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RESEARCH ARTICLE

Bevacizumab in combination with pemetrexed and platinum for elderly patients with advanced non-squamous non-small-cell lung cancer: a retrospective analysis

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Abstract **Bevacizumab, an anti-VEGF monoclonal antibody, has significantly improved the clinical outcomes of patients with advanced non-squamous NSCLC (ns-NSCLC). However, the safety and efficacy of bevacizumab for elderly patients with advanced NSCLC require further investigation. Thus, 59 patients were included in the present retrospective study, 22 patients in the bevacizumab plus pemetrexed and platinum (B + PP) group, and 37 patients in the pemetrexed and platinum (PP) group. For the entire cohort of patients, the median OS was 33.3 months, and the 1-year and 2-year overall survival rates were 88.5% and 67.8%, respectively. The median OS and 1-year and 2-year OS rates were 20.5 months, 70.3% and 0%, respectively, in the B + PP group and 33.4 months, 97.0% and 89.4%, respectively, in the PP group ($P < 0.001$). The incidence of grade $\geqslant 3$ adverse events was higher in the B + PP group than in the PP group (27.3% vs. 10.8%, respectively; $P = 0.204$). Univariate and multivariate analyses suggested that the receipt of $\geqslant 5$ cycles of first-line chemotherapy was an independent favorable prognostic factor for OS, whereas the addition of bevacizumab was an unfavorable prognostic factor. With increased toxicities, the addition of bevacizumab to PP does not improve the overall survival of elderly patients with advanced ns-NSCLC.**

Keywords bevacizumab; elderly patient; advanced non-small-cell lung cancer; overall survival; toxicity

Introduction

Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer deaths (18.4% of total cancer deaths) worldwide [1]. Non-small-cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers. Chemotherapy still plays an important role in the management of advanced NSCLC, particularly for patients who are unsuitable or unavailable for targeted therapy and immunotherapy [2]. Angiogenesis is one of the hallmarks of cancer [3]. Vascular endothelial growth factor (VEGF), with elevated expression in most tumors, is the major regulator in tumor angiogenesis [4]. A new paradigm for the combination therapy of VEGF-targeted therapy and chemotherapy has provided significant clinical benefits for patients with advanced-stage malignancies by normalizing tumor vasculature and increasing drug delivery [5,6]. Bevacizumab, an anti-VEGF monoclonal antibody, has significantly improved the clinical outcome of patients with advanced non-squamous NSCLC (ns-NSCLC), as shown in phase III clinical trials (ECOG4599, AVAiL, and BEYOND) [7–9]. In ECOG4599, the addition of bevacizumab to paclitaxel–carboplatin (PC) has prolonged overall survival (OS) by 2 months compared with chemotherapy alone (median OS, 12.3 vs. 10.3 months; hazard ratio (HR), 0.79; $P = 0.003$) [7]. This trial led to the approval of bevacizumab–paclitaxel–carboplatin as a treatment for advanced ns-NSCLC by the US Food and Drug Administration in October 2006 [10]. For Chinese patients in BEYOND, OS was prolonged with bevacizumab plus chemotherapy (median OS, 24.3 vs. 17.7 months; HR, 0.68; $P = 0.015$) [8].

Elderly patients with decreased renal and liver functions, a compromised immune response, a low marrow regenerative capacity, and frequent comorbid illnesses were

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usually excluded from clinical trials [11]. Furthermore, bevacizumab was associated with a high incidence of hypertension, proteinuria, and bleeding in phase III and phase IV trials [7–9,12]. Thus, the safety and efficacy of bevacizumab for elderly patients with advanced NSCLC have not been sufficiently evaluated. Considering the lack of clinical data, we conducted this retrospective study to assess the therapeutic index of first-line bevacizumab-containing regimens and justify the prospective application of bevacizumab in elderly patients with advanced ns-NSCLC.

