after commencing treatment and repeated every 2 to 3 weeks thereafter. Chest CT was performed for a tumor assessment every 4 to 6 weeks. Physical examinations, symptom evaluations, routine blood tests and biochemical blood examinations were performed every week until 3 weeks after commencing treatment and repeated every 2 to 3 weeks thereafter.

The responses to treatment were evaluated in accordance with the RECIST criteria (version 1.1). Patients who were documented as having a complete response (CR)/partial response (PR) underwent a confirmatory evaluation after an interval of at least 4 weeks. Patients were regarded as having stable disease (SD) if a response was confirmed and sustained for at least 6 weeks after commencing treatment.

Adverse events were graded in accordance with the Common Terminology Criteria for Adverse Events (version 4.0). The quality of life (QOL) was assessed with a visual analog scale (VAS) and the European Organization for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-C30). Patients were asked to complete each instrument at the time of enrollment (baseline), every four to 6 weeks after treatment initiation and at the end of the study.

Statistical analysis

The primary endpoint was the objective response rate by the RECIST criteria (version 1.1). The secondary endpoints included the PFS, overall survival (OS), disease control rate (DCR), adverse events and QOL. The PFS was defined as the time from registration to progression or death from any cause. The OS was defined as the time from registration to death from any cause or when the patient was last known to be alive. In a phase III study of DTX in elderly (≥70 years old) Japanese patients with advanced NSCLC, the overall response rate (ORR) was reported to be 22.7%.[3] In addition, in a phase III trial of PEM versus DTX in patients with advanced Non-Sq NSCLC previously treated with chemotherapy, the ORRs were 11.5% and 9.0% for PEM plus DTX, respectively.[6] In contrast, in phase II/III studies of first-line chemotherapy with or without Bev in advanced Non-Sq NSCLC, the response rates were shown to be doubled in patients treated with chemotherapy plus Bev compared to those with chemotherapy alone.[7,8] Given these observations, the threshold response rate was set at 20.0%, and the expected response rate was set at 40.0%.

According to Simon's minimax and optimal two-stage designs, we estimated that 18 and 33 patients at the interim and final analysis, respectively, would be required for the study to have statistical power of ≥80.0% with a type I error rate of 0.05. If the number of valid cases was ≤4 at the interim analysis, this study would be stopped due to futility. In contrast, if ≥5 cases were considered valid at the interim analysis, the study would be continued until the target number of patients was enrolled. We assumed that >10% of enrolled patients would drop out of the study. The target number of enrolled patients was therefore set at 36. The survival (PFS and OS) was estimated using the Kaplan–Meier method. The 95% confidence intervals (CIs) were calculated by a logistic regression analysis. All statistical tests were two-sided, and values of $p < 0.05$ were considered to indicate statistical significance.

All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing).[9]

RESULTS

Patient characteristics

From September 2012 through October 2020, 29 patients with advanced or recurrent Non-Sq NSCLC were enrolled in this study from six institutions. Two patients were excluded due to withdrawal of consent, and 27 patients were analyzed. The clinical characteristics of the 27 patients are listed in Table 1. Seventeen patients (63.0%) were male, and 10 (37.0%) were female. The median age was 80 years,

TABLE 1 Patient characteristics.

No.	27	
Age, years		
Median (range)	80	(75–88)
Gender, *n* (%)		
Male	17	(63.0)
Female	10	(37.0)
ECOG PS, *n* (%)		
0	7	(25.9)
1	20	(74.1)
Stage, *n* (%)		
IIIB	3	(11.1)
IV	23	(85.2)
Recurrence	1	(3.7)
Histology, *n* (%)		
Adenocarcinoma	25	(92.6)
NSCLC NOS	2	(7.4)
Smoking status, *n* (%)		
Smoker	14	(51.9)
Nonsmoker	13	(48.1)
Activating *EGFR* mutation, *n* (%)		
Positive	7	(25.9)
Del19	1	(3.7)
L858R	6	(22.2)
Negative	20	(74.1)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; NSCLC NOS, non-small cell lung cancer not otherwise specified.

with a range of 75–88 years. Seven (25.9%) and 20 (74.1%) had an ECOG PS of 0 and 1, respectively. The disease stage was stage IIIB for three patients and stage IV for 23, and one experienced postoperative recurrence. The predominant histological type was adenocarcinoma (92.6%). Fourteen patients (51.9%) had a smoking history. Seven patients (25.9%) harbored activating *EGFR* mutations. Two patients were previously treated with an EGFR-TKI prior to enrollment in this study.