Materials and methods

Patients

We retrospectively evaluated elderly patients ($\geqslant$ 65 years) with advanced ns-NSCLC at our cancer center between April 2013 and March 2018. Eligible criteria included the following: cytologically or histologically confirmed ns-NSCLC; at least 65 years of age; previously untreated disease; stage IIIB or IV; and a Karnofsky performance status (KPS) score $\geqslant$ 70. Patients were excluded if they had the following conditions: dominant squamous histology, a recent history of bleeding or thrombotic events, tumors invading major blood vessels, medically uncontrolled hypertension, ongoing therapeutic anticoagulants, regular use of aspirin, and inadequate organ function or KPS score $<$ 70. All procedures involving patients conformed to *Declaration of Helsinki*. All patients provided written informed consent before their participation in this study.

Treatments

All patients in this study received pemetrexed and platinum (PP) or bevacizumab plus PP (B + PP) every 21 days for 4–6 cycles. Pemetrexed was administered at 500 mg/m^2 on day 1, and bevacizumab was administered at 7.5 mg/kg intravenously on the day before chemotherapy. Platinum drugs included cisplatin 30 mg/m^2 on days 1–3 and carboplatin 0.3–0.4 g/m^2 on day 1. For patients who achieved a response or stable disease after the first-line therapy, maintenance therapy could be administered with bevacizumab plus pemetrexed (BP), pemetrexed monotherapy, or a TKI (tyrosine kinase inhibitor). During the first-line and maintenance therapy or after disease progression, combined thoracic radiation therapy was permitted, with a total dose of 30–60 Gy delivered at 1.8–2.0 Gy per fraction for 5 days weekly.

Assessments of response and toxicity

Tumor status evaluation was performed every 2 cycles for 4–6 cycles since initial treatment, every 2 months for the remaining treatment period, and every 3–6 months thereafter. Responses were assessed in accordance with Response Evaluation Criteria in Solid Tumors version 1.0. Toxicities were evaluated in accordance with the National Cancer Institute-Common Toxicity Criteria version 3.0.

Endpoints

The primary endpoint was OS, defined as the period from the date of diagnosis to the date of death from any cause or the last known follow-up date. Secondary endpoints were progression-free survival (PFS), adverse events (AEs), overall response rate (ORR), disease control rate (DCR), 1-year OS rate, and 2-year OS rate. PFS was measured from the date of diagnosis to the date of disease progression either in the thorax or at distant lesions, the date of death from any cause, or the last known follow-up date. AEs were evaluated in all patients.

Statistical analysis

Differences within categorical variables, response rates, and AEs between the two groups were assessed using Chi-square test and Fisher's exact test. OS and PFS were calculated using the Kaplan–Meier method, and differences in survival curves between the two groups were compared using the log-rank test. Univariate survival analysis was performed using the Kaplan–Meier method to determine associations between OS and clinical characteristics. Important clinical variables were applied to a multivariate model in which a backward-forward, stepwise method of a Cox proportional hazards model was used to determine significant factors. All reported P values are two-sided, and confidence intervals (CIs) are at the 95% level. Statistical significance was considered at $P < 0.05$.

Results

Patient characteristics

From April 2013 to March 2018, approximately 5470 patients were diagnosed with stage IV ns-NSCLC at our cancer center, and approximately 1330 patients were 65 years or older. Only a few patients received first-line pemetrexed or in combination with bevacizumab because pemetrexed was expensive and bevacizumab was not covered by medical insurance. Thus, 65 elderly patients ($\geqslant$ 65 years) with stage IIIB or IV NSCLC at our cancer center were identified. Six patients were lost during the follow-up, resulting in a follow-up rate of 92.3%. Finally, 59 patients who were fully eligible were included in the current study. The median follow-up was 14.1 months

(range, 2.5–42.0 months) for all the patients and 13.8 months (range, 6.6–42.0 months) for the patients who were alive. In the entire cohort of patients, the median age was 69 years and their age ranged from 65 to 89 years. Forty-one (69.5%) were men, and 18 (30.5%) were women. Depending on their treatment modality, 22 (37.3%) patients were allocated to the B + PP group and 37 (62.7%) patients were allocated to the PP group.

Patient characteristics are summarized in Table 1. No significant differences in the distribution of all the variables were found between the groups. The epidermal growth factor receptor (EGFR) mutation rate in the entire cohort was 38.1% (16 of 42 patients who were assessable). The treatment details are summarized in Table 2. Most of the treatment characteristics were balanced except the maintenance therapy ($P = 0.014$). In the PP group, 24 of the 37 (64.9%) patients received maintenance therapy with pemetrexed (21 patients), BP (1 patient), and TKI (2 patients). However, in the B + PP group, only 7 of the 22 (31.8%) patients received maintenance therapy with pemetrexed (1 patient) and BP (6 patients). The reasons that the patients did not receive maintenance therapy were intolerable toxicities (2 and 2 in the B + PP and PP groups, respectively), patient refusal (8 and 5 patients in the two groups, respectively), and disease progression (5 and 6 patients in the two groups, respectively).

Survival

As shown in Table S1, among all 59 patients, 32 (54.2%) achieved a response and 55 (93.2%) achieved disease control. The ORRs were 50.0% and 56.8% in the B + PP and PP groups, respectively ($P = 0.614$). The DCRs were also not significantly different with 90.0% and 94.6% in the two groups, respectively ($P = 0.993$).

For the entire cohort of patients, the median OS was 33.3 months (95% CI 24.4–42.2), and the 1-year and 2-year OS rates were 88.5% and 67.8%, respectively (Fig. 1). The median OS was 20.5 months, and the 1-year and 2-year OS rates were 70.3% and 0%, respectively, in the B + PP

Table 1 Patient characteristics

Characteristic	Number of patients (%)			*P*
	Total	B + PP ($n = 22$)	PP ($n = 37$)	
Age, year				
Median	69	69	69	
Range	65–85	65–76	65–85	
⩾ 69	34	13 (59.1)	21 (56.8)	0.861
< 69	25	9 (40.9)	16 (43.2)	
Sex				
Male	41	13 (59.1)	28 (75.7)	0.181
Female	18	9 (40.9)	9 (24.3)	
KPS score				
⩾ 80	56	20 (90.9)	36 (97.3)	0.640
< 80	3	2 (9.1)	1 (2.7)	
Smoking status				
Never smoker	24	10 (45.5)	14 (37.8)	0.565
Ever smoker	35	12 (54.5)	23 (62.2)	
Histology				
Adenocarcinoma	58	21 (95.5)	37 (100)	0.373
Others	1	1 (4.5)	0 (0)	
Stage				
IIIB	11	6 (27.3)	5 (13.5)	0.334
IV	48	16 (72.7)	32 (86.5)	
Hypertension				
Yes	16	5 (22.7)	11 (29.7)	0.559
No	43	17 (77.3)	26 (70.3)	
EGFR mutation status assessment[a]	42	16	26	
EGFR mutation positive	16	5 (31.3)	11 (42.3)	0.474
EGFR wild type	26	11 (68.8)	15 (57.7)	

[a]EGFR mutation status was assessed in 42 patients.
Abbreviations: B + PP, bevacizumab plus pemetrexed–platinum; PP, pemetrexed–platinum; EGFR, epidermal growth factor receptor.

Table 2 Treatment details of the two groups

Treatment	Number of patients (%)			*P*
	Total	B + PP (*n* = 22)	PP (*n* = 37)	
Number of first-line chemotherapy cycles				
Median	5	4	6	
Range	2–9	2–9	2–9	
⩾ 5	32	9 (40.9)	23 (62.2)	0.113
< 5	27	13 (59.1)	14 (37.8)	
Maintenance				
Yes	31	7 (31.8)	24 (64.9)	0.014
No	28	15 (68.2)	13 (35.1)	
Maintenance regimens	31	7	24	
Bevacizumab + pemetrexed	7	6	1	
Pemetrexed	22	1	21	
TKIs	2	0	2	
Thoracic radiation				
Yes	16	6 (27.3)	10 (27.0)	0.984
No	43	16 (62.3)	27 (73.0)	
Second-line treatment				
Yes	28	8 (72.7)	20 (83.3)	0.785
No	7	3 (27.3)	4 (16.7)	
Second-line regimens				
Chemotherapy	19	5 (62.5)	14 (70.0)	1.000
TKIs	9	3 (37.5)	6 (30.0)	

Abbreviations: B + PP, bevacizumab plus pemetrexed–platinum; PP, pemetrexed–platinum; TKI, tyrosine kinase inhibitor.