TABLE 2 Treatment responses.

BOR	*N*	(%)
CR	1	(3.7)
PR	10	(37.0)
SD	16	(59.3)
PD	0	(0.0)
ORR	11/27	(40.7)
DCR	27/27	(100.0)

Abbreviations: BOR, best overall response; CR, complete response; DCR, disease control rate; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

The treatment delivery, response and survival

A median of six cycles of treatment were administered (range, 1–30), and 17 patients (62.9%) received ≥6 cycles. A total of 243 cycles were administered to 27 patients. The median follow-up duration was 27.6 (range, 3.5–47.2) months. Among study participants, one showed a CR, and 10 showed a PR, yielding an ORR of 40.7% (95% CI: 22.4%–61.2%). SD and PD were observed in 16 (59.2%) and 0 (0.0%) patients, respectively. Thus, the DCR was 100.0% (95% CI: 87.2%–100.0%) (Table 2). Next, we exploratorily sought to determine patient characteristics affecting the response to treatment with PEM plus Bev; however, no factors were identified that might predict the therapeutic response (Table 3). Reasons for treatment discontinuation were disease progression in seven (25.9%); toxicities, such as thromboembolic events, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevation, proteinuria, pneumonitis and peripheral sensory neuropathy in seven (25.9%); withdrawal at the patient's request in seven (25.9%), mainly due to treatment-related adverse events; and investigator's discretion in six (22.2%). The median PFS was 8.8 (95% CI: 5.2–12.9) months (Figure 1a). The median survival time was 27.2 (95% CI: 16.9–41.0) months, and the 1-year survival rate was 79.0% (95% CI: 56.5%–90.7%) (Figure 1b).

TABLE 3 Analysis of factors affecting the response to treatment with pemetrexed plus bevacizumab.

Variables	*N*	Responder (*N* = 11)	Nonresponder (*N* = 16)	RR (%)	*p*-value
Age, years					0.26
<80	11	6	5	54.5	
≥80	16	5	11	31.3	
Gender					1.00
Male	17	7	10	41.2	
Female	10	4	6	40.0	
ECOG PS					0.08
0	7	5	2	71.4	
1	20	6	14	30.0	
Stage					0.06
IIIB	2	2	0	100.0	
IV	24	8	16	33.3	
Recurrence	1	1	0	100.0	
Histology					0.50
Adenocarcinoma	25	11	14	44.0	
NSCLC NOS	2	0	2	0.0	
Smoking status					0.70
Smoker	14	5	9	35.7	
Nonsmoker	13	6	7	46.2	
Activating *EGFR* mutation					0.39
Positive	7	4	3	57.1	
Negative	20	7	13	35.0	

Note: "Responder" indicates patients whose best overall response to treatment with pemetrexed plus bevacizumab was either a complete or partial response. "Nonresponder" indicates patients whose best overall response to treatment with pemetrexed plus bevacizumab was either stable or progressive disease.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; NSCLC NOS, non-small cell lung cancer not otherwise specified; RR, response rate.

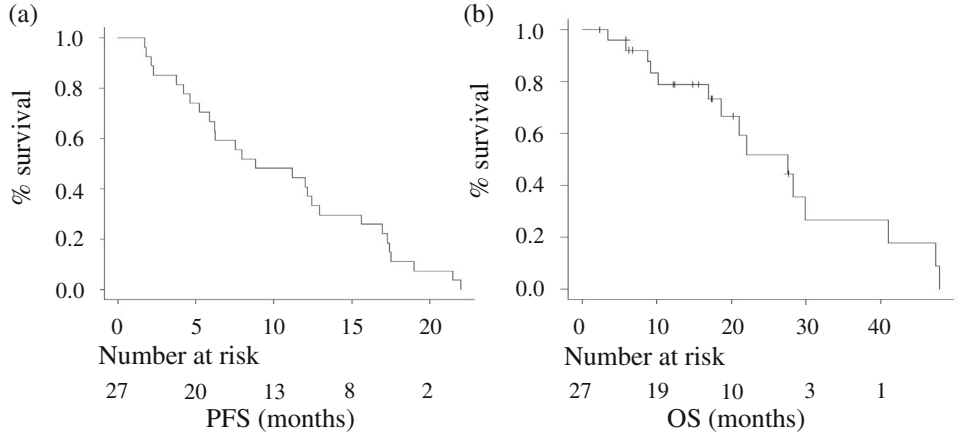

FIGURE 1 (a) Progression-free survival (PFS) and (b) overall survival (OS) curves of patients. At a median follow-up duration of 27.6 (range, 3.5–47.2) months, the median PFS and median OS were 8.8 (95% CI: 5.2–12.9) months and 27.2 (95% CI: 16.9–41.0) months, respectively.