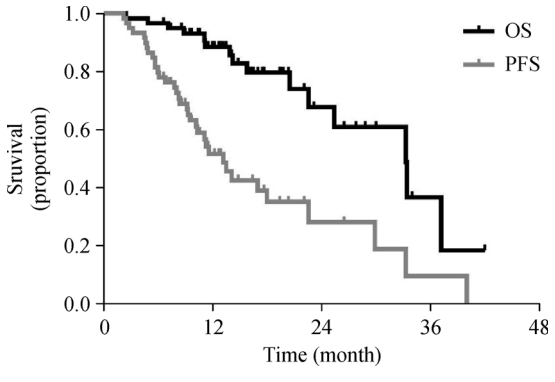

Fig. 1 PFS and OS in the entire cohort.

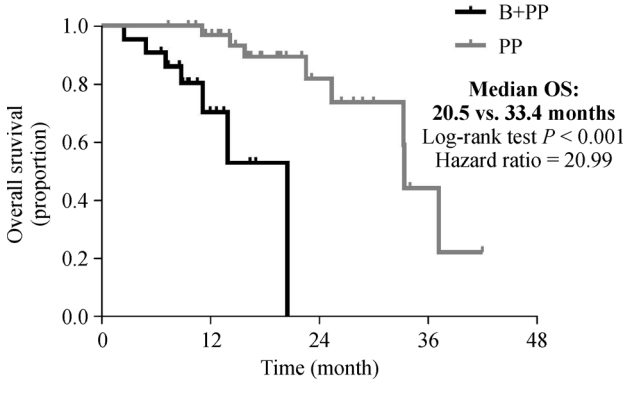

Fig. 2 Comparison of OS between the B + PP and PP groups.

group. In the PP group, the median OS was 33.4 months (95% CI 33.2–33.6), and the 1-year and 2-year OS rates were 97.0% and 89.4%, respectively ($P < 0.001$) (Fig. 2).

The median PFS was 13.2 months (95% CI 10.2–16.2) and the 1-year and 2-year PFS rates were 51.6% and 28.0%, respectively, for all the patients (Fig. 1). In the B + PP group, the median PFS was 11.3 months (95% CI 7.0–15.6), and the 1-year and 2-year PFS rates were 28.3% and 0%, respectively. In the PP group, the median PFS was 14.1 months (95% CI 8.3–19.9), and the 1-year and 2-year PFS rates were 59.0% and 36.0%, respectively ($P = 0.101$) (Fig. 3).

Prognostic factors

Univariate analysis indicated that age at diagnosis, sex, smoking status, disease stage, EGFR mutation status, maintenance therapy, and thoracic radiation were not associated with OS. However, the KPS score, receipt of ⩾ 5 cycles of first-line chemotherapy, and addition of

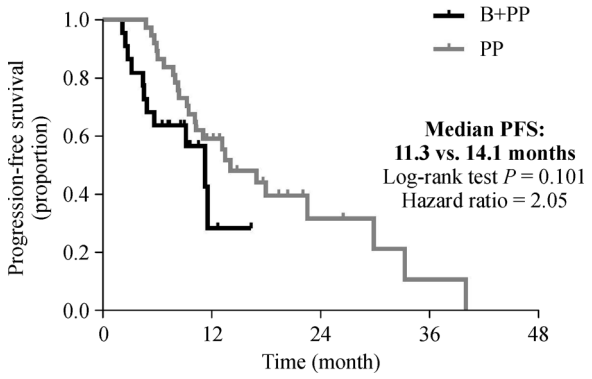

Fig. 3 Comparison of PFS between the B + PP and PP groups.

bevacizumab were significant prognostic factors of OS (Table 3). Multivariate analysis suggested that the receipt of ⩾ 5 cycles of first-line chemotherapy and bevacizumab therapy were the only two independent prognostic factors of OS (Table 4). The receipt of ⩾ 5 cycles of first-line chemotherapy was a favorable prognostic factor of OS (HR, 0.045; $P = 0.007$), whereas the receipt of bevacizumab was an unfavorable prognostic factor (HR, 13.733; $P = 0.010$).

Toxicities

The incidence of any grade toxicity, including hematologic, gastrointestinal toxicities, and hypertension did not significantly differ between the groups (Table S2). In addition, none of the patients had thrombosis, hemorrhage, or pneumonia after bevacizumab treatment. Although not significantly different, the incidence of grade ⩾ 3 AEs, particularly hematologic toxicity, was higher in the B + PP group than in the PP group (27.3% vs. 10.8%, respectively; $P = 0.204$). Among 22 patients in the B + PP group, 3 (13.6%) developed bevacizumab-related hypertension.

Table 3 Univariate analysis of prognostic factors for overall survival in elderly patients with advanced NSCLC

Characteristic	mOS, month	1-Year OS, %	2-Year OS, %	Chi-square statistic	*P*
Age, year					
⩾ 69	25.4	86.6	60.5	3.13	0.077
< 69	NR	91.0	75.9		
Sex					
Male	33.3	89.6	70.1	0.32	0.569
Female	NR	83.7	62.7		
KPS score					
⩾ 80	33.4	89.7	74.2	4.98	0.026
< 80	22.6	66.7	0.0		
Smoking status					
Never smoker	NR	89.3	71.4	1.58	0.209
Ever smoker	33.3	87.6	65.3		
Stage					
IIIB	25.4	64.3	64.3	1.40	0.237
IV	33.4	91.2	66.9		
EGFR mutation status assessment					
EGFR mutation positive	37.2	79.1	69.2	0.37	0.542
EGFR wild type	33.4	95.2	71.1		
Number of first-line chemotherapy cycles					
⩾ 5	37.2	100.0	95.0	12.52	<0.001
< 5	22.6	74.6	42.6		
Maintenance					
Yes	NR	93.1	74.8	2.64	0.104
No	33.3	82.6	55.1		
Thoracic radiation					
Yes	NR	93.3	62.2	0.35	0.555
No	33.3	87.1	67.8		
Bevacizumab					
Yes	20.5	70.3	0.0	14.68	<0.001
No	33.4	97.0	81.9		

Abbreviations: B + PP, bevacizumab plus pemetrexed–platinum; PP, pemetrexed–platinum; mOS, median overall survival; NR, not reached.

Table 4 Multivariate analysis of the prognostic factors for OS in elderly patients with advanced ns-NSCLC

Characteristic	HR	95% CI	Chi-square statistic	*P*
Age, year ($\geqslant$ 69 vs. $<$ 69)	2.023	0.513–7.977	1.013	0.314
Sex (male vs. female)	0.891	0.131–6.043	0.014	0.906
Number of first-line chemotherapy cycles ($\geqslant$ 5 vs. $<$ 5)	0.045	0.005–0.426	7.288	0.007
Maintenance (yes vs. no)	0.864	0.218–3.419	0.043	0.835
Thoracic radiation (yes vs. no)	0.176	0.015–2.117	1.875	0.171
Bevacizumab (yes vs. no)	13.733	1.855–101.675	6.579	0.010

Abbreviations: HR, hazard ratio; CI, confidence interval.

The severe AEs led to drug withdrawal in 2 (9.1%) patients receiving bevacizumab, one of whom had intolerable hypertension. None of the patients died of toxicities.

Discussion

The current study explored the safety and efficacy of bevacizumab in combination with first-line PP in elderly patients with advanced ns-NSCLC and is valuable to guide clinical bevacizumab application in elderly patients. Our study suggests that bevacizumab in addition to first-line PP does not improve OS and PFS in elderly patients ($\geqslant$ 65 years) with ns-NSCLC. In addition, the incidence of grade $\geqslant$ 3 AEs was higher in the B + PP group than in the PP group. Univariate and multivariate analyses suggested that the receipt of $\geqslant$ 5 cycles of first-line chemotherapy was a favorable prognostic factor of OS, but the addition of bevacizumab was an unfavorable prognostic factor.