Safety

The treatment-related adverse events are summarized in Table 4. The most frequently reported hematological adverse event of all grades was neutropenia (33.3%), and one patient (3.7%) experienced grade 3 febrile neutropenia. Thrombocytopenia and anemia of grade ≥3 were observed in two (7.4%) and one (3.7%) patients, respectively. Frequently observed nonhematological adverse events were malaise (48.1%), anorexia (44.4%) and constipation (44.4%) for all grades and AST and ALT elevation (11.1%) for grade ≥3. Pneumonitis of grade 2 was observed in three patients (11.1%). Toxicities of special interest for Bev observed in this study were proteinuria (29.6%), epistaxis (22.2%), hypertension (18.5%), gastrointestinal hemorrhage (7.4%), bronchopulmonary hemorrhage (3.7%) and thromboembolic events (3.7%) for all grades.

TABLE 4 Treatment-related adverse events.

	N (%)			
Adverse events	**All grades**		**Grade ≥3**	
Hematological toxicities				
Neutropenia	9	(33.3)	2	(7.4)
Anemia	7	(25.9)	1	(3.7)
Thrombocytopenia	6	(22.2)	2	(7.4)
Febrile neutropenia	1	(3.7)	1	(3.7)
Nonhematological toxicities				
Malaise	13	(48.1)	1	(3.7)
Anorexia	12	(44.4)	0	(0.0)
Constipation	12	(44.4)	0	(0.0)
AST/ALT elevation	7	(25.9)	3	(11.1)
Urticaria	7	(25.9)	0	(0.0)
Mucositis oral	6	(22.2)	2	(7.4)
Fatigue	6	(22.2)	0	(0.0)
Nausea	3	(11.1)	0	(0.0)
Diarrhea	3	(11.1)	0	(0.0)
Pulmonary infection	3	(11.1)	1	(3.7)
Pneumonitis	3	(11.1)	0	(0.0)
Vertigo	1	(3.7)	0	(0.0)
Creatinine increased	1	(3.7)	0	(0.0)
Peripheral sensory neuropathy	1	(3.7)	1	(3.7)
Toxicities of special interest for bevacizumab				
Proteinuria	8	(29.6)	2	(7.4)
Epistaxis	6	(22.2)	0	(0.0)
Hypertension	5	(18.5)	2	(7.4)
Gastrointestinal hemorrhaging	2	(7.4)	0	(0.0)
Bronchopulmonary hemorrhaging	1	(3.7)	0	(0.0)
Thromboembolic event	1	(3.7)	1	(3.7)

Note: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

The QOL

Patients completed the VAS and the EORTC QLQ-C30 questionnaires at fixed points of the study, as described above. There were no significant differences in the VAS scores between the baseline and each point of assessment. Similarly, there were no significant differences in the major scale or subscale scores in the EORTC QLQ-C30 between the baseline and each point of assessment (data not shown).

DISCUSSION

In the present study, we conducted a prospective phase II study to investigate the efficacy and safety of combination chemotherapy with PEM plus Bev for previously untreated Non-Sq NSCLC patients ≥75 years old. Among 27 study participants, one showed a CR, and 10 showed a PR, yielding an ORR of 40.7% (95% CI: 22.4%–61.2%). Furthermore, PEM plus Bev exerted better outcomes with regard to the PFS and OS than seen in previous reports,[10–12] the treatment was well-tolerated, and no treatment-related death (TRD) was observed. These observations suggested that PEM plus Bev might be a viable treatment option for treatment-naïve Non-Sq NSCLC in elderly individuals.

DTX monotherapy is considered a standard treatment regimen for elderly patients with advanced or recurrent NSCLC based on the results of two phase III trials in Japan.[3,13] PEM exhibited a superior OS and caused significantly fewer adverse events than DTX in Non-Sq NSCLC patients.[6,14] Furthermore, in elderly patients (≥70 years old) with previously treated NSCLC, PEM demonstrated a longer PFS (4.6 vs. 2.9 months) and OS (9.5 vs. 7.7 months) than DTX in a subset analysis.[15] Given its favorable antitumor activity and mild toxicity profile, PEM might be a promising agent for elderly Non-Sq NSCLC.