Several studies have evaluated the clinical efficiency of bevacizumab in elderly patients with ns-NSCLC. The subgroup analyses in 366 patients aged 65 years or older and 224 patients aged 70 years or older in ECOG4599 demonstrated that the addition of bevacizumab to PC was associated with a higher degree of toxicities and found no significant improvement in PFS and OS [7,13]. For patients aged 70 years or older, the median OS was 11.3 months in the bevacizumab-PC group and 12.1 months in the PC group (P = 0.40) [13]. In a retrospective cohort study from the SEER database, 4168 patients aged 65 years or older with stage IIIB or IV NSCLC were analyzed [14]. The median OS was 9.7 months for bevacizumab-PC, 8.9 months for PC diagnosed in 2006–2007, and 8.0 months for PC in 2002–2005. In the propensity score-stratified models, the HR for the OS of bevacizumab-PC compared with PC in 2006–2007 was 1.01, and that in 2002–2005 was 0.93. In our study, OS with B + PP was significantly inferior to PP (median OS, 20.5 vs. 33.4 for the 2 groups, respectively; HR, 20.99; $P < 0.001$). Multivariate analysis also suggested that the addition of bevacizumab was an unfavorable prognostic factor of OS (HR, 14.801; P = 0.016). A phase II trial enrolled 12 patients, and the ORR, PFS, and OS were 58%, 8.4 months and 33.9 months, respectively, in elderly patients with non-squamous NSCLC receiving bevacizumab-PC followed by maintenance bevacizumab. The toxicities were generally mild with no treatment-related deaths [15]. Although this single-arm phase II trial showed that bevacizumab was feasible and potentially efficacious in elderly patients with non-squamous NSCLC, the sample size is too small and larger randomized controlled trials are needed to reach firm conclusions.

Previous studies have shown that bevacizumab is associated with a higher incidence of severe AEs in the elderly [13], a finding that could otherwise influence the first- and second-line chemotherapy and maintenance therapy. Adverse events are major concerns in the application of bevacizumab. For the subgroup of 224 patients aged 70 years or older in ECOG4599, grade $\geqslant$ 3 toxicities occurred in 87% of elderly patients in the bevacizumab-PC group versus 61% in the PC group ($P < 0.001$) [13]. In BEYOND, the higher incidence of grade $\geqslant$ 3 hypertension, proteinuria, and hemorrhage was associated with bevacizumab [8]. Bevacizumab-associated grade $\geqslant$ 3 thromboembolism occurred in 8% of patients, hypertension in 6%, bleeding in 4%, proteinuria in 3%, and pulmonary hemorrhage in 1% from the SAiL trial [12]. Furthermore, the temporary interruption of bevacizumab was attributed to 2% of bleeding events and 7% of hypertension events, and permanent discontinuation was due to 8% of bleeding events and 4% of hypertension events. With the addition of bevacizumab to PP, a higher incidence of severe toxicities was also observed in our study. The incidence rates of grade $\geqslant$ 3 AEs were 27.3% and 10.8% for patients receiving B + PP and PP, respectively. Three of 22 (13.6%) patients in the B + PP group developed bevacizumab-related hypertension, and one of them had bevacizumab interruption.

Maintenance therapy is associated with prolonged OS in patients with advanced NSCLC [16–20]. Consistent with previous studies, our study demonstrated that maintenance therapy, fewer first-line chemotherapy cycles, and second-line therapy might account for the worse OS in patients treated with bevacizumab. Maintenance therapy, as an

important part of the whole course treatment, produces a survival benefit in NSCLC. In JMEN, maintenance therapy with pemetrexed after first-line platinum-based chemotherapy was well tolerated and significantly improved PFS and OS compared with placebo in patients with advanced NSCLC [16,17]. The PARAMOUNT study suggested that continuation maintenance with pemetrexed after induction therapy with pemetrexed-cisplatin produced significant reductions in the risk of progression and death over the placebo [18]. In the retrospective analysis of living and progression-free patients in ECOG 4599, significant reductions in HRs for progression and survival were associated with bevacizumab maintenance therapy [19]. The phase III PointBreak study also revealed a significantly improved PFS in patients receiving BP maintenance after first-line bevacizumab-PC therapy in stage IIIB or IV non-squamous NSCLC [20]. In the current study, the lower proportion of patients receiving maintenance therapy in the B + PP group may be at least one reason accounting for the poorer prognosis compared with PP alone.

In addition to maintenance therapy, bevacizumab could also influence first- and second-line chemotherapy. In the current study, patients in the B + PP group tended to receive fewer cycles of first-line chemotherapy compared with those in the PP group, with median cycles of 4 and 6 for the 2 groups, respectively. Furthermore, second-line chemotherapy was administered to 8 of 11 (72.7%) patients who showed disease progression and 20 of 24 (83.3%) patients in the B + PP and the PP groups, respectively.

The median OS of the B + PP group in our study (20.5 months) was longer than that in ECOG4599 (12.3 months) [7]. However, it was comparable with 24.3 months in the bevacizumab-PC group in the BEYOND study [8], which also enrolled Chinese patients. Asian populations with advanced NSCLC showed more favorable survival outcomes than the mainly white population [21]. In addition, the higher incidence of patients with confirmed EGFR mutation-positive disease in the Chinese population (27% in BEYOND and 31.3% in our study) may account for the better clinical outcome compared with that in the western population.

Our study has some limitations. First, this retrospective study included only a small number of patients from a single cancer center, which may not represent all patients with non-squamous NSCLC in the whole country. Second, biases of baseline characteristics, such as the basic lung and heart function, were not introduced in this study. Furthermore, in clinical practice, patients with relative contraindications to bevacizumab, such as hypertension and bleeding, are more likely to be included in the PP group, influencing the final survival results. Although a Cox regression model was used to adjust for all available characteristics, all possible confounding factors could not be controlled.

Conclusions

Our study suggests that the addition of bevacizumab to PP is associated with an increased risk of severe toxicities and does not improve the OS of elderly patients with advanced non-squamous NSCLC. Despite some uncontrolled confounding factors, such as the basic lung and heart function and contraindications to bevacizumab that may influence the treatment regimens and therapeutic effect, our study supplements the subgroup analysis of elderly patients in ECOG4599 and other retrospective findings and substantiates that bevacizumab may not be a standard of care for elderly patients with advanced NSCLC. Elderly-specific prospective trials must establish the effects of bevacizumab in treating elderly patients with advanced NSCLC.

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Compliance with ethics guidelines

Yaru Tian, Hairong Tian, Xiaoyang Zhai, Hui Zhu, and Jinming Yu declare that they have no competing interests. All procedures involving patients were conformed to *Declaration of Helsinki*. All patients provided written informed consent before their participation in this study.

Electronic Supplementary Material Supplementary material is available in the online version of this article at https://doi.org/10.1007/s11684-021-0827-8 and is accessible for authorized users.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68(6): 394–424
2. Herbst RS, Morgensztern D, Boshoff C. The biology and management of non-small cell lung cancer. Nature 2018; 553(7689): 446–454
3. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell 2000; 100(1): 57–70
4. Kerbel RS. Tumor angiogenesis. N Engl J Med 2008; 358(19): 2039–2049
5. Jain RK. Normalizing tumor vasculature with anti-angiogenic therapy: a new paradigm for combination therapy. Nat Med 2001; 7(9): 987–989
6. Ellis LM, Hicklin DJ. VEGF-targeted therapy: mechanisms of anti-