The addition of Bev to standard chemotherapy is expected to have additional benefits against Non-Sq NSCLC.[7,16] However, in a subset analysis of the ECOG4599 study, no additional effects of Bev were demonstrated in patients ≥70 years old, while more toxicities and a higher incidence of TRD were also observed in these patients than in those <70 years old.[17] In contrast, recent evidence has shown that Bev tends to have weak additional effects on the OS and PFS in Non-Sq NSCLC patients >75 years old[18] and that Bev-containing regimens have benefits over Non-Bev regimens in a real-world study of Non-Sq NSCLC patients, including elderly patients.[19] Thus, regimens containing Bev might be beneficial for elderly patients with Non-Sq NSCLC.

Recently, a few prospective studies of PEM plus Bev in elderly Non-Sq NSCLC have been reported (Table 5);[10–12] however, these studies failed to prove the significant clinical benefit of PEM plus Bev compared to standard regimens. A phase III, randomized, open-label study failed to meet its primary endpoint concerning the noninferiority of PEM plus Bev versus CBDCA/PEM pus Bev in elderly patients (≥65 years old) with previously untreated Non-Sq NSCLC.[12] Furthermore, in a randomized phase II study comparing the clinical impact of PEM plus Bev with that of PEM in Non-Sq NSCLC patients ≥75 years old, PEM monotherapy showed more favorable toxicity and cost-effectiveness than PEM plus Bev.[10] In the aforementioned previous studies, the ORR, PFS and OS were reported to be 25%–55%, 4.8–5.5 months and 11.6–16.4 months, respectively. In the present study, PEM plus Bev exhibited a similar effect on the ORR (40.7%) compared to previous studies and tended to produce better survival outcomes with regard to the median PFS (8.8 months) and median OS (27.5 months) than previous studies. Although it is difficult to directly compare the outcomes of prospective studies conducted in different situations, our results suggest that combination chemotherapy with PEM plus Bev might be an optional regimen for elderly patients with previously untreated Non-Sq NSCLC. Chemotherapy with ICIs is currently considered as a standard treatment for advanced Non-Sq NSCLC. However, the efficacy and safety of ICIs in elderly patients, especially aged ≥75 years old, remain to be fully elucidated. While a pooled analysis of the KEYNOTE-010, KEYNOTE-024, and KEYNOTE-042 studies showed the efficacy and safety of ICIs in patients aged ≥75 years,[20] an improvement in OS was not observed in patients aged ≥75 years in a meta-analysis of four randomized controlled trials of anti-PD-1 antibody.[21] A pooled analysis of 21 randomized controlled trials of ICIs also found that nivolumab was not effective in patients with NSCLC aged ≥75 years.[22] In addition, a particular concern about treatment with ICIs should be required in some patients. Pneumonitis is the most serious immune-related adverse event (irAE) specific to ICIs. Previous reports have demonstrated that the incidence of pneumonitis due to ICIs were significantly higher in comorbid lung cancer patients with interstitial lung disease (ILD) including idiopathic pulmonary fibrosis compared to those without ILD.[23–26] An increased incidence of serious irAEs such as colitis has also been shown in melanoma patients with autoimmune diseases, particularly those with inflammatory bowel disease.[27] Therefore, ICIs may not be suitable for lung cancer patients with the above underlying conditions. In addition, the efficacy of ICIs may vary with age, and it has been suggested that the efficacy of ICIs may be reduced in people aged ≥75 years old due to so-called immunosenescence, a phenomenon which refers to the reduced activity of immunity with older age.[28] Given that there is an increase in comorbidity with increasing age, there may not be a therapeutic indication for ICIs in many elderly patients, thus PEM plus Bev might be a useful regimen for advanced Non-Sq NSCLC patients who are not fit for chemotherapy with ICIs.

The safety of Bev combination therapy in the elderly has not been well established. A subset analysis of the ECOG4599 study reported more toxicities and a higher incidence of TRD of 6.3% and 2.6% in the elderly cohorts, respectively, than younger patients.[17] The SAiL study, a phase IV large-scale cohort study investigating the efficacy and safety of Bev-containing

TABLE 5 Prospective studies of pemetrexed plus bevacizumab in elderly patients with previously untreated nonsquamous non-small cell lung cancer.