tumour activity. Nat Rev Cancer 2008; 8(8): 579–591

7. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, Lilenbaum R, Johnson DH. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006; 355(24): 2542–2550
8. Zhou C, Wu YL, Chen G, Liu X, Zhu Y, Lu S, Feng J, He J, Han B, Wang J, Jiang G, Hu C, Zhang H, Cheng G, Song X, Lu Y, Pan H, Zheng W, Yin AY. BEYOND: a randomized, double-blind, placebo-controlled, multicenter, phase III study of first-line carboplatin/paclitaxel plus bevacizumab or placebo in Chinese patients with advanced or recurrent nonsquamous non-small-cell lung cancer. J Clin Oncol 2015; 33(19): 2197–2204
9. Reck M, von Pawel J, Zatloukal P, Ramlau R, Gorbounova V, Hirsh V, Leighl N, Mezger J, Archer V, Moore N, Manegold C. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAil. J Clin Oncol 2009; 27(8): 1227–1234
10. Cohen MH, Gootenberg J, Keegan P, Pazdur R. FDA drug approval summary: bevacizumab (Avastin) plus carboplatin and paclitaxel as first-line treatment of advanced/metastatic recurrent nonsquamous non-small cell lung cancer. Oncologist 2007; 12(6): 713–718
11. Balducci L, Ershler WB. Cancer and ageing: a nexus at several levels. Nat Rev Cancer 2005; 5(8): 655–662
12. Crinò L, Dansin E, Garrido P, Griesinger F, Laskin J, Pavlakis N, Stroiakovski D, Thatcher N, Tsai CM, Wu YL, Zhou C. Safety and efficacy of first-line bevacizumab-based therapy in advanced non-squamous non-small-cell lung cancer (SAiL, MO19390): a phase 4 study. Lancet Oncol 2010; 11(8): 733–740
13. Ramalingam SS, Dahlberg SE, Langer CJ, Gray R, Belani CP, Brahmer JR, Sandler AB, Schiller JH, Johnson DH; Eastern Cooperative Oncology Group. Outcomes for elderly, advanced-stage non small-cell lung cancer patients treated with bevacizumab in combination with carboplatin and paclitaxel: analysis of Eastern Cooperative Oncology Group Trial 4599. J Clin Oncol 2008; 26(1): 60–65
14. Zhu J, Sharma DB, Gray SW, Chen AB, Weeks JC, Schrag D. Carboplatin and paclitaxel with vs without bevacizumab in older patients with advanced non-small cell lung cancer. JAMA 2012; 307(15): 1593–1601
15. Takeoka H, Yamada K, Naito Y, Matsuo N, Ishii H, Tokito T, Azuma K, Ichiki M, Hoshino T. Phase II trial of carboplatin and pemetrexed plus bevacizumab with maintenance bevacizumab as a first-line treatment for advanced non-squamous non-small cell lung cancer in elderly patients. Anticancer Res 2018; 38(6): 3779–3784
16. Ciuleanu T, Brodowicz T, Zielinski C, Kim JH, Krzakowski M, Laack E, Wu YL, Bover I, Begbie S, Tzekova V, Cucevic B, Pereira JR, Yang SH, Madhavan J, Sugarman KP, Peterson P, John WJ, Krejcy K, Belani CP. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. Lancet 2009; 374(9699): 1432–1440
17. Belani CP, Brodowicz T, Ciuleanu TE, Krzakowski M, Yang SH, Franke F, Cucevic B, Madhavan J, Santoro A, Ramlau R, Liepa AM, Visseren-Grul C, Peterson P, John WJ, Zielinski CC. Quality of life in patients with advanced non-small-cell lung cancer given maintenance treatment with pemetrexed versus placebo (H3E-MC-JMEN): results from a randomised, double-blind, phase 3 study. Lancet Oncol 2012; 13(3): 292–299
18. Paz-Ares LG, de Marinis F, Dediu M, Thomas M, Pujol JL, Bidoli P, Molinier O, Sahoo TP, Laack E, Reck M, Corral J, Melemed S, John W, Chouaki N, Zimmermann AH, Visseren-Grul C, Gridelli C. PARAMOUNT: final overall survival results of the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer. J Clin Oncol 2013; 31(23): 2895–2902
19. Lopez-Chavez A, Young T, Fages S, Leon L, Schiller JH, Dowlati A, Brahmer JR, Johnson DH, Sandler A. Bevacizumab maintenance in patients with advanced non-small-cell lung cancer, clinical patterns, and outcomes in the Eastern Cooperative Oncology Group 4599 Study: results of an exploratory analysis. J Thorac Oncol 2012; 7(11): 1707–1712
20. Patel JD, Socinski MA, Garon EB, Reynolds CH, Spigel DR, Olsen MR, Hermann RC, Jotte RM, Beck T, Richards DA, Guba SC, Liu J, Frimodt-Moller B, John WJ, Obasaju CK, Pennella EJ, Bonomi P, Govindan R. PointBreak: a randomized phase III study of pemetrexed plus carboplatin and bevacizumab followed by maintenance pemetrexed and bevacizumab versus paclitaxel plus carboplatin and bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV nonsquamous non-small-cell lung cancer. J Clin Oncol 2013; 31(34): 4349–4357
21. Soo RA, Loh M, Mok TS, Ou SH, Cho BC, Yeo WL, Tenen DG, Soong R. Ethnic differences in survival outcome in patients with advanced stage non-small cell lung cancer: results of a meta-analysis of randomized controlled trials. J Thorac Oncol 2011; 6(6): 1030–1038