Study	TORG1015	65Plus	LOGIK1201	Our study
Author	Kozuki et al.	Schuette et al.	Fukuda et al.	Yabuki et al.
Year	2016[11]	2017[12]	2019[10]	2023
Reference number	11	12	10	-
N	12	119	20	27
Age, years	≥70	≥65	≥75	≥75
ORR, % (95% CI)	25 (5.5–57.2)	31.1 (22.7–39.4)	55 (31.5–76.9)	40.7 (22.4–61.2)
PFS, months (95% CI)	5.4 (1.1–8.8)	4.8 (4.3–6.0)	5.5 (3.6–9.9)	8.8 (5.2–12.9)
OS, months (95% CI)	13.6 (5.3–15.6)	11.6 (8.6–14.2)	16.4 (7.9–36.0)	27.5 (16.9–41.0)

Abbreviations: CI, confidence interval; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

regimens for Non-Sq NSCLC, demonstrated a slightly higher incidence of severe adverse events in elderly patients >65 years old than in their younger counterparts (45.3% and 34.7%, respectively).[29] However, the incidence of adverse events of special interest (AESIs) for Bev was comparable between these age groups. In another prospective cohort study evaluating the toxicity of Bev-containing regimens in elderly patients (≥65 years old), there were no significant increases in hematological toxicity, nonhematological toxicity, hospitalizations, dose reduction, dose delay or discontinuation of treatment by the addition of Bev. However, of note, the addition of Bev was associated with a high frequency of grade 3–5 toxicities with an odds ratio of 2.86 (95% CI: 1.06–7.70).[30] In the present study, nine patients (33.3%) experienced grade 3–4 adverse events, three developed grade 2 pneumonitis, and 14 (44.4%) experienced AESIs for Bev. All adverse events were already known and predictable for the safety profiles of PEM or Bev. The reported toxicities were mild and manageable, consistent with previous studies of PEM plus Bev in elderly patients with previously untreated Non-Sq NSCLC. We observed no occurrence of TRDs or grade 3–4 pneumonitis. Furthermore, no significant reductions in the QOL were noted by the patient-reported outcome assessment. These findings indicated that combination chemotherapy with PEM plus Bev had acceptable toxicity profiles for elderly Non-Sq NSCLC patients.

Several limitations associated with the present study warrant mention. First, the sample size was small due to slow patient accrual and premature closure of the study. During this study period (from 2012 to 2020), CBDCA plus PEM, CBDCA plus nanoparticulate albumin-bound paclitaxel and ICIs ± platinum combination therapies became available as first-line treatments for elderly NSCLC, and the expansion of therapeutic options may have slowed patient enrollment. Second, while adverse events observed in this study were already known and predictable based on the toxicity profiles of PEM or Bev, there may not have been sufficient power to extract an increment in relatively rare events. Third, we did not evaluate the cost-effectiveness of PEM plus Bev in this study, although the total cost of treatment, as well as therapeutic efficacy and safety, is an important factor influencing treatment choice, especially in elderly patients. Further larger-scale studies are warranted to determine the efficacy and tolerability of combination chemotherapy with PEM plus Bev for elderly patients with previously untreated Non-Sq NSCLC.

In conclusion, we conducted a multicenter, open-label, phase II trial of PEM plus Bev in elderly patients with advanced or recurrent Non-Sq NSCLC. Combination chemotherapy with PEM plus Bev exhibited favorable antitumor activity and tolerability, suggesting that a combination of PEM plus Bev might be a promising treatment option in elderly patients with previously untreated advanced or recurrent Non-Sq NSCLC.

AUTHOR CONTRIBUTIONS

Conception and design: Masaki Hanibuchi, and Yasuhiko Nishioka, Collection and assembly of data: Yohei Yabuki, Eiji Takeuchi, Takashi Haku, Takanori Kanematsu, Naoki Nishimura, Yuko Toyoda, Kenji Otsuka, Seidai Sato, Hisatsugu Goto, and Hiroto Yoneda, Data analysis and interpretation: all authors. Manuscript writing: Yohei Yabuki, Masaki Hanibuchi, and Yasuhiko Nishioka, Final approval of manuscript: all authors. Accountable for all aspects of the work: all authors.

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CONFLICT OF INTEREST STATEMENT

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